Endoscopic Islet Autotransplantation Into Gastric Submucosa—1000-Day Follow-up of Patients

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ABSTRACT

Background. Total pancreatectomy and autologous transplantation of pancreatic islets is a treatment option for patients with severe pain due to chronic pancreatitis. In the standard procedure, pancreatic islets are isolated and subsequently administered into the portal vein. In the case of patients with a history of thrombosis or at risk of thrombosis, this route of administration is not viable. Animal studies conducted in our department led to the development of a technique of endoscopic islets transplantation into the gastric submucosa. In 2013 and 2014, the first human autologous transplant procedures were performed. The objective of this study was to present the results of a 3-year follow-up of these patients.

Methods. Two pancreatectomies were performed in our department, the first in 2013 and another in 2014, along with subsequent autologous transplantation of pancreatic islets into the gastric submucosa.

Results. Both patients had been diagnosed previously with diabetes, and both had endogenous islet activity detected. Peptide C concentration after pancreatectomy and before pancreatic cell transplantation was 0.1 ng/mL. After the transplantation, peptide C concentrations for the 2 patients were 0.8 and 0.5 ng/mL on day 7, 1.2 and 0.6 ng/mL on day 30, 1.3 and 0.8 ng/mL on day 180, 1.1 and 0.7 ng/mL on day 360, and 3.0 and 0.6 ng/mL at 3 years, respectively, after transplantation. The pain symptoms resolved in both cases.

Conclusion. Pancreatic islets may survive in the gastric wall. Endoscopic submucosal transplantation may present an alternative for the management of patients who cannot undergo a classic transplantation procedure.

ISLET transplantation has become a standard procedure in management of unstable diabetes [1]. It is also used to prevent diabetes in patients who undergo pancreatectomy due to chronic pancreatitis resulting in severe pain [2]. From the beginning of the 20th century, more than 20 new centers specializing in performing islets transplantation have been established in Europe. Since then, according to Berney, European sites have performed 1400 islet transplantations in 775 patients, twice this number in the United States [3]. In the United States, the prevalence of chronic pancreatitis has led to pancreatectomy and islet autotransplantation becoming a substantial part of activity of most transplant centers [3]. Autotransplantation of islets in chronic pancreatitis gives hope for cure and improvement of quality of life in many patients.

Diabetes developing after pancreatectomy is a serious problem as up to 50% of patients may die as a result of hypoglycemia [4]. Islets isolated from the resected pancreas and transplanted back to patients may prevent brittle diabetes, even if it does not lead to full insulin independence. Full pancreatectomy, performed to proceed with islet isolations, may prevent the development of pancreatic cancer

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[5]—a possible complication of the chronic inflammation. In Europe, pancreatitis, is mainly caused by biliary stones or excessive alcohol intake [6]. Unfortunately, excessive alcohol intake may lead to liver problems such as cirrhosis, and portal vein thrombosis that may result in portal hypertension. Portal hypertension can make islet transplantation into the portal vein risky or even impossible. In such patients, alternative implementation sites should be researched. For the last 10 years, many alternative implementation sites have been analyzed in preclinical and clinical models [7–17]. the gastric submucosa seems to be an attractive site for transplantation due to good oxygen perfusion [8], easy endoscopic access, and the most physiologic insulin outflow to the portal vein. Our aim in this study was to report on the 3-year follow-up of clinical endoscopic islet autotransplantation into the gastric submucosa.

MATERIALS AND METHODS

Between 2013 and 2014, 2 procedures of pancreatectomy and endoscopic autotransplantation into the gastric wall were performed in our department.

Medical History

First patient. A 53-year old man, with alcohol-related chronic pancreatitis for 15 years, was operated upon on March 14, 2013. Three months before surgery the patient was diagnosed with diabetes, but only dietary treatment was introduced. The patient had chronic pain, which was treated with opioid analgesics. Fifteen years earlier he underwent an operation for a peptic ulcer perforation, which was sutured. Laboratory testing showed anti-HBc and anti-HBe antibodies, suggesting hepatitis in the past. Computed tomography (CT) scanning showed right portal vein thrombosis. The patient qualified for a pancreatectomy (Child's procedure) and splenectomy, with experimental endoscopic islet transplantation into the gastric submucosa.

Second patient. A 42-year old man, with alcohol-related chronic pancreatitis for 10 years, was operated upon on March 24, 2014. The patient was diagnosed with diabetes 2 years before surgery (60 IU/d insulin). Chronic pain was managed with opioid analgesics. Laboratory testing showed anti-HBc and anti-HBe antibodies. CT scanning revealed narrowing and possible partial thrombosis of the portal vein.

Surgical Procedure

Both patients underwent distal near-total pancreatectomy with preservation of duodenum (Child-type procedure) and splenectomy. In both cases, the pancreas was resected along with the splenic artery. On the right side, the pancreas was resected up to the gastrodudodenal artery.

Isolation of Pancreatic Islet Procedure

After the removal of the pancreas, the organ was immediately flushed with University of Wisconsin (UW) solution (1000 mL), packed in 3 sterile bags, and then transported to the pancreatic islet isolation laboratory. The pancreas was removed from the inner bag inside a laminar hood, placed on sterile ice, and then decontaminated in the following solutions: betadine/Hank's balanced salt solution (Cellgro/Mediatech) and Hank's balanced salt solution (Cellgro/Mediatech)/ceftriaxone/Fungizone wash solution (Cellgro/Mediatech) containing penicillin/streptomycin. The duodenum, spleen, vessels, and fat tissue were removed from the pancreas and a cannula was inserted into the pancreatic duct. The pancreas was then weighed and manually injected with NB 1 GMP-grade collagenase dissolved in perfusion solution (Cellgro/Mediatech) and neutral protease. The pancreas was then fragmented into 10–15 pieces and transferred to a Ricordi chamber. Samples were taken at 120-second intervals to monitor digestion of the exocrine tissue and the release of the islets under a microscope. When free-floating islets were observed, digestion was halted by thinning down the tissue with a dilution solution (Mediatech, Herndon, VA) enriched with 20% human serum albumin and penicillin/streptomycin. The digested tissue was washed and centrifuged twice at 1200 rpm. The pellets were collected and resuspended in CMRL-1066 medium containing 20% human serum albumin and penicillin/streptomycin. An aliquot was stained with dithizone for quantitative analysis. Due to the small graft volume, no purification was performed. A sample was taken to estimate the number of isolated islets, and another sample was taken for quality assessment (microbiologic culture, direct Gram stain, PIAO-propidium iodine and acridine orange, viability testing, endotoxin contamination). After confirming the quality and islet equivalents, the suspension was transferred to a 50-mL syringe for transplantation into the gastric submucosa.

Gastroscopy and EUS Observation

Both patients underwent a standard gastroscopy procedure during preparation for autotransplantation, 48 hours after the procedure, and then at 30, 90, 180, 360, and 1000 days posttransplantation. Biopsies for histopathologic staining for insulin/glucagon-producing cells were taken 1000 days posttransplantation. Endoscopic ultrasound (EUS) examination was performed at 7 days posttransplant in both cases.

Metabolic Analyses

Levels of fasting C-peptide were measured prior to the procedure and at 1, 2, 3, 4, 5, 7, 14, 30, 90, 180, 360, and 1000 days after autotransplantation. C-peptide stimulation (CPS) tests were performed before the procedure and at 30, 90, 180, and 1000 days after autotransplantation. Fasting glycemia and oral glucose tolerance testing (OGTT) were performed before and at 7, 30, 90, 180, 360, and 1000 days posttransplant.

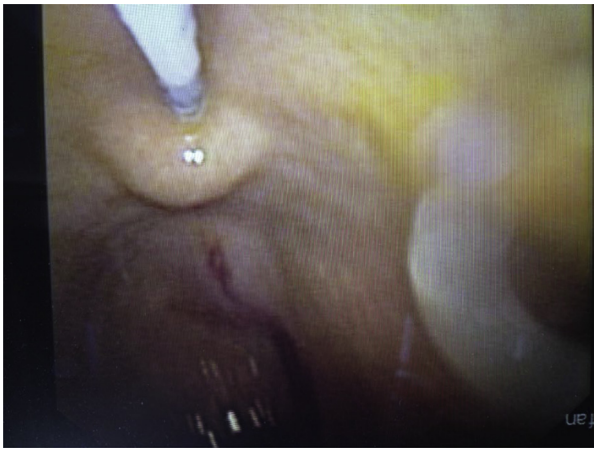

Fig 1. Endoscopic transplantation into the gastric wall.