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Liver transaminase levels after intraportal autologous islet transplantation after partial pancreatectomy were associated with long-term metabolic outcomes

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ABSTRACT

Aims: To investigate the changes of post-procedural liver transaminase levels after autologous islet transplantation (ITx), and their associations with glycemic outcomes.
Methods: Non-diabetic patients who underwent distal pancreatectomy for benign tumors were enrolled. Islets isolated from the healthy part of the resected pancreas were transplanted via the portal vein. Metabolic parameters were evaluated in the subjects for 5 years.
Results: Eight patients completed the study and four developed postoperative diabetes mellitus (PODM). Disposition index (DI) at postoperative 1 year showed prominent difference between the patients who develop PODM or not: DI was preserved in the PODM-free patients (49.7 ± 4.5 to 70.8 ± 14.4, P = 0.182), while it significantly decreased in the PODM patients (69.3 ± 9.9 to 28.5 ± 3.9, P = 0.019). The preoperative liver transaminase levels were not different between the two groups. However, transient increase in liver transaminase levels during the first week after ITx was observed only in the PODM patients, and their peak values demonstrated significant negative correlation with the changes in DI (r = −0.774 for alanine transaminase, r = −0.759 for aspartate transaminase; P < 0.05).
Conclusions: Elevation of serum transaminases after ITx could be one of the factors determining insulin secretion and PODM.

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1. Introduction

Postoperative development of diabetes mellitus (PODM) is a major clinical challenge in managing patients who underwent pancreatectomy. Although it was traditionally considered that PODM occurs only after more than 80% resection of the pancreas [1], PODM can occur after pancreatectomy of lesser volume. In a systematic review, the overall incidence of PODM was ranged from 7% to 51% after distal pancreatectomy for benign pancreatic diseases [2]. In a Korean study, 7-year diabetes free survival rate was only 45% after the resection of 50–60% volume of the pancreas [3]. In addition, even though overt diabetes does not develop in early years after pancreatectomy, the risk of PODM remains high due to the diminished insulin secretary reserve in long term follow-up period.

Autologous islet transplantation (ITx) can be considered for the patients who underwent pancreatectomy to treat non-malignant diseases. Unlike allogenic ITx, autologous ITx does not require immune suppression and generally have better graft survival. About 30–40% of the patients who underwent autologous ITx after total pancreatectomy achieve insulin independence [4]. For benign pancreatic tumors located in the body of pancreas, distal pancreatectomy is a standard treatment. After enucleation of the pancreatic tumor, the remaining healthy pancreas tissue distal to the lesion can be used for harvesting islets, then these harvested islets are transplanted to the patients. Only a few studies reported the results of autologous ITx in these patients [5–7].

Previously, we reported the 1-year outcome of autologous ITx in patients who underwent distal pancreatectomy for benign pancreatic diseases [8]. Here, we report 5-year outcome in these patients and examined the relationship between 5-year metabolic outcome and post-transplant plasma concentrations of liver transaminases, which would reflect not only liver injury by the procedure, but also the hepatic microenvironment where islets were engrafted.

2. Materials and methods

2.1. Subjects and study protocol

The inclusion criteria of this study were described in our previous study [8]. Briefly, nondiabetic patients who underwent distal pancreatectomy for benign pancreatic disease at Seoul National University Hospital from 2008 to 2011 were enrolled. The indication for ITx was those who agreed to have ITx and whose pancreas volume distal to the lesion was estimated as more than 25 g. They had regular examinations every 3 months during the first year after surgery and annually thereafter including biochemical tests. PODM was defined as either fasting plasma glucose (FPG) $\geq$ 126 mg/dl or 2-hour plasma glucose level (PP2) $\geq$ 200 mg/dl during a 75-g oral glucose tolerance test (OGTT). The study was approved by the Institutional Review Board of Seoul National University Hospital (IRB No. H-0710-007-221), and written informed consent was obtained from all the participants. The study was performed in accordance with the principles of the Declaration of Helsinki [9] and registered at ClinicalTrials.gov (NCT 01922492).

2.2. Autologous islet cell transplantation

The detailed protocol of autologous islet cell transplantation was described in our previous study [8]. Briefly, during distal pancreatectomy, the region of the pancreas distal to the mass with healthy gross appearance was transferred to the laboratory for islet isolation. Islets were isolated using with intraductal collagenase and the Ricordi chamber. Viable islets were counted as islet equivalent (IEQ) volume. After the confirmation of endotoxin and pathogen free, ITx was done on the day after surgery. Histology of the tumor and resection margin was confirmed before ITx. The islets were infused into the liver through percutaneous transhepatic portal vein catheterization.

2.3. Biochemical tests

Fasting plasma glucose (hexokinase method; Cobas Integra800; Roche, Basel, Switzerland), insulin, c-peptide (radioimmunoassay; Izotope, Budapest, Hungary), hemoglobin A1c (HbA1c) (high-performance liquid chromatography; Variant II Turbo; Bio-Rad, San Francisco, CA, USA), aspartate aminotransferase (AST; IFCC method; Cobas Integra800; Roche, Basel, Switzerland), and alanine aminotransferase (ALT; IFCC method; Cobas Integra800; Roche, Basel, Switzerland) levels were measured at each examinations. Serum levels of high mobility group box 1 protein (HMGB1) and soluble receptor for advanced glycation end product (sRAGE) were measured using ELISA Kits (MyBioSource Inc., San Diego, CA, USA, for HMGB1; R&D Systems Inc., Minneapolis, MN, USA, for sRAGE) before and after islet infusion.

2.4. Calculation of metabolic indices and statistical analysis

The homeostasis model assessment of beta cell function (HOMB-β), and insulin resistance (HOMA-IR) were calculated as follows: HOMA-IR = (fasting insulin [μU/mL] × fasting glucose [mg/dL])/405; HOMA-β = 360 × fasting insulin (μU/mL)/[-fasting glucose (mg/dL) − 63] [10]. The Matsuda index was calculated as 10,000/$\sqrt{}$(fasting glucose × fasting insulin × me an glucose × mean insulin) [11]. The insulinogenic index was used to estimate insulin secretion and was calculated as follows: (insulin [30 min] − insulin [0 min])/(glucose [30 min] − glucose [0 min]). The disposition index was used to evaluate the insulin secretion considering the degree of insulin sensitivity, and was calculated as follows: Matsuda index × insulinogenic index [12]. The beta score was calculated as previously reported [13]. Data are expressed as mean ± stan dard deviation. The continuous variables were compared using Student's *t*-test and the categorical variables were compared using Fisher's exact test or chi-square test. For serial changes, 2-way repeated measures ANOVA and the Bonferroni post-tests were applied. The associations between