

ORIGINAL CONTRIBUTION

Islet Transplantation Provides Superior Glycemic Control and Maintenance of Better Islet Architecture Compared to Early Insulin Treatment in 50% Pancreatectomized Mice

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ABSTRACT

Early insulin intervention is speculated to promote β -cell rest, potentially preserving and regenerating residual β -cells in β -cell-deficient environments, such as recent-onset type 1 diabetes. However, exogenous insulin supplementation is supposed not to be enough to fulfill these beneficial outcomes. To investigate this, we employed a 50% partial pancreatectomy (Px) in mice as a model for β -cell deficiency. Four experimental groups are included: 1. a sham group that underwent 50% Px (sham group), 2. control group that underwent 50% Px with saline injection for 7 days (Px group), 3. insulin group that administered insulin injection for 7 days post-Px (PX+INS group) and 4. islet transplantation group that islet transplantation after 50% Px. (PX+IT group). Intraperitoneal glucose tolerance tests (IPGTTs) were performed at 3- and 7-days postinsulin treatment or IT, and glycemic control was assessed by calculating the area under the curve (AUC) of blood glucose concentrations. Histomorphometric analysis was used to evaluate islet distribution, islet morphology and the composition of β - and α -cells. The results showed significantly improved glucose tolerance at 3- and 7- days in the islet-transplantation group compared to the insulin-treated group. Islet proportions in the pancreas were similar across groups; however, the insulin-treated group exhibited a significant increase in α -cell numbers, with their distribution extending both to the periphery and inner core of the islets. Our findings demonstrate that islet transplantation is superior to insulin treatment for glycemic control following 50% pancreatectomy in mice. Short-term insulin treatment was associated with α -cell expansion and worsened glycemic outcomes. These results suggest that islet transplantation is more effective in β -cell-deficient conditions, and caution is warranted when implementing early preventive insulin interventions.

DIABETES mellitus (DM) is broadly categorized into type 1 and type 2 DM, both characterized by a reduction in β -cell mass [1]. In type 1 DM, autoreactive CD8+ T cells target β -cell self-antigens such as proinsulin, glutamate decarboxylase 65 (GAD65), and zinc transporter 8 (ZnT8), leading to the destruction of pancreatic β -cells [2]. In advanced stages of type 2 DM, β -cell apoptosis occurs due to β -cell exhaustion,

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endoplasmic reticulum (ER) stress, and oxidative stress [3]. Studies have indicated that when β -cell mass declines below 30% of its original level, overt hyperglycemia typically develops [4].

It has been hypothesized that early insulin treatment in β -cell-deficient states, such as recent-onset type 1 DM or advanced type 2 DM, could reduce the workload on residual β -cells, preserving their functionality and potentially promoting regeneration. However, this hypothesis has not been experimentally validated.

In this study, we utilized a 50% pancreatectomy (Px) mouse model, as a marginal β -cell mass reduction, while normoglycemia is maintained. One group received subcutaneous insulin injections for 7 days, and the other was transplanted with syngeneic islets. This model provided a controlled environment to evaluate whether exogenous insulin injection could support residual β -cell rest and regeneration and to compare the outcome between the group of insulin injection and group of islet transplantation with respect of glycemic control and change of islet architecture.

MATERIALS AND METHODS

Animals

All animal studies were approved by Institutional Animal Care and Use Committee (IACUC) at the Gachon College of Medicine (LCDI-2022-0135) and performed in accordance with NIH guide for the care and use of laboratory animals. Eight-week-old C57BL/6 mice were purchased from Orient Bio, Inc. and housed in pathogen-free facility until use.

Study Design

Five to 7 C57BL/6 mice of 10 to 12 weeks of age were used in 1 of 4 experimental groups: sham operation (sham group), 50% distal Px only (Px group), 50% Px followed by insulin administration (Px+INS group, 0.1 U/kg of human insulin lispro (Humalog®) subcutaneous, twice a day; Eli Lilly, IN), and 50% Px followed by syngeneic islet transplantation (IT) (Px+IT group).

Islet Transplantation

IT was performed as previously described [5]. In brief, syngeneic islet cells were isolated using intraductal collagenase infusion and Ficoll gradient purification. Isolated islets were incubated in M199 media with 200 mg/dL of glucose for 24 hr, and then handpicked for transplantation. A total of 200 islet equivalent (IEQ) volumes of islets were placed under the kidney capsules of mice 3 days after Px.

Metabolic Parameters

From the day before Px, body weight and tail vein blood glucose level were monitored every morning during fed state (Accu-Check glucometer, Roche, Swiss). At the indicated days or weeks after Px, an intraperitoneal glucose tolerance test

(IPGTT, 2 g/kg bodyweight) was performed after a 16-hour fasting period. Blood glucose concentrations were measured at 0, 15, 30, 60 and 120 min after a bolus of glucose injection intraperitoneally.

Histologic Examination

At the indicated days or weeks after Px, the pancreas was harvested. Staining for insulin (Abcam, Cambridge, United Kingdom) and glucagon (Abcam) was done to assess β - and α -cell mass, respectively. The paraffin-embedded pancreas was sectioned serially (4 μ m), and randomly selected 7 slides per mouse were used for each staining. Fluorescent images were visualized using a confocal microscope LSM710 (Zeiss, Germany).

Statistics

Data are presented as means $\pm$ SEM. Student's *t* test was used for comparisons between 2 groups, and 1-way ANOVA with post hoc Tukey test was used among multiple groups. All statistical analyses were conducted using SPSS version 11.0. A value of *P* less than .05 was considered statistically significant.

RESULTS

Study Design

To compare the outcome between the group of exogenous insulin supply and the islet transplantation in marginal insulin-deficient conditions, we utilized a 50% partial pancreatectomy (Px) mouse model combined with short-term insulin injection or marginal mass islet transplantation (IT) (Fig 1). The sham-operated group served as a negative control, while the Px-only group served as a positive control (Fig. 2).

Metabolic Effects of Insulin Supply and Islet Transplantation After 50% Partial Pancreatectomy

To evaluate the metabolic effects of different strategies for glycemic control, intraperitoneal glucose tolerance tests (IPGTT) were performed at 3- and 7- days after insulin treatment or IT. Before treatment, the Px group exhibited a marginal increase in the area under the curve (AUC) for glucose, though this was not statistically significant. Notably, the AUC was the best in the Px+IT group, indicating superior glycemic control, while the Px+INS group showed the worst AUC compared to the other groups. The increase in AUC in the Px+INS group persisted through day 7, reaching nearly double that of the other groups.

Histomorphological Examination of the Pancreas

Pancreatic tissues from cohorts of each group were harvested for histomorphometric analyses. As shown in Fig 3, the proportion of islet area relative to total pancreas area was approximately 0.3% to 0.4%, with no significant differences among groups. Intriguingly, the α -cell mass in the Px+INS group was

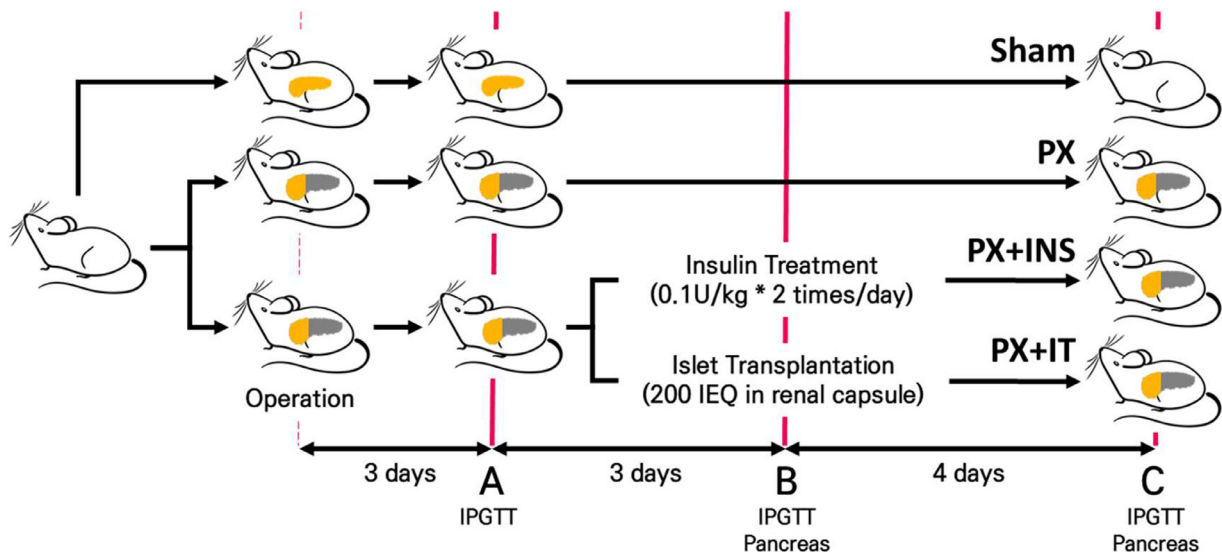


Fig. 1. Schematic study design. Five to 7 Balb/c mice of 10 to 12 weeks of age were used in 1 of 4 experimental groups: sham operation (sham group), 50% distal Px only (Px group), 50% Px followed by insulin administration (Px+INS group), and 50% Px followed by syngeneic islet transplantation (IT) (Px+IT group).

significantly elevated, increasing to ~38% compared to ~22% in other groups. Furthermore, the α -cell distribution in the Px+INS group was unique, with increases observed both in the islet core and periphery. [Fig. 4](#)

Long-term Effects of Insulin Injection

Given the unexpected glycemic excursions and α -cell expansion observed with short-term insulin injection, we

further investigated these effects over the long term. Separate cohorts of 50% pancreatectomized mice received insulin injections, and glucose tolerance and islet morphology were assessed at 1, 2-, 8-, 16-, and 24-weeks post-treatment. As shown in [Fig 5](#), AUC for glucose was significantly elevated at 1, 16, and 24 weeks after insulin treatment. The increase in α -cell mass persisted through 24 weeks post-treatment.

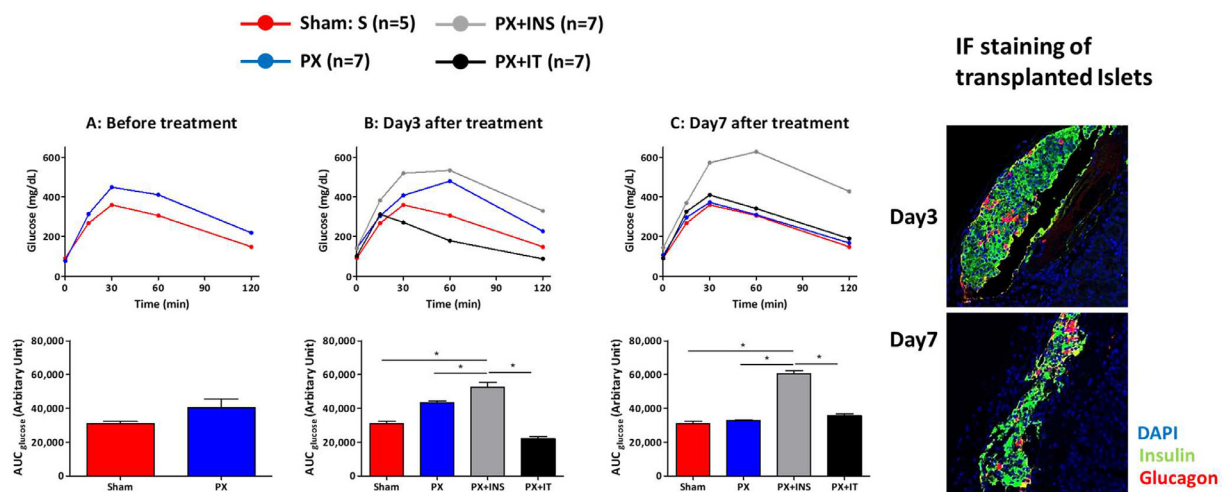


Fig. 2. Intraperitoneal glucose tolerance test (IPGTT). At the indicated days after insulin injection or IT, IPGTT was performed after a 16-hour fasting period. Area under the curve (AUC) for glucose concentration was calculated and compared among the groups. Right panel shows beta- and alpha-cells as revealed by anti-insulin and glucagon antibodies in the graft in the kidney subcapsule.

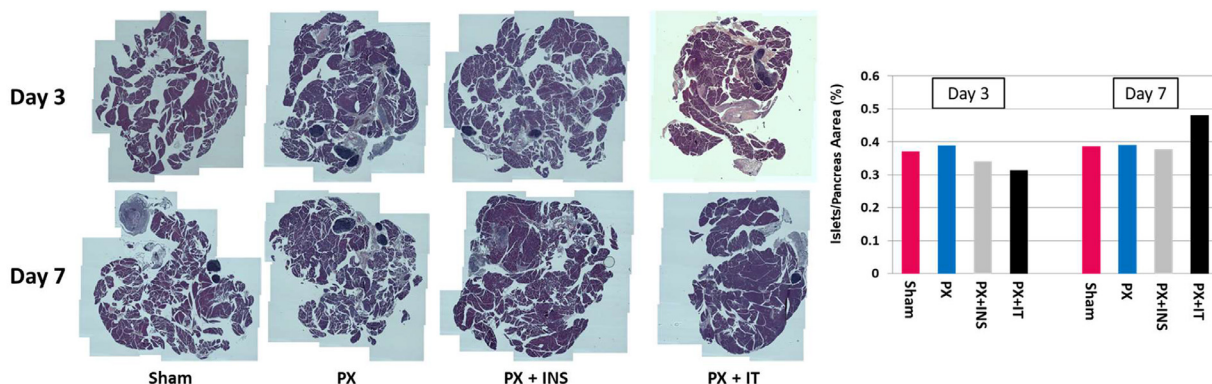


Fig. 3. Gross histomorphology of the pancreas. Pancreatic sections from each group were prepared and stained with hematoxylin and eosin. Islet area per pancreas area was calculated with point-count method.

DISCUSSION

In this study, we demonstrated that islet transplantation is superior to insulin injection in insulin-deficient conditions, as modeled by 50% partial pancreatectomy in mice, in terms of glucose tolerance and islet morphology. We initially hypothesized that early insulin intervention would allow residual β -cells to rest and regenerate and prevent further deterioration of glucose homeostasis. However, our results contradicted this expectation. Instead, short-term insulin injections worsened glycemic control and unexpectedly promoted α -cell expansion in the pancreas, effects that persisted for up to 24 weeks.

Why is islet transplantation better than exogenous insulin injection in term of glycemic control and change of islet architecture? The result of better glycemic control in the transplantation group is understandable. However, the insulin

injection group is even worse than the PX only group in glycemic control. One possible explanation is that intraperitoneal insulin injection caused a transient but localized increase in pancreatic insulin concentration, which may have stimulated α -cell expansion in marginal insulin deficiency condition [6]. This disturbance in islet composition likely impaired β -cell function and disrupted insulin secretion, leading to deteriorated glycemic control. In contrast, islet transplantation appeared to be regulated by the physiological needs of the mice, preserving normal glucose tolerance and islet cell composition. Our metabolic and histomorphometric findings support this hypothesis.

In conclusion, islet transplantation is a more effective strategy than subcutaneous insulin injection in marginal insulin-deficient conditions. These findings highlight the need for cautious consideration of early insulin interventions for diabetic prevention.

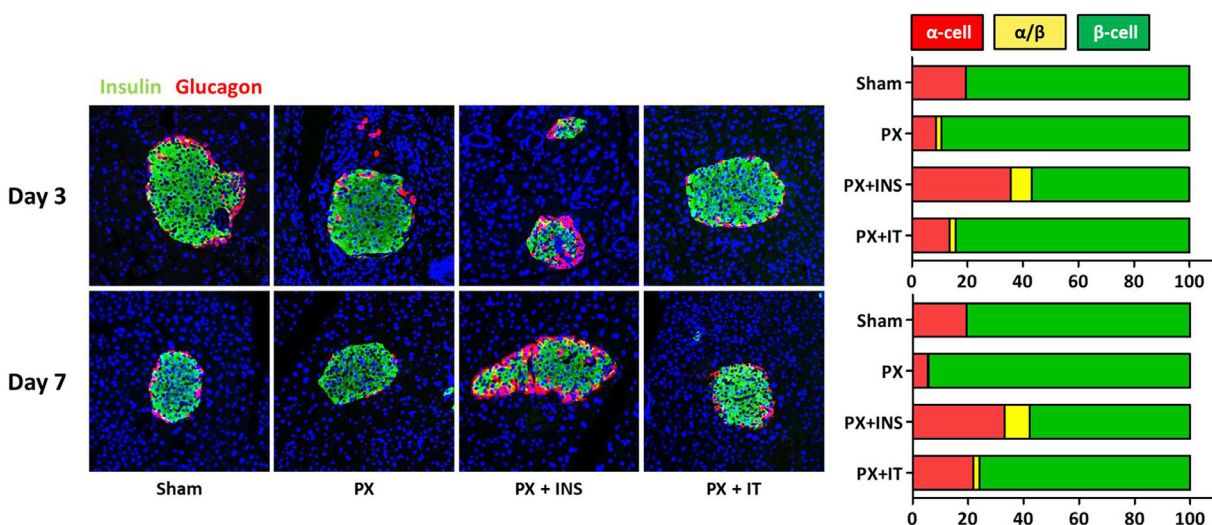


Fig. 4. Immunohistochemistry of the pancreas. Pancreatic sections from each group were prepared and stained with anti-insulin and glucagon antibodies. Proportion of alpha cells, beta cells and alpha+beta cells were measured by morphometric analyses.

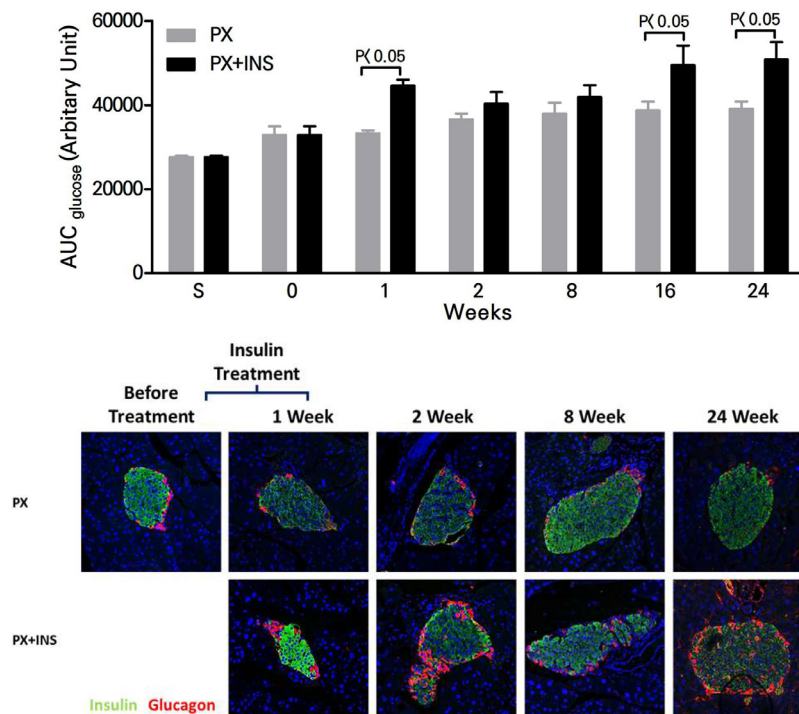


Fig. 5. Long-term effect of insulin injection. AUC for glucose concentrations were measured at the indicated time points after insulin injection and pancreatic sections from each group were stained with anti-insulin and glucagon antibodies.

DATA AVAILABILITY

Data will be made available on request.

DECLARATION OF COMPETING INTEREST

All the authors declare no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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