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Predictive factors of posttransplant glucose intolerance in Japanese patients with type 1 diabetes after pancreas transplantation

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Abstract. Pancreas transplantation (PTx) has been performed worldwide for patients with type 1 diabetes accompanied with end-stage renal disease or uncontrollable glycemic fluctuation. Nevertheless, risk factors of posttransplant glucose intolerance, which is responsible for progress of diabetic complications, remains unclear, especially in cases without pancreatic graft function loss. Therefore, this study was conducted to search for predictive factors of future glucose tolerance in PTx recipients without pancreatic graft function loss. Subjects were selected from among 41 Japanese patients with type 1 diabetes who received PTx between 2000 and 2016 in Osaka University Hospital, and 24 subjects free from rejections and thromboses were analyzed. Several examinations to evaluate insulin secretion and insulin sensitivity within 6 months after transplantation (initial examination) were performed. Glucose tolerance was evaluated by 120-minute post-load plasma glucose level during 75-g oral glucose tolerance tests (OGTT), referred to as $PG_{OGTT}120$, at the initial examination and between 1 year and 2 years posttransplantation (maintenance period). The initial examination factors that were correlated with $PG_{OGTT}120$ in the maintenance period were $PG_{OGTT}120$ [r = 0.52 (p = 0.01)], insulinogenic index [r = –0.65 (p < 0.01)], and the ratio of incremental area under the curve of insulin to that of plasma glucose (iAUCR) calculated from data of OGTT [r = –0.65 (p < 0.01)]. Insulinogenic index [β = –0.28 (p = 0.02)] and iAUCR [β = –0.29 (p = 0.02)] were still significantly correlated with $PG_{OGTT}120$ in the maintenance period after adjustment for $PG_{OGTT}120$ at the initial examination. In conclusion, insulinogenic index and iAUCR from OGTT performed in the early posttransplantation period were predictive factors of future glucose intolerance.

Key words: Type 1 diabetes mellitus, Pancreas transplantation, Posttransplant glucose intolerance, 75-g oral glucose tolerance test

TYPE 1 DIABETES MELLITUS (T1DM) is a disorder of glucose metabolism that results from a destruction of pancreatic beta cells, and consequent hyperglycemia induces various diabetic complications. To treat T1DM, administration of exogenous insulin is the first-line and the almost only therapy available in daily clinical practice, but pancreas or islet transplantation is optionally adopted when kidney transplantation is required for end-stage renal disease, or when unexpected severe hypoglycemia or hyperglycemia frequently occur in spite of best efforts with insulin therapy.

Pancreas transplantation (PTx) has been performed worldwide since the first PTx at the University of Minnesota in 1966 [1], and in spite of progress in operation techniques and immunosuppressive agents, 3-year pancreas graft survival rate was reported to be no more than about 85% and 81% in the US in 2014 [2] and in Japan in 2016 [3], respectively. Since major causes of pancreatic graft function loss are rejections and venous thromboses, which accounted for 50% and 20%, respectively, in the cases of pancreatic graft failure within the first 3 months after transplantation [4], many past studies about PTx have been focused on pancreatic graft failure from rejections and venous thromboses.

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In contrast, prognosis of pancreatic graft function in rejection- and venous thrombosis-free cases remained unclear. Even if recipients do not experience rejections or thromboses, some recipients are experienced to present glucose intolerance after successful PTx. Although previous studies had been conducted that investigated risk factors regarding pancreatic graft function loss mainly caused by rejections or thromboses [4, 5], there have been no studies investigating risk factors of glucose intolerance in rejection- and venous thrombosis-free cases after successful transplantation for T1DM. Progress of posttransplant glucose intolerance may cause re-development of diabetic complications and require re-introduction of insulin therapy, which would lower QOL and increase health care costs [6-10]. If we can predict progress of posttransplant glucose intolerance beforehand, development of glucose intolerance and consequent diabetic complications may be inhibited with careful treatment. So far, it has been reported that indices calculated based on results of insulin secretion tests were useful markers for future glucose intolerance in patients with type 2 diabetes and in healthy individuals, neither of whom had received PTx (non-PTx population) [11-13]. Thus, it is expected that these markers would be also useful for predicting future glucose intolerance in patients undergoing PTx.

The aim of the current study was to search for useful markers of future glucose tolerance in PTx recipients free from rejections and thromboses.

Materials and Methods

Subjects

Forty-one Japanese patients with T1DM received PTx between 2000 and 2016 in Osaka University Hospital. Recipients were scheduled to undergo examinations of pancreas graft function annually after transplantation. Data from these patients were analyzed retrospectively. All these recipients received posttransplant immunosuppression with tacrolimus, mycophenolate mofetil (MMF), and prednisolone, which were started at 15 μg/kg/day, 2,000 mg/day and 50 mg/day, respectively. Insulin therapy was introduced intravenously or subcutaneously if blood glucose levels were elevated during the postoperative period. If blood glucose levels were elevated after oral feeding was started, subcutaneous insulin therapy was resumed on the judgment of attending diabetologists. The initial examinations of insulin secretion and insulin sensitivity were performed as soon as postoperative conditions of recipients became stable.

Details of the examinations were as follows: The initial examinations were performed between 1 month and 6 months after transplantation. Doses of immunosuppression agents were gradually decreased to maintenance dose over about 1 or 2 years (maintenance period). Tacrolimus was maintained with targeting trough concentration of 3–5 ng/mL. MMF was maintained at 1,000 mg/day, or if there was a suspicion of an adverse reaction, at 750 mg/day. Prednisolone was maintained at 2.5 mg/day or discontinued if possible. After transplantation, patients were annually followed up with 75-g oral glucose tolerance test (OGTT), in principle. The outcome in this study was set as glucose tolerance in the maintenance period when immunosuppressive agents reached maintenance dose 1 to 2 years after transplantation, and factors associated with the outcome were searched for.

Recipients as described below were excluded from analyses: Recipients in whom loss of pancreatic graft function occurred before 2 years posttransplantation, somatostatin analog preparation was used at the time of the examinations, steroid pulse therapy was performed from 6 months to 2 years after transplantation, or immunosuppressive agents did not reach maintenance dose within 2 years after transplantation. Details of those excluded were as follows: Loss of pancreatic graft function occurred in 6 patients within 1 year after transplantation. The reasons for pancreatic graft function loss were death (n = 2), venous thrombosis (n = 2), and acute rejection reaction (n = 2). Somatostatin analog preparation, which was considered to affect insulin secretion [14] and glucose homeostasis [15, 16], was used against drug-resistant diarrhea (n = 1). Five other patients (n = 5) developed chronic rejection and received steroid pulse therapy from 6 months to 2 years after transplantation. In 5 other patients (n = 5), more than 2.5 mg/day of prednisolone was still used at 2 years posttransplantation. In summary, the remaining 24 subjects were analyzed in the current study, after the 17 above-mentioned patients were excluded (Fig. 1).

Insulin secretion tests

To stimulate insulin secretion of a pancreas graft, an OGTT, a glucagon stimulation test, an arginine stimulation test, and a hyperglycemic clamp test were performed after a 10-h overnight fast on a separate day during the initial examination. A series of insulin secretion examinations were carried out within 2 weeks. In the subjects using insulin therapy, insulin administration was stopped during insulin secretion tests.

75-g oral glucose tolerance test (OGTT)

Subjects ingested a solution containing equivalent of 75 g glucose (TRELAN-G75; AY Pharmaceuticals Co., Ltd., Tokyo, Japan), and venous blood samples were obtained at 0, 30, 60, and 120 minutes for determination of plasma glucose and serum insulin. OGTTs were per-

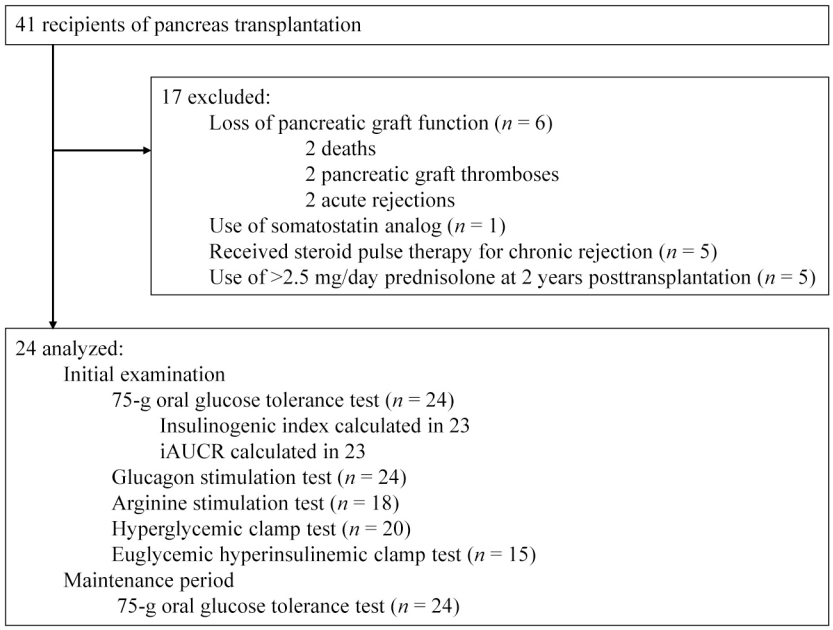

Fig. 1 Flow of patients and subjects through the study.

formed in all subjects at the initial examination.

Glucagon stimulation test

Blood samples were obtained 0 minutes before and 6 minutes after an intravenous bolus injection of 1 mg glucagon (Glucagon G Novo; Novo Nordisk Pharma Ltd., Tokyo, Japan) [17] and serum C-peptide concentration (CPR) of these samples was measured. Glucagon stimulation tests were also performed in all subjects at the initial examination.

Arginine stimulation test

After baseline blood samples were drawn for measuring glucose and insulin levels, 300 mg L-arginine monohydrochloride as a 10% solution in normal saline (AY Pharmaceuticals) was infused over 30 minutes. Samples for plasma glucose and insulin were collected at 0, 5, 10, 20, 30, 45, 60, and 90 minutes after the start of arginine infusion. Arginine stimulation tests were performed in 18 of the 24 subjects.

Hyperglycemic clamp test

Hyperglycemic clamp experiments were performed with the use of an artificial endocrine pancreas (STG-22; Nikkiso Co., Ltd., Tokyo, Japan) [18-20]. Three cannulas were positioned intravenously, for blood glucose monitoring, for extraction of venous blood, and for infusion of exogenous glucose as a 10% solution (Physio35 Injection; Otsuka Pharmaceutical Factory, Inc., Tokushima, Japan). An exogenous glucose infusion was given to achieve steady-state blood glucose levels (200 mg/dL) within 5 minutes, and blood glucose was maintained at 200 mg/dL thereafter for 90 minutes. Serum insulin levels were measured at 5 and 90 minutes after commencement of the clamp test. Hyperglycemic clamp tests were performed in 20 subjects at the initial examination.

Insulin secretion indices

In this study, the following 9 insulin secretion indices, which were originally used in non-PTx population, were calculated (Table 1). Homeostasis model assessment (HOMA) beta and secretory units of islets in transplantation (SUIT) were calculated from fasting plasma glucose (FPG) (mg/dL), fasting serum insulin (FIRI) (μU/mL), and fasting C-peptide (FCPR) (ng/mL). HOMA beta was calculated using the equation 360 * FIRI/(FPG–63) [21], and SUIT was calculated using FCPR * 1,500/(FPG–61.7) [22]. From data of 120-min OGTT, the ratio of incremental area under the curve of insulin to that of plasma glucose (iAUCR) [23], and the ratio of the difference between insulin at 30 minutes and insulin at 0 minutes to the difference between plasma glucose at 30 minutes and plasma glucose at 0 minutes (known as insulinogenic index, or II) [24] was calculated (n = 23, 1 subject was excluded in analysis of iAUCR because of strong hemolysis of the insulin specimen at 60 minutes after glucose load). Another subject was also excluded from analysis of insulinogenic index because plasma glucose at 30 minutes (79 mg/dL) was lower than pre-load plasma glucose (81 mg/dL) and the calculated value of insulinogenic index was less than zero. With data from glucagon stimulation tests, ΔCPR was calculated by sub-

Table 1 Insulin secretion indices used in this study

Indices from fasting laboratory data
Homeostasis model assessment (HOMA) beta
Secretory units of islets in transplantation (SUIT)
Indices from 75-g oral glucose tolerance test
Ratio of incremental area under the curve of insulin to that of plasma glucose (iAUCR)
Ratio of the difference between insulin at 30 minutes and insulin at 0 minutes to the difference between plasma glucose at 30 minutes and plasma glucose at 0 minutes (insulinogenic index)
Index from glucagon stimulation test
difference between 6- and 0-minute C-peptide level after glucagon injection (ΔCPR)
Indices from arginine stimulation test
Area under the curve of insulin from 0 minutes to 10 minutes (AUC_{arg}Ins0–10)
Area under the curve from 10 minutes to 90 minutes (AUC_{arg}Ins10–90)
Indices from hyperglycemic clamp test
Serum insulin levels measured at 5 minutes after commencement of the clamp test (Ins_{clamp}5)
Serum insulin levels measured at 90 minutes after commencement of the clamp test (Ins_{clamp}90)

tracting CPR at 0 minutes from CPR at 6 minutes. From data of arginine stimulation tests, area under the curve of insulin from 0 minutes to 10 minutes (AUC_{arg}Ins0–10) and area under the curve from 10 minutes to 90 minutes (AUC_{arg}Ins10–90), assumed to be early and late phases of additional insulin secretion, respectively, were calculated [25]. From data of hyperglycemic clamp tests, serum insulin levels measured at 5 and 90 minutes after commencement of the clamp test (Ins_{clamp}5, and Ins_{clamp}90), which reflect early and late phases of additional insulin secretion, respectively [18-20], were also used.

Evaluation of insulin sensitivity

In 15 subjects, euglycemic hyperinsulinemic clamp tests were also performed, consecutively following a hyperglycemic glucose clamp test at the initial examination.

During the euglycemic hyperinsulinemic clamp period, subjects were given a primed-constant infusion of regular insulin (Humulin R; Eli Lilly Japan KK, Kobe, Japan) [1.12 mU/(kg min)] and an exogenous glucose infusion as a 10% solution (Physio35 Injection) to achieve the desired steady-state serum insulin level (100 μU/mL) and to maintain blood glucose at 100 mg/dL. When the rate of exogenous glucose infusion reached a steady-state level, insulin sensitivity was evaluated as the average glucose infusion rate (GIR) calculated using a method mentioned in previous reports [19, 20].

Outcome measure

The outcome measure in the current study was glucose tolerance, which was assessed using 120-minute postload plasma glucose level during OGTT (referred to as PG_{OGTT}120) in the maintenance period. In accordance with the Japanese diabetes classification [26], PG_{OGTT}120 was classified as 140 mg/dL or 200 mg/dL. OGTTs to evaluate glucose tolerance in the maintenance period were performed between 1 to 2 years posttransplantation, and as far as immunosuppressive agents reached maintenance dose, the examinations were performed at 1 year posttransplantation in principle. OGTTs in the maintenance period were carried out at 1 year posttransplantation in 22 subjects and at 2 years posttransplantation in 2 subjects. Of the latter subjects, one subject used 5 mg/day of prednisolone 1 year after transplantation, and the other subject did not receive the examination 1 year after transplantation because ileostomy was performed soon after transplantation due to anastomotic leakage, and closure of ileostomy was performed 1 year after transplantation.

Statistical analysis

Plasma glucose, serum insulin, and insulin secretion indices were statistically analyzed after being logarithmically transformed, because distributions were right-skewed, and the values were expressed as median [1st–3rd quartile]. Other continuous variables were expressed as the mean ± standard deviation, and discrete variables were described as sample numbers and frequencies with percentages. First, correlations among various baseline characteristics, insulin secretion indices (HOMA beta, SUIT, insulinogenic index, iAUCR, ΔCPR, AUC_{arg}Ins0–10, AUC_{arg}Ins10–90, Ins_{clamp}5, Ins_{clamp}90), GIR, and glu-

cose tolerance at the initial examination were examined using Pearson's correlation coefficient. A change of $PG_{OGTT}120$ from the initial examination to the examination in the maintenance period was analyzed using paired Student's *t*-test. Next, correlations among baseline characteristics, insulin secretion indices, and GIR, with glucose tolerance in the maintenance period were examined using Pearson's correlation coefficient. Multivariate regression analysis was used to determine independent risk factors for $PG_{OGTT}120$ in the maintenance period. In additional analyses, subjects were classified into two subgroups according to the level of $PG_{OGTT}120$ in the maintenance period, and baseline characteristics, insulin secretion indices, and GIR were analyzed using Student's *t*-test between subgroups. All statistical tests were two-sided, and a *p*-value of less than 0.05 was considered to be statistically significant. All statistical analyses were performed using JMP Pro version 13.1 (SAS Institute Inc., Cary, NC, USA) software.

Human rights statement and informed consent

The current study was conducted in accordance with the principles of Declaration of Helsinki, and was approved by the ethics committees of Osaka University Hospital. Since the current study was retrospective research, using only existing medical records, informed consent was exempted and instead relevant information regarding the study was open to the public, in accordance with the Ethical Guidelines for Medical and Health Research Involving Human Subjects in Japan.

Results

Characteristics of subjects

Characteristics of the subjects in this study are as follows: 12 subjects (50.0%) were male and 12 (50.0%) were female; 20 (83.3%) and 4 (16.7%) received simultaneous pancreas-kidney transplantation (SPK) and pancreas after kidney transplantation (PAK), respectively; 2 subjects undergoing SPK received PTx with bladder drainage, whereas the other subjects, including those with PAK, received PTx with enteric drainage. Table 2 shows subject backgrounds at the initial examination. Prior to the initial examination, 1 subject continued postoperative insulin treatment (2 units/day) for glycemic control. Median $PG_{OGTT}120$ was 120 mg/dL (1st–3rd quartile; 105–153), as shown in Table 2; 17 subjects had $PG_{OGTT}120$ <140 mg/dL, 4 subjects had $PG_{OGTT}120$ ≥140 mg/dL and <200 mg/dL, and 3 subjects had $PG_{OGTT}120$ ≥200 mg/dL. In addition to the 1 subject who used insulin before the initial examination, 4 subjects resumed bolus insulin for glycemic control after the initial examination; thus, 5 subjects in total received insulin treatment until the examination in the maintenance period after PTx (1–18 units/day). None of them used long-acting insulin analogues.

Table 2 Subject background and various indices at the initial examination after pancreatic transplantation

Sex (male/female) (*n* = 24)	12 (50)/12 (50)
Age at onset of diabetes (years) (*n* = 24)	15 ± 7
Age at pancreas transplantation (years) (*n* = 24)	43 ± 8
Duration of diabetes (years) (*n* = 24)	28 ± 6
Duration of dialysis (years) (*n* = 24)	6.5 ± 5.2
Body mass index (kg/m²) (*n* = 24)	19.6 ± 2.3
Prednisolone (mg/day) (*n* = 24)	5.8 ± 3.2
Tacrolimus (mg/day) (*n* = 24)	5.7 ± 2.8
Mycophenolate mofetil (mg/day) (*n* = 24)	1,396 ± 436
Serum creatinine (mg/dL) (*n* = 24)	1.2 ± 0.4
eGFR (mL/min/1.73 m²) (*n* = 24)	52.5 ± 16.3
Fasting plasma glucose (mg/dL) (*n* = 24)	87 [84–96]
$PG_{OGTT}120$ (mg/dL) (*n* = 24)	120 [105–153]
GIR (mg/kg min) (*n* = 23)	7.0 [5.1–11.4]
HOMA beta (*n* = 24)	158 [87–232]
SUIT (*n* = 24)	105 [90–161]
Insulinogenic index (*n* = 23)	0.73 [0.43–1.80]
iAUCR (*n* = 23)	0.73 [0.54–1.61]
ΔCPR (ng/mL) (*n* = 24)	2.6 [1.7–4.6]
$AUC_{arg}Ins0–10$ (*n* = 18)	487 [230–648]
$AUC_{arg}Ins10–90$ (*n* = 18)	3,738 [2,222–6,198]
$Ins_{clamp}5$ (μU/mL) (*n* = 20)	50.4 [20.9–76.8]
$Ins_{clamp}90$ (μU/mL) (*n* = 20)	47.3 [28.1–77.5]

Abbreviations: eGFR, estimated glomerular filtration rate; $PG_{OGTT}120$, 120-minute post-load plasma glucose level during oral glucose tolerance test; GIR, glucose infusion rate in euglycemic hyperinsulinemic clamp test; HOMA beta, homeostasis model assessment of beta cell function; SUIT, secretory units of islets in transplantation; iAUCR, ratio of incremental area under the curve of insulin to that of plasma glucose during oral glucose tolerance test; ΔCPR, difference between 6- and 0-minute C-peptide level after glucagon injection; $AUC_{arg}Ins0–10$, AUC of insulin from 0 to 10 minutes during arginine stimulation test; $AUC_{arg}Ins10–90$, AUC of insulin from 10 to 90 minutes during arginine stimulation test; $Ins_{clamp}5$, insulin level at 5 minutes after commencement of hyperglycemic clamp test; $Ins_{clamp}90$, insulin level at 90 minutes after commencement of hyperglycemic clamp test.
Data are expressed as discrete variables (%), mean ± standard deviation, or median [1st–3rd quartile].

Table 3 Correlation between various values and insulin secretion indices on the initial examination after transplantation

	HOMA beta	SUIT	insulinogenic index	iAUCR	ΔCPR (ng/mL)	AUC_{arg}Ins0–10	AUC_{arg}Ins10–90	Ins_{clamp}5 (μU/mL)	Ins_{clamp}90 (μU/mL)
Fasting plasma glucose (mg/dL)	–0.45* (24)	–0.42* (24)	–0.10 (23)	–0.04 (23)	–0.19 (24)	–0.31 (18)	–0.28 (18)	–0.48* (20)	–0.27 (20)
PG_{OGTT}120 (mg/dL)	–0.19 (24)	–0.23 (24)	–0.62** (23)	–0.70** (23)	–0.59** (24)	–0.46 (18)	–0.37 (18)	–0.52* (20)	–0.28 (20)
Clamp glucose infusion rate (mg/(kg min)	–0.33 (15)	–0.24 (15)	0.39 (15)	0.48 (15)	0.12 (15)	–0.16 (10)	–0.33 (10)	0.24 (15)	0.14 (15)
HOMA beta		0.57** (24)	0.25 (23)	0.16 (23)	0.47* (24)	0.69** (18)	0.69** (18)	0.57** (20)	0.48* (20)
SUIT			0.39 (23)	0.24 (23)	0.60** (24)	0.53* (18)	0.51* (18)	0.49* (20)	0.19 (20)
Insulinogenic index				0.93** (22)	0.70** (23)	0.47 (17)	0.21 (17)	0.63** (20)	0.57** (20)
iAUCR					0.59** (23)	0.31 (17)	0.07 (17)	0.50* (19)	0.47* (19)
ΔCPR (ng/mL)						0.82** (18)	0.63** (18)	0.75** (20)	0.57** (20)
AUC_{arg}Ins0–10							0.85** (18)	0.78** (14)	0.58* (14)
AUC_{arg}Ins10–90								0.61* (14)	–0.35 (14)
Ins_{clamp}5 (μU/mL)									0.82** (20)

Abbreviations: eGFR, estimated glomerular filtration rate; PG_{OGTT}120, 120-minute post-load plasma glucose level during oral glucose tolerance test; HOMA beta, homeostasis model assessment of beta cell function; SUIT, secretory units of islets in transplantation; AUC, area under the curve; iAUCR, ratio of incremental AUC of insulin to incremental AUC of plasma glucose during OGTT; ΔCPR, difference between 6- and 0-minute C-peptide level after glucagon injection; AUC_{arg}Ins0–10, AUC of insulin from 0 to 10 minutes during arginine stimulation test; AUC_{arg}Ins10–90, AUC of insulin from 10 to 90 minutes during arginine stimulation test; Ins_{clamp}5, insulin level at 5 minutes after commencement of hyperglycemic clamp test; Ins_{clamp}90, insulin level at 90 minutes after commencement of hyperglycemic clamp test.

Data are expressed as correlation coefficients (numbers of subjects). *: $p < 0.05$, **: $p < 0.01$.

Correlation among baseline characteristics, indices of insulin secretion, and insulin resistance at the initial examination

Most of the insulin secretion indices were correlated with one another (Table 3). Fasting plasma glucose showed a significant inverse correlation with HOMA beta, SUIT, and Ins_{clamp}5. PG_{OGTT}120 was correlated with insulinogenic index, iAUCR, ΔCPR, and Ins_{clamp}5. GIR was correlated with PG_{OGTT}120 [$r = –0.59$ ($p < 0.05$)]. Insulin secretion indices had no significant correlation with baseline values other than FPG (data not shown).

Comparison of glucose tolerance at the initial examination and in the maintenance period

The median of PG_{OGTT}120 in the maintenance period was 138 [1st–3rd quartile; 102–192] mg/dL and was not significantly changed from PG_{OGTT}120 at the initial examination ($p = 0.35$) (Table 4). Doses of prednisolone, tacrolimus, and MMF were decreased significantly from 5.8 ± 3.2 mg at the initial examination to 1.3 ± 1.2 mg in the maintenance period ($p < 0.01$), from 5.7 ± 2.8 mg to 3.3 ± 1.5 mg ($p < 0.01$), and 1,396 ± 436 mg to 938 ± 247 mg ($p < 0.01$), respectively.

Association of values and indices at the initial examination with glucose tolerance in the maintenance period

Table 5 shows associations among various values and indices at the initial examination with glucose tolerance in the maintenance period. PG_{OGTT}120 [$r = 0.52$ ($p = 0.01$)], insulinogenic index [$r = –0.65$ ($p < 0.01$)], and iAUCR [$r = –0.65$ ($p < 0.01$)] at the initial examination were significantly correlated with PG_{OGTT}120 in the maintenance period. GIR at the initial examination was not correlated with PG_{OGTT}120 in the maintenance period [$r = –0.42$ ($p = 0.15$)]. Multivariate regression analysis demonstrated that insulinogenic index and iAUCR were still significantly correlated with PG_{OGTT}120 in the maintenance period after adjustment for PG_{OGTT}120 at the initial examination (Table 6).

Table 4 Comparison of glucose tolerance at the initial examination and in the maintenance period

		Maintenance period		
		$PG_{OGTT}120$ <140	$PG_{OGTT}120$ ≥140 <200	$PG_{OGTT}120$ ≥200
Initial examination	$PG_{OGTT}120$ <140 (*n* = 17)	11	4	2
	$PG_{OGTT}120$ ≥140 <200 (*n* = 4)	0	3	1
	$PG_{OGTT}120$ ≥200 (*n* = 3)	1	0	2
	Total (*n* = 24)	12	7	5

Abbreviations: $PG_{OGTT}120$, 120-minute post-load plasma glucose level during oral glucose tolerance test.
Data are expressed as numbers of subjects.

In additional analyses, various values and indices at the initial examination between subgroups classified by $PG_{OGTT}120$ level in the maintenance period were analyzed (Table 7). $PG_{OGTT}120$, insulinogenic index, iAUCR, and $Ins_{clamp}90$ were significantly different between subgroups of <140 mg/dL and ≥140 mg/dL. GIR, insulinogenic index, iAUCR, $Ins_{clamp}5$, and $Ins_{clamp}90$ were significantly different between subgroups of <200 mg/dL and ≥200 mg/dL.

Discussion

This study revealed that insulinogenic index and iAUCR were predictive factors for impairment of glucose tolerance in recipients free from rejections and thromboses after PTx. In non-PTx population, iAUCR and insulinogenic index were reported to predict future glucose tolerance [23, 27]. On the other hand, it was unclear whether these insulin secretion indices similarly predict future glucose tolerance in PTx recipients. Dynamics of endogenous insulin are altered after PTx by direct secretion into systemic circulation from a grafted pancreas, while a native pancreas secretes insulin to portal vein followed by ~50% of insulin clearance in the liver [28, 29]. These differences make it unclear whether these insulin secretion indices similarly reflect insulin secretion of a grafted pancreas adequately in PTx recipients.

The current findings indicated that even in PTx recipients, iAUCR and insulinogenic index could predict future glucose intolerance as can those in non-PTx population, although those indices do not adequately reflect insulin secretion after PTx, unlike in non-PTx population. Meanwhile, indices from arginine stimulation tests, glucagon stimulation tests, and hyperglycemic clamp tests were not correlated with $PG_{OGTT}120$ in PTx recipients. Among non-PTx population, indices from glucagon stimulation tests and arginine stimulation tests were not reported to predict future glucose tolerance as far as we searched, although ΔCPR of glucagon stimulation tests were related to current glucose tolerance [30] and arginine stimulation tests distinguished the ability of insulin secretion between normal glucose tolerance subgroup and diabetic subgroup [31, 32]. On the other hand, we found a report that hyperglycemic clamp tests can predict the development of T1DM [33]: results of hyperglycemic clamp tests among persistently islet autoantibody-positive first-degree relatives of patients with T1DM were correlated with developed diabetes within 3 years. However, there have been no reports that the results of hyperglycemic clamp tests were correlated with future glucose intolerance among other population. Namely, indices from glucagon stimulation tests, arginine stimulation tests, or hyperglycemic clamp tests were not reported to predict future glucose tolerance, even for non-PTx population. These facts suggest that those indices are not suitable to predict future glucose intolerance after PTx as well.

HOMA beta and SUIT were correlated with FPG at the initial examination, but they were not related to $PG_{OGTT}120$ at the initial examination. Reasons for these results are unclear. This may be because HOMA beta and SUIT index were calculated from FPG, not $PG_{OGTT}120$. Moreover, HOMA beta and SUIT were not also correlated with $PG_{OGTT}120$ in the maintenance period. That is, HOMA beta and SUIT were not predictive factors of future glucose tolerance after PTx. To the best of our knowledge, HOMA beta and SUIT have not been reported to predict future glucose tolerance in non-PTx population; HOMA beta was not correlated with future glucose tolerance in postpartum women [34] and SUIT was not correlated with progression of type 2 diabetes mellitus [35]. Therefore, HOMA beta and SUIT could not possibly predict future glucose tolerance in PTx recipients, nor could glucagon stimulation tests, hyperglycemic clamp tests, or arginine stimulation tests.

The following factors are considered in selection of recipients of PTx currently in Japan [36]: (1) compatibility of blood type and human leukocyte antigen between donor and recipient, (2) expected type of transplant, (3) waiting time, and (4) estimated time required to deliver organs. In terms of posttransplant glucose tolerance, this

Table 5 Correlation between values at the initial examination and glucose tolerance in the maintenance period

	r	*p*
Age at onset of diabetes (years) (*n* = 24)	–0.14	0.52
Age at pancreas transplantation (years) (*n* = 24)	–0.02	0.92
Duration of diabetes (years) (*n* = 24)	0.14	0.53
Duration of dialysis (years) (*n* = 23)	–0.25	0.24
Body mass index (kg/m^2) (*n* = 24)	0.06	0.77
Prednisolone (mg/day) (*n* = 24)	–0.05	0.83
Tacrolimus (mg/day) (*n* = 24)	0.12	0.58
Mycophenolate mofetil (mg/day) (*n* = 24)	0.17	0.43
Serum creatinine (mg/dL) (*n* = 24)	0.02	0.93
eGFR (mL/min/1.73 m^2) (*n* = 24)	–0.03	0.90
Fasting plasma glucose (mg/dL) (*n* = 24)	–0.09	0.68
$PG_{OGTT}120$ (mg/dL) (*n* = 24)	0.52	0.01
GIR (mg/(kg min)) (*n* = 15)	–0.42	0.15
HOMA beta (*n* = 24)	0.11	0.60
SUIT (*n* = 24)	–0.16	0.46
Insulinogenic index (*n* = 23)	–0.65	<0.01
iAUCR (*n* = 23)	–0.65	<0.01
ΔCPR (ng/mL) (*n* = 24)	–0.36	0.09
AUC_{arg}Ins0–10 (*n* = 18)	–0.19	0.45
AUC_{arg}Ins10–90 (*n* = 18)	0.01	0.96
Ins_{clamp} 5 (μU/mL) (*n* = 20)	–0.28	0.23
Ins_{clamp} 90 (μU/mL) (*n* = 20)	–0.37	0.11

Abbreviations: eGFR, estimated glomerular filtration rate; $PG_{OGTT}120$, 120-minute post-load plasma glucose level during oral glucose tolerance test; GIR, glucose infusion rate in euglycemic hyperinsulinemic clamp test; HOMA beta, homeostasis model assessment of beta cell function; SUIT, secretory units of islets in transplantation; AUC, area under the curve; iAUCR, ratio of incremental AUC of insulin to incremental AUC of plasma glucose during oral glucose tolerance test; ΔCPR, difference between 6- and 0-minute C-peptide level after glucagon injection; AUC_{arg}Ins0–10, AUC of insulin from 0 to 10 minutes during arginine stimulation test; AUC_{arg}Ins10–90, AUC of insulin from 10 to 90 minutes during arginine stimulation test; $Ins_{clamp}5$, insulin level at 5 minutes after commencement of hyperglycemic clamp test; $Ins_{clamp}90$, insulin level at 90 minutes after commencement of hyperglycemic clamp test.
Data are expressed as correlation coefficients (*r*) and *p*-values.

Table 6 Multivariable regression analysis between insulin secretion indices at the initial examination and glucose tolerance on the maintenance period adjusted by $PG_{OGTT}120$ at the initial examination

	β	*p*
HOMA beta (*n* = 24)	0.19	0.25
SUIT (*n* = 24)	–0.04	0.83
Insulinogenic index (*n* = 23)	–0.28	0.02
iAUCR (*n* = 23)	–0.29	0.02
ΔCPR (ng/mL) (*n* = 24)	–0.04	0.74
AUC_{arg}Ins0–10 (*n* = 18)	0.01	0.97
AUC_{arg}Ins10–90 (*n* = 18)	0.15	0.47
Ins_{clamp} 5 (μU/mL) (*n* = 20)	–0.01	0.94
Ins_{clamp} 90 (μU/mL) (*n* = 20)	–0.17	0.26

Abbreviations: HOMA beta, homeostasis model assessment of beta cell function; SUIT, secretory units of islets in transplantation; AUC, area under the curve; iAUCR, ratio of incremental AUC of insulin to incremental AUC of plasma glucose during oral glucose tolerance test; ΔCPR, difference between 6- and 0-minute C-peptide level after glucagon injection; AUC_{arg}Ins0–10, AUC of insulin from 0 to 10 minutes during arginine stimulation test; AUC_{arg}Ins10–90, AUC of insulin from 10 to 90 minutes during arginine stimulation test; $Ins_{clamp}5$, insulin level at 5 minutes after commencement of hyperglycemic clamp test; $Ins_{clamp}90$, insulin level at 90 minutes after commencement of hyperglycemic clamp test.
Data are expressed as regression coefficients (β) and *p*-values.

result may suggest that no additional factors other than those mentioned above may need to be considered to select a recipient of PTx in Japan, because no factors of recipient background were correlated with insulin secretion indices or glucose tolerance.

Moreover, the outcome of our study was glucose tolerance evaluated by OGTT, because OGTT has been used as the standard way to evaluate glucose tolerance in many past studies. Stimulant of OGTT is oral glucose absorption, which stimulates both glucose transporter 2 (GLUT2) pathway and incretin pathway, and therefore $PG_{OGTT}120$ may be also affected by both glucose and incretin effects. Hyperglycemic clamp tests stimulate only GLUT2 pathway of insulin secretion, arginine stimulation tests affect downstream of GLUT2 pathway, and glucagon stimulation tests activate only glucagon pathway, downstream of which is shared with incretin pathway. Only OGTT stimulates both GLUT2 pathway and incretin pathway among insulin secretion tests used in this study. This may be one of the reasons why indices from OGTT were correlated with $PG_{OGTT}120$ in the maintenance period.

Furthermore, GIR, an index of insulin sensitivity, at the initial examination was correlated with glucose tolerance at the initial examination, but not with glucose tolerance in the maintenance period. One possible explanation would be decrease of prednisolone dose in the maintenance period. GIR at the initial examination might be considerably influenced by prednisolone-induced insulin resistance, which was expected to be decreased in the maintenance period. Consequently, GIR

Table 7 Relations of various values and indices at the initial examination between subgroups classified by $PG_{OGTT}120$ level in the maintenance period

	$PG_{OGTT}120$ <140	$PG_{OGTT}120$ ≥140	*p*	$PG_{OGTT}120$ <200	$PG_{OGTT}120$ ≥200	*p*
Age at onset of diabetes (years) (*n* = 24)	15 ± 2 (12)	15 ± 2 (12)	0.96	15 ± 2 (19)	13 ± 3 (5)	0.60
Age at pancreas transplantation (years) (*n* = 24)	43 ± 2 (12)	43 ± 2 (12)	0.94	43 ± 2 (19)	40 ± 3 (5)	0.46
Duration of diabetes (years) (*n* = 24)	28 ± 2 (12)	28 ± 2 (12)	0.98	28 ± 1 (19)	27 ± 3 (5)	0.78
Duration of dialysis (years) (*n* = 23)	7.8 ± 1.5 (12)	5.3 ± 1.5 (12)	0.25	7.4 ± 1.1 (19)	3.3 ± 2.2 (5)	0.12
Body mass index (kg/m²) (*n* = 24)	20.0 ± 0.7 (12)	19.2 ± 0.7 (12)	0.44	19.5 ± 0.6 (19)	20.3 ± 1.1 (5)	0.49
Prednisolone (mg/day) (*n* = 24)	5.3 ± 0.9 (12)	6.4 ± 0.9 (12)	0.41	5.9 ± 0.8 (19)	5.3 ± 1.5 (5)	0.68
Tacrolimus (mg/day) (*n* = 24)	5.1 ± 0.8 (12)	6.3 ± 0.8 (12)	0.31	5.6 ± 0.7 (19)	6.0 ± 1.3 (5)	0.77
Mycophenolate mofetil (mg/day) (*n* = 24)	1,333 ± 127 (12)	1,458 ± 127 (12)	0.49	1,368 ± 101 (19)	1,500 ± 198 (5)	0.56
Serum creatinine (mg/dL) (*n* = 24)	1.2 ± 0.1 (12)	1.2 ± 0.1 (12)	0.76	1.1 ± 0.1 (19)	1.5 ± 0.2 (5)	0.05
eGFR (mL/min/1.73 m²) (*n* = 24)	52.0 ± 4.8 (12)	53.0 ± 4.8 (12)	0.88	55.0 ± 3.6 (19)	43.0 ± 7.1 (5)	0.14
Fasting plasma glucose (mg/dL) (*n* = 24)	91 [84–96] (12)	86 [84–90] (12)	0.90	86 [83–96] (19)	87 [83–106] (5)	0.61
$PG_{OGTT}120$ (mg/dL) (*n* = 24)	107 [86–121] (12)	138 [119–180] (12)	0.03	117 [97–129] (19)	154 [119–275] (5)	0.02
GIR (mg/(kg min)) (*n* = 15)	8.7 [5.2–12.2] (7)	5.8 [4.7–9.5] (6)	0.37	8.1 [6.1–12.7] (10)	4.9 [4.3–5.4] (3)	0.04
HOMA beta (*n* = 24)	166 [90–209] (12)	129 [85–239] (12)	0.76	165 [81–214] (19)	105 [80–242] (5)	0.75
SUIT (*n* = 24)	111 [96–138] (12)	92 [77–203] (12)	0.86	109 [92–167] (19)	87 [46–261] (5)	0.28
Insulinogenic index (*n* = 23)	1.80 [0.99–1.87] (11)	0.56 [0.22–0.72] (12)	<0.01	1.04 [0.57–1.83] (18)	0.20 [0.14–0.72] (5)	<0.01
iAUCR (*n* = 23)	1.61 [0.66–2.24] (11)	0.66 [0.32–1.06] (12)	0.01	1.22 [0.64–1.71] (18)	0.28 [0.15–0.28] (5)	<0.01
ΔCPR (ng/mL) (*n* = 24)	3.4 [2.4–5.35] (12)	1.9 [1.5–3.3] (12)	0.06	2.9 [1.8–4.6] (19)	2.0 [0.7–4.5] (5)	0.07
$AUC_{arg}Ins0–10$ (*n* = 18)	585 [272–723] (11)	256 [229–540] (7)	0.14	572 [268–716] (14)	230 [194–463] (4)	0.11
$AUC_{arg}Ins10–90$ (*n* = 18)	4,712 [1,818–6,055] (11)	2,597 [2,357–6,627] (7)	0.51	4,658 [2,236–6,198] (14)	2,477 [1,678–5,925] (4)	0.42
Ins_{clamp} 5 (μU/mL) (*n* = 20)	72.4 [31.2–110.4] (10)	39.8 [18.8–55.0] (10)	0.07	55.8 [34.7–93.2] (16)	17.4 [10.2–48.7] (4)	0.02
Ins_{clamp} 90 (μU/mL) (*n* = 20)	68.4 [47.8–112.6] (10)	30.1 [22.6–45.3] (10)	0.01	52.8 [31.6–97.2] (16)	22.3 [18.1–30.1] (4)	<0.01

Abbreviations: eGFR, estimated glomerular filtration rate; $PG_{OGTT}120$, 120-minute post-load plasma glucose level during oral glucose tolerance test; GIR, glucose infusion rate in euglycemic hyperinsulinemic clamp test; HOMA beta, homeostasis model assessment of beta cell function; SUIT, secretory units of islets in transplantation; AUC, area under the curve; iAUCR, ratio of incremental AUC of insulin to incremental AUC of plasma glucose during oral glucose tolerance test; ΔCPR, difference between 6- and 0-minute C-peptide level after glucagon injection; $AUC_{arg}Ins0–10$, AUC of insulin from 0 to 10 minutes during arginine stimulation test; $AUC_{arg}Ins10–90$, AUC of insulin from 10 to 90 minutes during arginine stimulation test; $Ins_{clamp}5$, insulin level at 5 minutes after commencement of hyperglycemic clamp test; $Ins_{clamp}90$, insulin level at 90 minutes after commencement of hyperglycemic clamp test. Data are expressed as mean ± standard deviation or median [1st–3rd quartile], (number of subjects), and *p*-values.

assessed at the initial examination would no longer reflect recipients' insulin sensitivity, and would lose a significant association with glucose tolerance in the maintenance period.

Further analyses were performed with $PG_{OGTT}120$ in the maintenance period as a categorical variable. $PG_{OGTT}120$ in the maintenance period was classified into subgroups of <140 and ≥140, or <200 and ≥200, corresponding with normal glucose tolerance and glucose intolerance, or non-diabetes and diabetes, respectively. We did not perform multivariate logistic regression analyses, because sample numbers of the subgroups were small. Student's *t*-test analyses revealed that GIR, $Ins_{clamp}5$, and $Ins_{clamp}90$ in addition to $PG_{OGTT}120$, insuli-

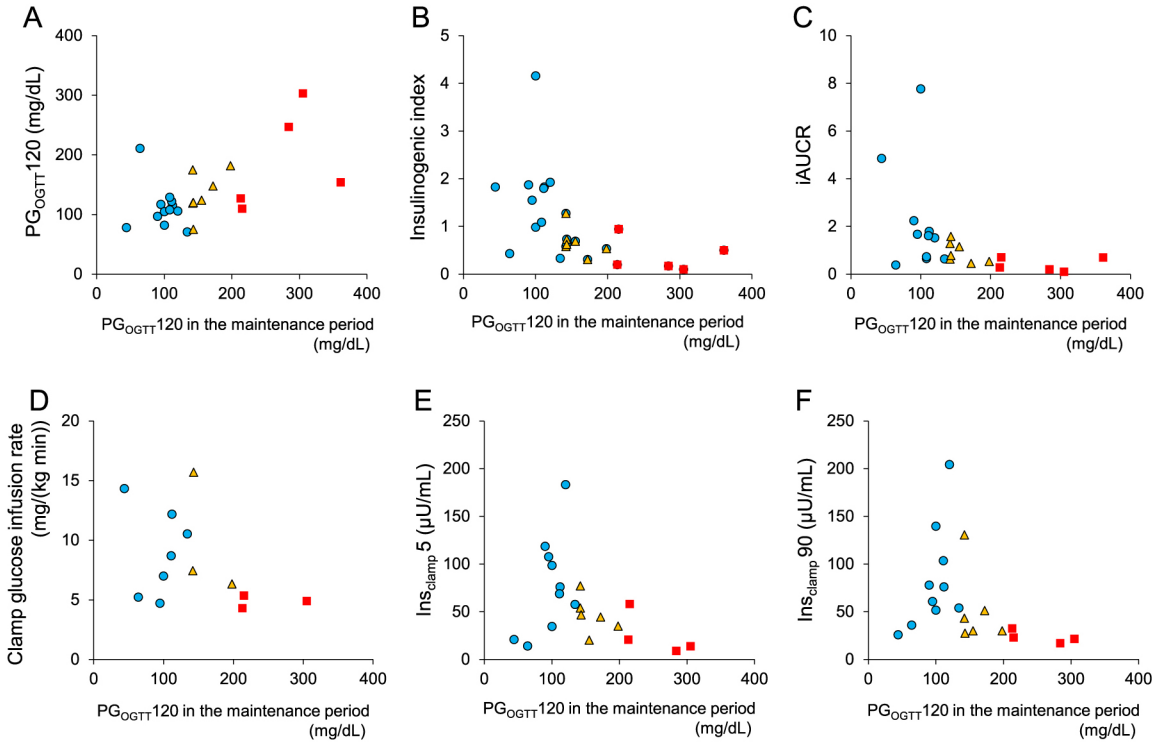

Fig. 2 Relationship of factors at the initial examination and PG$_{OGTT}$120 in the maintenance period.

Blue circles, yellow triangles, and red squares indicate subjects of which PG$_{OGTT}$120 in the maintenance period was <140, ≥140 <200, and ≥200, respectively. The horizontal axis represents PG$_{OGTT}$120 in the maintenance period. The vertical axis represents A) PG$_{OGTT}$120, B) insulinogenic index, C) iAUCR, D) GIR, E) Ins$_{clamp}$5, and F) Ins$_{clamp}$90 at the initial examination.

Abbreviations: PG$_{OGTT}$120, 120-minute post-load plasma glucose level during oral glucose tolerance test; GIR, glucose infusion rate in euglycemic hyperinsulinemic clamp test; AUC, area under the curve; iAUCR, ratio of incremental AUC of insulin to incremental AUC of plasma glucose during OGTT; Ins$_{clamp}$5, insulin level at 5 minutes after commencement of hyperglycemic clamp test; Ins$_{clamp}$90, insulin level at 90 minutes after commencement of hyperglycemic clamp test.

nogenic index, and iAUCR at the initial examination showed significant group differences (Table 7). Relation between PG$_{OGTT}$120 in the maintenance period and PG$_{OGTT}$120 at the initial examination (Fig. 2A), insulinogenic index (Fig. 2B), or iAUCR (Fig. 2C) was linear in the all ranges, but on the other hand relation between PG$_{OGTT}$120 in the maintenance period and GIR (Fig. 2D), Ins$_{clamp}$5 (Fig. 2E), or Ins$_{clamp}$90 (Fig. 2F) was linear only under a certain threshold value. Therefore GIR, Ins$_{clamp}$5, and Ins$_{clamp}$90 may be predictors of diabetic state or glucose intolerance state but not predictors of PG$_{OGTT}$120 in the maintenance period.

This study has several limitations. First, this was a single-center study. Second, the number of PTx recipients was only 24. This sample size can only detect correlation greater than $r = 0.55$ with a significance level of 5% and power of 80%. Despite these limitations, we believe that this study provides valuable information, because prediction of glucose intolerance after PTx enables extraction of high-risk group.

The results indicated that decrement of iAUCR and insulinogenic index from OGTT in the early period after PTx could predict impairment of glucose tolerance in the maintenance period after PTx. In other words, OGTT after PTx is important for prediction of future glucose tolerance.

In conclusion, in PTx recipients free from rejections and thrombosis, iAUCR and insulinogenic index derived from 120-min OGTT performed as soon as postoperative conditions became stable were independently associated with glucose intolerance in the maintenance period of posttransplant immunosuppressive treatment.

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Disclosure

Conflict of interest statement

All authors declare that they have no conflict of interest.

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