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Delayed improvement of insulin secretion after autologous islet transplantation in partially pancreatectomized patients

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Abstract

The purpose of this study was to evaluate the effects of autologous islet transplantation (ITx) on glucose homeostasis and insulin secretory function after partial pancreatectomy (Px). Fourteen nondiabetic patients who underwent distal Px and autologous ITx for benign pancreatic tumors were enrolled in the study (Px + ITx group). Fourteen normal glucose-tolerant controls and 6 Px without ITx controls were recruited, and all groups were followed over a 24-month period. They performed the 75-g oral glucose tolerance test and the 1-mg glucagon stimulation test. Hemoglobin A_{1c} was measured, and indices of insulin secretion were calculated. In the Px + ITx group, insulin secretion increased after a nadir at 6 months. Glucose tolerance, which had been abruptly impaired immediately after Px, recovered until 6 months and stabilized thereafter. As a result, differences in glucose intolerance emerged between the subjects in the Px group and those in the Px + ITx group at 24 months after Px. Characteristic variables in the better insulin secretory subjects in the Px + ITx group included younger age, less extensive pancreas resection, and a greater number of total islets. In summary, delayed amelioration of glucose intolerance was induced by autologous ITx after partial Px, even with a small number of islets.
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1. Introduction

Ever since clinical islet transplantation (ITx) became available, the main focus of posttransplantation care has been insulin independency as evaluated by exogenous insulin requirement or endogenous insulin secretion as evaluated by fasting serum C-peptide levels [1]. However, indices of insulin secretion and glucose metabolism over a period of several years have not been analyzed in detail. β-Cell function after allogeneic ITx is affected by multiple factors such as alloimmunity, immunosuppressive therapy, and autoimmunity [2]. Autologous ITx is different from allogeneic transplantation in that the graft is not threatened by immune reaction nor is immune suppression required. In

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cases of autologous ITx, islet cells are isolated from living donors, a procedure that has provided better islet yield, isolation success rate, and purity compared with cadaveric donors [3]. In this regard, autologous ITx is a more appropriate model for analysis of islet graft behavior.

Cystic neoplasms of the pancreas are detected more commonly, and sometimes they require pancreatectomy (Px). Autologous ITx in partially pancreatectomized patients has been reported to result in favorable outcomes with regard to insulin secretion [4,5]. The favorable effects of ITx appear to result from the supplemental insulin because hyperglycemia after partial Px has been shown to be the result of insulin deficiency [6]. However, partial Px usually does not induce the sharp increase in glucose concentration that total Px does [7-9]; and blood glucose levels are determined by various factors, including age, sex, body mass index (BMI), insulin resistance, remnant pancreas after resection, and preoperative (Pre-Op) glucose homeostasis, in addition to insulin secretion. Therefore, the precise effects of ITx need to be prospectively compared with a control group with matching Pre-Op characteristics.

In this study, we evaluated glucose homeostasis and insulin secretion over a 24-month period in patients who underwent 50% to 60% distal Px followed by autologous ITx.

2. Subjects and methods

2.1. Subjects

Among patients who underwent distal Px for benign pancreatic tumors at the Samsung Medical Center from 2000 to 2006, those who accepted ITx were allocated into the Px + ITx group; and those who refused it or whose islet cells could not be prepared were assigned to the Px control group. Tumor characteristics and patient comorbidities were unrelated to the allocation. Nondiabetic subjects were selected for analysis to exclude the influences of long-standing hyperglycemia. Fourteen patients were enrolled in the Px + ITx group, and 6 patients were enrolled in the Px control group. The 2 groups were matched for age, sex, BMI, pancreatic lesions, and Pre-Op glucose homeostasis. The extent of pancreatic resection was slightly greater in the Px + ITx group, with marginal statistical significance (Table 1). Because of the small sample size, normal controls were used as the standard in statistical analyses. The normal control group was composed of 14 sex- and BMI-matched volunteers with normal glucose tolerance. All the groups were followed for 24 months. Informed consent was obtained from all subjects before the study, and the protocol was approved by the Institutional Review Board of Samsung Medical Center.

2.2. Distal Px and ITx

The methods for Px and ITx have been described previously [5]. In brief, distal Px was performed for pancreatic masses that required pathologic diagnosis. Islet transplantation was performed 2 to 3 days after Px only if the mass was pathologically confirmed as benign. Islets were isolated from the normal part of the resected pancreas using a modified Ricordi method. Islet yield was expressed as islet

Table 1
Preoperative characteristics

Variables	Normal	Px	Px + ITx	P^a	P^b
n (enrollment/completion)	14/14	6/4	14/11	NA	NA
Sex ratio (male-female)	0:14	1:5	0:14	NS	NS
Age (y)	51 ± 1	43 ± 9	47 ± 7	NS	.05[c]
BMI (kg/m^2)	23.3 ± 0.8	23.0 ± 1.3	23.2 ± 0.5	NS	NS
Body weight (kg)	59.4 ± 2.8	58.6 ± 4.3	56.8 ± 1.5	NS	NS
NGT:IGT:DM	14:0:0	3:3:0	11:2:1	NS	.068
Fasting plasma glucose (mmol/L)	5.15 ± 0.08	4.63 ± 0.26	4.70 ± 0.15	NS	.03[c]
OGTT 120-min glucose (mmol/L)	6.29 ± 0.27	7.45 ± 0.89	7.02 ± 0.59	NS	NS
HbA_{1c} (%)	5.2 ± 0.1	5.4 ± 0.1	5.0 ± 0.1	NS	NS
Pancreas tumor	NA	2 SCTs; 2 MCTs; 1 IPMT; 1 teratoma	6 SCTs; 2 MCTs; 4 SPTs; 1 IPMT; 1 endocrine tumor[d]	NS	NA
Extent of pancreas resection (%)	NA	54 ± 4	63 ± 2	.064	NA
Cold ischemic time (h)	NA	NA	1.5 ± 0.3	NA	NA
Purity of islets (%)	NA	NA	80 ± 3	NA	NA
Cell viability (AO/PI stain)	NA	NA	>90%	NA	NA
Infused cell volume (mL)	NA	NA	0.95 ± 0.23	NA	NA
Islet graft (IEQ/kg body wt)	NA	NA	3500 ± 300	NA	NA

AO/PI indicates acridine orange and propidium iodide; DM, diabetes mellitus; IGT, impaired glucose tolerance; IPMT, intraductal papillary mucinous tumor; MCT, mucinous cystic tumor; NA, not applicable; NGT, normal glucose tolerance; NS, no significant difference; SCT, serous cystic tumor; SPT, solid pseudopapillary tumor.

[a] *t* test between Px and Px + ITx groups.

[b] One-way ANOVA among 3 groups.

[c] Normal vs Px group.

[d] It was not an insulin-producing tumor.

equivalent volume (IEQ). Before transplantation, a simple and rapid method for estimating the viability of isolated islets was applied with acridine orange and propidium iodide staining [10]. The islets were implanted in the liver through percutaneous transhepatic portal vein catheterization. During the peritransplantation period, heparin and insulin were used to prevent thrombosis and to maintain normoglycemia, respectively. None of the subjects in the Px + ITx group had severe adverse events or tumor recurrence during the follow-up period.

2.3. Assessment of metabolic parameters

In the Px + ITx group, the 75-g oral glucose tolerance test (OGTT) and 1-mg glucagon stimulation test were performed during the Pre-Op period; at 1 week; and at 1, 3, 6, 12, and 24 months after Px. The OGTT in the Px group was done during the Pre-Op period and at 6, 12, and 24 months after Px, whereas it was done at baseline and at 24 months in the normal control group. Fasting serum C-peptide, insulin, and hemoglobin A_{1c} (HbA_{1c}) were also measured. The area under the glucose curve of OGTT (AUCglc) was calculated. Glucose homeostasis was assessed according to the American Diabetes Association criteria [11]. Homeostasis model assessment for insulin resistance (HOMA-IR = fasting insulin [in picomoles per liter] × fasting glucose [in millimoles per liter]/135) [12] and 4 indices for insulin secretion were calculated: insulinogenic index (INSindex) ($\Delta insulin_{30min}$ [in picomoles per liter]/$\Delta glucose_{30min}$ [in millimoles per liter] during OGTT) [13], insulin reserve determined by 1-mg glucagon stimulation test (ΔC-peptide$_{6min}$/basal C-peptide$_{0min}$) [5], homeostasis model assessment for β-cell function (HOMA-BC = fasting insulin {in picomoles per liter} × 120/[fasting glucose {in millimoles per liter} − 3.5]) [12], and a secretory unit of islet transplant objects index (SUITO = fasting C-peptide {in nanograms per milliliter} × 1500/[glucose {in milligrams per deciliter} − 63]) [14].

2.4. Statistical analysis

Data are presented as means ± SEM. Student t test and 1-way analysis of variance (ANOVA) were applied for independent variables. Repeated-measures ANOVA and paired t test with Bonferroni correction were applied for serial comparisons. All statistical analyses were conducted using SPSS version 11.0 (SPSS, Chicago, IL). A $P < .05$ was considered to be statistically significant.

3. Results

3.1. Comparisons of glucose homeostasis between Px and Px + ITx groups

Glucose homeostasis was dissected in the Px + ITx group and was compared with that in the control groups. Glucose tolerance evaluated with 75-g OGTT is depicted in Fig. 1. It was no different among the 3 groups preoperatively (Fig. 1A); but after 24 months, it was impaired in the Px and Px + ITx groups compared with the normal control group. The former group showed more impairment (Fig. 1B; F = 11.0 [$P < .005$] between the Px and the normal control groups, F = 5.4 [$P < 05$] between the Px + ITx and the normal control groups by repeated-measures ANOVA). At 24 months after Px, the normal glucose tolerance:impaired glucose tolerance:diabetes mellitus ratio was 1:4:1 in the Px group and 4:7:3 in the Px + ITx group. Even the diabetic subjects had HbA_{1c} levels lower than 6%, and none of the subjects used insulin or oral hypoglycemic agents to control blood glucose levels.

When glucose homeostasis was monitored serially over 24 months, fasting plasma glucose levels in the Px + ITx group slightly increased 1 week after the procedure ($P < .05$) and remained stable without significant changes (Fig. 2A). It was similar in the Px group, and there was no statistically significant differences between the 2 Px groups (Fig. 2A). However, OGTT 120-minute glucose levels of the Px + ITx group sharply increased at 1 week (Fig. 2B), with gradual recovery to the Pre-Op state at 6 months ($P < .05$ between those in 1 week and 6 months). After then, the stimulated glucose levels increased significantly ($P < .05$) in both the Px groups. As a result, oral glucose tolerance of the Px subjects assessed by AUCglc was partially impaired (about 120% of Pre-Op value) at 6 months, as shown in Fig. 2C. Hemoglobin A_{1c} was also significantly increased at 6 months ($P < .05$) and showed no changes until 24 months in the Px groups, although it was within normal limits. In normal glucose control subjects, glucose homeostasis went unchanged over the 24-month period.

3.2. Comparisons of insulin secretion between Px and Px + ITx groups

Insulin secretion was dissected in the Px + ITx group and was compared with that in the control groups with respect to fasting and stimulated conditions. Insulin secretion in the fasting state was demonstrated with the SUITO index and HOMA-BC. The SUITO index decreased from 132 ± 12 down to 42 ± 4 (30% of Pre-Op SUITO) in both Px groups at 6 months (Fig. 3A). The HOMA-BC decreased from 147 ±

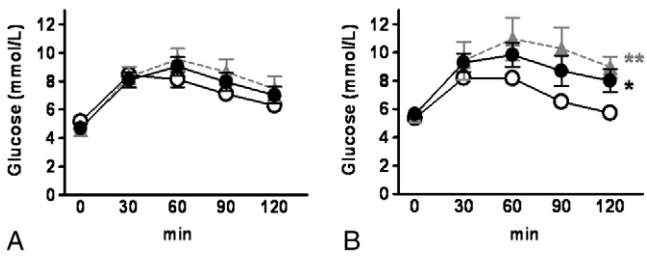

Fig. 1. The 75g-OGTT curves of the normal, Px, and Px + ITx groups at Pre-Op (A) and at 24 months after operation (B). Open circles, normal control; gray triangles, Px control; solid circles, Px + ITx group. Values are means ± SEM. *F = 5.4 ($P < .05$) vs normal control group; **F = 11.0 ($P < .005$) vs normal control group by repeated-measures ANOVA.

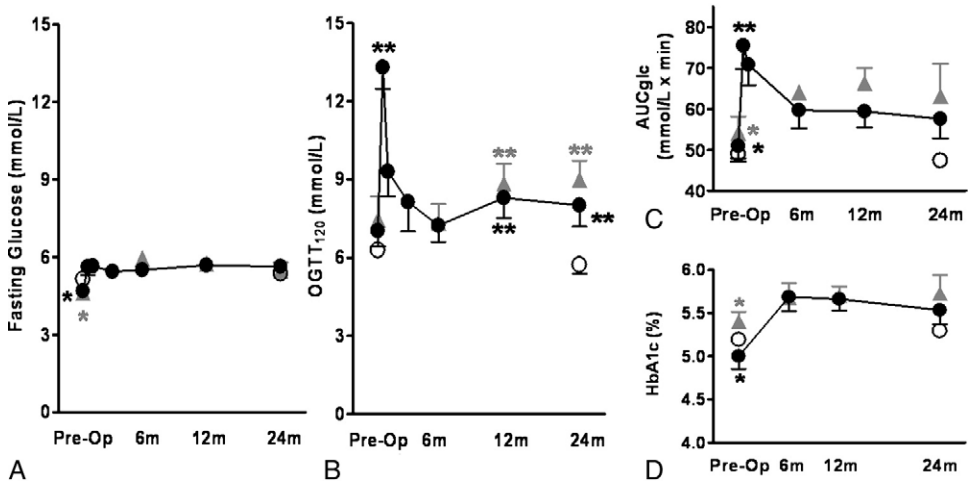

Fig. 2. Glucose homeostasis of the subjects through the 24-month study period. Fasting plasma glucose levels (A), OGTT 120-minute glucose levels (B), AUCglc during the 75-g OGTT (C), and HbA_{1c} (D) were compared among the normal, Px, and Px + ITx groups using Student *t* test, 1-way ANOVA, and paired *t* test with Bonferroni correction. Open circles, normal control; gray triangles, Px control; solid circles, Px + ITx group. Values are means ±SEM. **P* < .05 vs other variables in each group; ***P* < .05 vs 6 months in each group.

22 to 61 ± 8 (40% of Pre-Op HOMA-BC) in the Px + ITx group and from 186 ± 31 down to 73 ± 23 (40% of Pre-Op HOMA-BC) in the Px group (Fig. 3B). In the Px + ITx group, the suppressed secretory function rebounded after 6 months, causing partial recovery at 24 months (74 ± 14, 55% of Pre-Op SUITO and 116 ± 27, 80% of Pre-Op HOMA-BC; solid circles). In the meantime, the suppressed insulin secretion in the Px group did not recover (58 ± 5, 45% of Pre-Op SUITO and 102 ± 20, 55% of Pre-Op HOMA-BC; gray triangles).

Oral glucose–induced first-phase insulin secretion, represented as the INSindex (Fig. 3C), decreased just after Px + ITx and partially recovered gradually until 6 months (63 ± 15, 57% of Pre-Op INSindex); but no further increase followed (solid circles). This pattern in the INSindex was similar to that seen in the AUCglc (Fig. 2C) in that the deteriorated index partially improved at 6 months and remained steady thereafter. There was no statistical difference in INSindex between the Px and the Px + ITx groups through 24 months. Unlike the INSindex, the insulin reserve in the Px + ITx group did not change significantly (Fig. 3D). In normal glucose control subjects, insulin secretion went unchanged over the 24-month period.

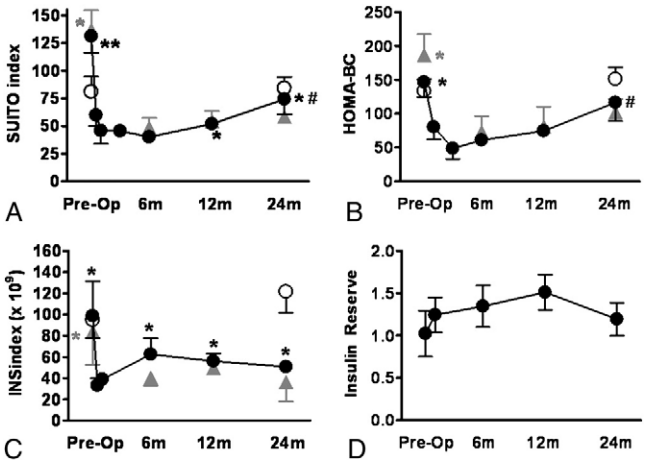

Fig. 3. Insulin secretion of the subjects through the 24-month study period. The SUITO index (A), HOMA-BC (B), and INSindex (C) were compared among the normal, Px, and Px + ITx groups using Student *t* test, 1-way ANOVA, and paired *t* test with Bonferroni correction. Insulin reserve by glucagon-stimulated C-peptide levels of the Px + ITx group (D). Open circles, normal control; gray triangles, Px control; solid circles, Px + ITx group. Values are means ± SEM. **P* < .05 and ***P* < .005 vs each nadir; $^{\#}P$ < .05 vs 12 months in the Px + ITx group.

Another factor determining glucose homeostasis is insulin resistance. This was evaluated with the HOMA-IR, which increased in both the Px and the Px + ITx groups over 24 months: from 1.87 ± 0.39 to 2.87 ± 0.61 in the Px group and from 1.60 ± 0.22 to 2.39 ± 0.31 in the Px + ITx group (each $P < .05$), whereas it did not increase in the normal control subjects.

3.3. Factors determining insulin secretion in the Px + ITx group

As shown in Fig. 3, insulin secretion stabilized or improved after 6 months in the Px + ITx group. We analyzed the factors related to outcomes at 6 and 24 months after ITx. Correlation or regression analysis could not be done because of the small sample size. Rather, the subjects in the Px + ITx group were bisected according to the changes in serum C-peptide over 24 months (C-peptide levels at 24 months/Pre-Op, percentage). Age and body weight are well-known factors related to insulin secretion; so we compared age, BMI, resection extent, and total islet amount between the 2 subgroups (Fig. 4A, white and black bars). Age, resection extent, and total islet amount were significantly different between the subgroups. In other words, those subjects whose serum C-peptide improved at

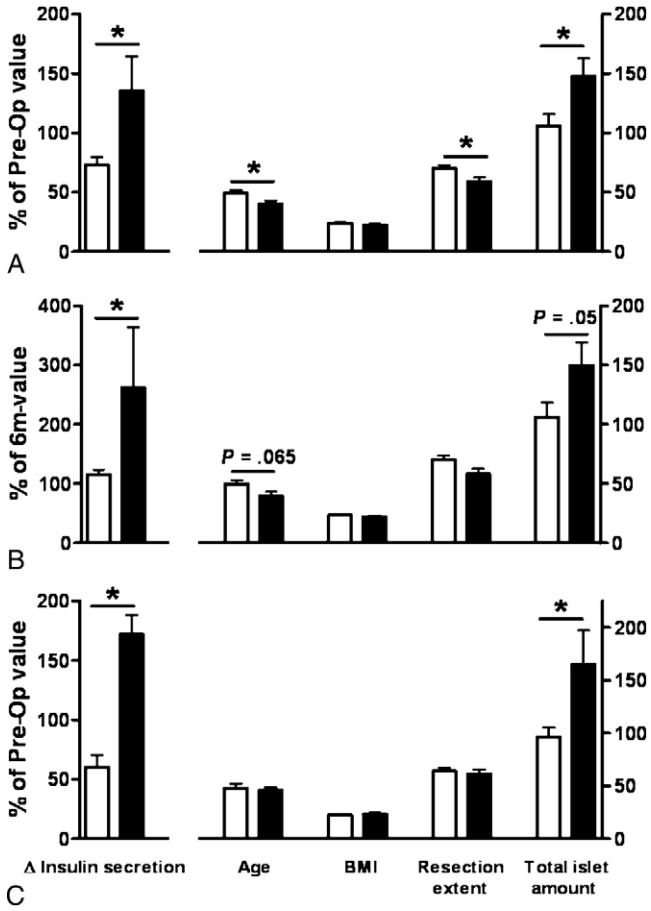

Fig. 4. Factors related to insulin secretory function in the Px + ITx group. Some variables known to be related to insulin secretion were compared according to the changes in (A) serum C-peptide over 24 months (C-peptide levels at 24 months/Pre-Op, percentage), (B) serum C-peptide through 6 to 24 months (C-peptide levels at 24 months/6 months, percentage), and (C) INSindex over 6 months (INSindex at 6 months/Pre-Op, percentage) in the subjects of the Px + ITx group. Total islet mass was calculated as follows: (100 − resection extent, percentage) × log (islet graft in islet equivalent volume per kilogram). White bars, deteriorating secretion group; black bars, improving secretion group. Values are means ± SEM. *$P < .05$ by Student t test.

24 months compared with the Pre-Op state were younger, had undergone less extensive Px, and had more islet mass. Total islet mass was calculated as follows: (100 − resection extent, percentage) × log (islet graft in islet equivalent volume per kilogram). The subjects in the Px + ITx group were bisected again according to the changes in serum C-peptide over 6 months (C-peptide levels at 6 months/Pre-Op, percentage) because C-peptide reached a nadir at that time. As for the changes in C-peptide over 6 months, none of the variables mentioned above was related (data not shown). Because fasting insulin secretion increased after 6 months, subjects were compared again according to C-peptide changes through 6 to 24 months (C-peptide levels at 24 months/6 months, percentage). The results were similar in pattern to those over 24 months (Fig. 4B), although the statistical power was decreased. When the subjects were bisected according to changes in the INSindex over 6 months (INSindex at 6 months/Pre-Op, percentage), only total islet mass was significantly different between the subgroups (Fig. 4C).

4. Discussion

Autologous ITx is a therapeutic procedure used for the prevention of diabetes after major Px. Two-hundred forty cases had been reported in the International Islet Transplant Registry as of 2001 [15]. If sufficient islets were implanted after total Px, the rate of insulin independence at 1 year was reported to be 71%, with 13 years being reported as the longest recorded period of insulin independence [16]. Unlike total Px, partial Px does not typically cause brittle diabetes [7-9]. Therefore, it is difficult to measure the effects of ITx after partial Px. As far as we know, this is the first prospective comparison between patients undergoing partial Px with and without ITx.

We found that 60% distal Px in nondiabetic patients resulted in impaired glucose tolerance regardless of ITx (Fig. 1), but it did not cause overt diabetes requiring pharmacologic intervention in 2 years. Although HbA_{1c} was significantly increased after Px, it was within reference range in both groups (Fig. 2D). There was a slight difference between the subjects in the Px group and the Px + ITx group in that (1) the OGTT curve was more changed in the Px group from the curve of the normal control group (Fig. 1B) and (2) the differences of glucose tolerance between the Px and the Px + ITx group seemed to appear after 12 months, although there was no statistical significance (Fig. 2B, C). If the sample size were larger or if further follow-up longer than 24 months were performed, we might have clearly demonstrated significant differences in glucose homeostasis according to ITx.

In addition, this is the first detailed description of long-term serial changes in insulin secretion after ITx. Very recently, Menge et al [9] described detailed metabolic consequences within 3 months after partial Px and reported that 50% partial Px for benign lesions in nondiabetic subjects led to a reduction in postchallenge insulin excursions by 55%. Similar or even poor results were obtained in the Px + ITx group of our study with various indices of insulin secretion in that period (reductions by 60%-70%, Fig. 3A-C). Therefore, ITx after partial Px might not affect insulin secretion so seriously within a few months after surgery. In the meantime, fasting insulin secretion after partial Px and ITx in our study started to increase at 6 months. The suppressed SUITO index and HOMA-BC started to increase in the Px + ITx group after 6 months, resulting in slightly higher levels than those in the Px group at 24 months. Rebounding of SUITO index and that of HOMA-BC in the Px group were insignificant. Therefore, the trend toward improved insulin secretion indices (at least for SUITO and HOMA-BC) and improved glucose tolerance after 6 to 12

months in the Px + ITx group suggests a major contribution by the transplanted tissue, rather than native pancreas regeneration alone.

It is not clear why there was a delayed improvement in insulin secretion after ITx. This phenomenon cannot be explained by graft function alone because graft function is known to gradually decrease [15,17,18]. Therefore, we believe that β-cell mass increased, individual β-cell function improved, or both. Increases in β-cell mass can result from β-cell regeneration [19]. Hamamoto et al [20] reported that ITx in streptozotocin-induced diabetic rats enhanced β-cell proliferation and increased β-cell mass in the pancreas. We reproduced these findings in the remnant pancreas of Px-induced diabetic mice [21]. Therefore, ITx might have enhanced β-cell regeneration from the remnant pancreas in human subjects, too. Although the capacity for β-cell regeneration after partial Px was known to differ between different species [22-24] and there was a report that partial Px had not provoked β-cell regeneration in humans [25], the possibility of β-cell regeneration in adult humans cannot yet be excluded. Another mechanism increasing β-cell mass is blockade of apoptosis. In contrast to β-cell regeneration, β-cell apoptosis has been observed in humans after partial Px, although the mechanism for it was not studied [25]. Therefore, inhibition of apoptosis can be another cause for the delayed effects of ITx on insulin secretory capacity as we found in the rodent model [21]. Preventive effect of ITx from β-cell apoptosis in human, if any, might be partly from improved glycemic control; but there should be other factors because the differences in glucose homeostasis according to ITx were not so large as in Figs. 1 and 2. We prudently hypothesize that some antiapoptotic factors could be released from islets. The possibility of ITx-induced improvement in individual β-cell function also remains. Another issue is the change in the islet graft itself: the islet graft could have changed in cell number or proportion. Especially if unpurified islets containing other pancreatic cells were transplanted, the change in the islet graft could be a contributor, as pancreatic tissues have been suggested to have progenitor cells [21,22,24]. In addition, islet engraftment is known to occur between 1 to 3 months after transplantation; and in some patients, it can take longer. This could be a contributing factor to the delayed improvement in the Px + ITx patients seen here.

Unlike indices of fasting insulin secretion, stimulated insulin secretion did not improve 6 months after ITx (Fig. 3C). The INSindex in the Px + ITx group was stationary after 6 months, showing a tendency similar to that in the Px control group. According to Lau et al [26], islets transplanted intraportally into the liver are stimulated to release insulin exclusively through hepatic glucose administered through the hepatic artery, but not through the portal vein. Therefore, the first phase of oral glucose–stimulated insulin release from islets transplanted to the liver was delayed and less prominent when compared with that from the pancreas. In our study, the subjects had 40% to 50% remnant pancreas, which must have functioned much better than islet grafts did. As a result, the INSindex, which reflects insulin release stimulated from oral glucose, demonstrated an acute insulin response mainly from the remnant pancreas, which should be comparable between the Px and Px + ITx groups (Table 1). According to the OGTT curve in Fig. 1, no differences in glucose levels were observed between the 2 Px groups at 30 minutes, which confirmed that the first-phase insulin response elicited by oral glucose was less influenced by ITx. However, we cannot conclude that the INSindex was unrelated to the islet graft altogether because those subjects who had increased INSindex 6 months after ITx had significantly greater islet amounts, which were calculated from the remnant pancreas and islet grafts (Fig. 4C, black bars). Therefore, transplanted islets were relevant to both fasting insulin secretion and oral glucose–stimulated insulin secretion; but the effect of the remnant pancreas was predominant in the latter. Interestingly, intravenous glucagon–stimulated insulin release was not changed after Px and ITx (Fig. 3D). We can speculate that insulin secretory capacity after ITx may depend on the stimulation to the islets. If other stimulation tests (eg, intravenous arginine test and mixed meal tolerance test) had been performed, they potentially would have shown differences between the Px and the Px + ITx groups that could be clinically meaningful.

Improved insulin secretion in the Px + ITx group seemed to contribute to the recovery of glucose tolerance after 6 months. Fasting glucose levels were not affected by ITx (Fig. 2A), but glucose tolerance started to induce a difference between the Px and Px + ITx groups after 6 months (Fig. 2B, C). Postprandial hyperglycemia is reported to be an important risk factor for overt diabetes and cardiovascular disease [27]. As the average life span and postoperative survival increase, long-term metabolic derangement after partial Px should become a target for therapy, even if the Pre-Op state is normal. Insulin can be supplied by subcutaneous injection; but it is difficult to achieve near-normal glucose levels through this route, and exogenous insulin administration presents the risk of hypoglycemia and a wide glycemic excursion. Oral hypoglycemic agents that enhance endogenous insulin secretion present the same difficulties. However, islet grafts can supply sufficient insulin and allow for physiologic glycemic control with a normal range of glycemic excursion. Although the number of islet grafts transplanted in this study (3500 ± 300 IEQ/kg, Table 1) was small, isolation yield was very good considering that the pancreas volume used for isolation was less than one third of the total pancreas [3]. In addition, autografts are not threatened by alloimmunity or immunosuppressant drugs. Clinical ITx should be regarded as a potential therapy in some selected patients undergoing Px for benign lesions. Some risks have been reported to be related to islet implantation in the liver, including procedure-related bleeding, portal vein thrombosis, hepatic steatosis, and hepatic tumorigenesis. In our Px + ITx pool of 22 patients (as long as 8 years of follow-up), 2 patients had hepatic hemorrhage

after percutaneous catheterization, which was not serious; neither portal vein thrombosis nor hepatic steatosis occurred. Hepatic steatosis has been reported in a subset of allotransplanted subjects, but clinical sequelae have not yet been noted [28]. Although liver neoplasms after ITx have been observed in rodents [29,30], no human cases have been reported. Insulin resistance estimated from the HOMA-IR index was increased in both the Px and Px + ITx groups, unlike in the normal control group. However, as there was no significant difference between the Px and Px + ITx groups, it is difficult to determine any influences of ITx on insulin resistance. Although pancreatogenic diabetes is reported to be characterized by both insulin deficiency and insulin resistance [6,31], insulin resistance after partial Px in nondiabetic persons should be further validated with more sophisticated methods.

In conclusion, we noted delayed favorable effects in insulin secretion and in glucose regulation in Px + ITx patients when they were directly compared with Px patients. This suggests that ITx after partial Px can be considered in selected patients with pancreatic benign tumors. Further follow-up of this study would establish this suggestion.

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