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Evaluation of Glucose Metabolism After Distal Pancreatectomy According to the Donor Criteria of the Living Donor Pancreas Transplantation Guidelines Proposed by the Japanese Pancreas and Islet Transplantation Association

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ABSTRACT

Background. Living donor pancreas transplantation (LDPT) reduces the number of deaths of diabetic patients on dialysis and of candidates on the waiting lists and helps to overcome the organ shortage. Stringent criteria must be applied to minimize the risk of metabolic complications for living donors. The Japanese Pancreas and Islet Transplantation Association (JPITA) proposed LDPT guidelines in 2010. In this study, we retrospectively evaluated glucose metabolism of the patients who underwent distal pancreatectomy (DP) according to the donor criteria of the LDPT guidelines proposed by the JPITA.

Methods. Fifty-two nondiabetic patients who underwent DP were divided into 2 groups according to the donor criteria: indication group (IG, $n = 14$) who had age ≤ 65, hemoglobin A1c (HbA1c) $< 5.9\%$, and body mass index (BMI) < 25 kg/m^2. The other patients were placed in the no indication group (NG, $n = 38$). Clinical data and percent resected volume (PRV) of each pancreas as determined by multi–detector row computed tomography volumetry were compared between the 2 groups.

Results. During the follow-up period (median 12 months), 14 patients (27%) developed new-onset diabetes within a median onset time of 10 months (range 3–24 months) postoperatively. No patient in the IG developed new-onset diabetes. On the other hand, 37% of the patients in the NG developed new-onset diabetes. There were significant between-group differences in changes in preoperative serum fasting glucose and HbA1c levels, whereas there were no significant between-group differences in preoperative serum albumin or body weight. Multivariate analysis identified preoperative HbA1c (odds ratio 51.6, $P = .002$) and PRV (odds ratio 2.07, $P = .033$) as independent risk factors for new-onset diabetes.

Conclusion. Living donor criteria in the LDPT guidelines proposed by the JPITA are appropriate for prevention of glucose metabolic complications in donors. Further long-term follow-up studies of living donors' metabolic function are needed to clarify the safety of the donor.

THE RATIONALE FOR LIVING DONOR PANCREAS TRANSPLANTATION (LDPT) was initially immunologic advantages compared to pancreas transplantation from deceased donors in the azathioprine and cyclosporine eras. The indication for LDPT is limited because the graft survival rate has remarkably improved for deceased donor pancreas transplants since the mid-1990s in

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the tacrolimus era. However, a severe shortage of deceased donors still exists, especially in Japan, and many patients die of diabetic complications during the waiting period [1]. In Japan, LDPTs have been performed since 2004 as an ultimate lifesaving treatment for diabetic patients with severe complications [2].

Donor safety has been the most important consideration in the conduct of LDPT. Although fewer than 5% of living donors have pancreas-related postoperative surgical complications and no pancreas living donor has died as a result of the surgical procedure [3,4], possible deterioration of glucose metabolism as a result of distal pancreatectomy (DP) remains a lifelong concern. Furthermore, since there are no definitive donor criteria to prevent the deterioration of glucose metabolism, stringent criteria must be applied to minimize the risk of metabolic complications in each living donor. The Japanese Pancreas and Islet Transplantation Association (JPITA) proposed the LDPT guidelines in 2010.

In this study, we retrospectively evaluated glucose metabolism of the patients who underwent DP according to the donor criteria of the LDPT guidelines proposed by the JPITA.

MATERIALS AND METHODS

A series of 106 consecutive patients who underwent DP at our institution between January 2006 and December 2010 were originally chosen from our prospectively maintained clinical database for this retrospective study. Of these, patients with preoperative diabetes and those who were lost to follow-up were excluded. Diabetes was defined either by (1) the World Health Organization criteria of fasting plasma glucose (FPG) level $\geq$126 mg/dL detected on 2 or more separate days, (2) this abnormal FPG level detected once and plasma glucose $\geq$200 mg/dL measured 2 hours after a 75-g glucose drink, or (3) treatment with oral antidiabetic agents or insulin. The final study population consisted of 52 nondiabetic patients who had undergone DP. We divided them into 2 groups according to the donor criteria of the LDPT guidelines (Table 1): the patients in the indication group (IG, $n = 14$) had age $\leq$ 65, hemoglobin A1c (HbA1c) $<$ 5.5%, and body mass index (BMI) $<$ 25 kg/m^2. The remaining patients were placed in the no indication group (NG, $n = 38$).

Table 1. Donor Criteria of LDPT Guidelines in 2010 Proposed by the JPITA (Excerpted Version)

Age $\leq$ 65 y (desirable)
No family history of hereditary diabetes within 2 degrees of relationship except for the recipient
Normal endocrine function
75-g OGTT: normal pattern (all plasma glucose levels $<$ 180 mg/dL)
Insulinogenic index $\geq$ 0.4, HOMA-β $\geq$ 40%
IVGTT: normal (desirable)
HbA1c $<$ 5.9%
HOMA-R $<$ 2.5
Negative for anti-GDA, IA-2, and insulin antibodies
Body mass index $<$ 25 kg/m^2

Abbreviations: LDPT, living donor pancreas transplantation; JPITA, Japanese Pancreas and Islet Transplantation Association; OGTT, oral glucose tolerance test; HOMA–β, homeostasis model assessment beta cell function; IVGTT, intravenous glucose tolerance test; HbA1c, hemoglobin A1c; HOMA-R, homeostasis model assessment ratio.

Clinical data on pre- and postoperative status of the patients were obtained from existing medical records. The preoperative data used for this study had been recorded within 14 days prior to surgery. Pancreatic endocrine function and nutritional status were assessed based on serum FPG, hemoglobin A1c (HbA1c), albumin levels, and body weight. HbA1c values were expressed as the National Glycohemoglobin Standardization Program (NGSP) equivalent values and in all cases were converted from previous Japan Diabetes Society (JDS) standard substance and measurement methods using the following formula: NGSP HbA1c (%) = JDS HbA1c (%) + 0.4%. The percent resected volume (PRV) of pancreatic parenchyma, excluding tumor volume, was determined from abdominal multi–detector row computed tomography (MDCT) measurements [5]. Patient data were collected until the time of diagnosis of new-onset diabetes or tumor recurrence.

Statistical Analysis

Patient characteristics are reported as means $\pm$ standard deviation, and results are presented as means $\pm$ standard error or, where indicated, medians (range). Categorical variables are expressed numerically as percentages. For analyses of repeated measurements of serum FPG, serum HbA1c level, serum albumin, and body weight prior to and at 3, 6, and 12 months after surgery, we used analysis of variance and the Mauchy test, the latter of which evaluates the sphericity assumption. We used Student t test or Mann–Whitney test for continuous variables. Multiple logistic regression analysis yielding odds ratios and 95% confidence intervals (CIs) was used to identify risk factors for postoperative new-onset diabetes (with $P <$ .05). All analyses were performed using JMP 9.0 for Macintosh (SAS Institute Inc, Cary, NC, United States).

RESULTS

Characteristics of the Patients and New-Onset Diabetes

Physiologic characteristics of the study patients are shown in Table 2. Age and preoperative serum HbA1c level were significantly lower in the IG. Preoperative serum FPG was significantly higher, operative time was significantly shorter, and PRV was significantly higher in the NG.

During the follow-up period (median 12 months), 14 patients (27%) developed new-onset diabetes within a median onset time of 10 months (range 3–24 months) postoperatively. No patient in the IG developed new-onset diabetes. On the other hand, 37% of the patients in the NG developed new-onset diabetes. The difference was significant ($P = .021$).

Sequential Changes in Diabetic and Nutritional Status After Surgery

We compared 4 physiologic parameters in the IG and NG at 4 time points: before and 3, 6, and 12 months after surgery. There were significant differences in the changes in FPG (Fig 1A; $P < .001$) and HbA1c (Fig 1B; $P = .02$) between the 2 groups over time. On the other hand, there were no significant differences in changes in serum albumin (Fig 1C; $P = .52$) or body weight (Fig 1D; $P = .53$).

Risk Factors for Postoperative New-Onset Diabetes

Univariate analysis identified 4 statistically significant risk factors for postoperative new-onset diabetes: living donor