

# TRANSPLANTATION PROCEEDINGS

# Characterization of Early Graft Damage After Pancreatic Transplantation

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**A**LLOGRAFTS are confronted perioperatively with a series of noxious factors, eg, circulatory instability, electrolyte disorders, organ removal, or extended ischemia time. Each type of organ graft reacts to these factors in a very specific way. In contrast to liver or kidney transplantation, clinical pancreatic transplantation is complicated by specific local problems in a significant percentage of patients.<sup>1</sup> These problems result from the so-called graft pancreatitis, which is mainly caused by ischemia and/or reperfusion injury of the grafts.

To clarify the sequence of potential changes within human pancreatic allografts, a series of morphological, functional, and biochemical parameters were studied sequentially in a prospective study.

## MATERIALS AND METHODS

A consecutive group of 10 patients was studied prospectively. All patients received combined pancreaticoduodenal/renal grafts (PDK) with bladder drainage. Organ procurement was performed by intra-aortal in situ flush with ice-cold UW solution. Pure pancreatic juice was selectively drained via a small pancreatic duct catheter for 6 weeks postoperatively. Closed continuous abdominal lavage (CCAL) was carried out routinely.

### Morphology

Sequential biopsies were taken from the pancreatic tail during the donor and recipient operation and examined by light- and electron-microscopy.

### Blood Chemistry

Blood samples were taken prior and after reperfusion of the pancreatic grafts. Analysis included amylase, lipase, antithrombin III,  $\alpha$ -2 macroglobulin, and glucose.

### Pancreatic Juice

Pancreatic juice was analyzed quantitatively (mL/h) and qualitatively by electrophoresis.

### Peritoneal Lavage Chemistry

The effluent of the CCAL was analyzed for lipase and amylase content.

## RESULTS

### Morphology

At the end of the cold ischemia period, the endoplasmic reticulum of several acinar cells were distended and, in part, vacuolated. Immediately after reperfusion, a marked infiltration by neutrophils took place. In the cytoplasm, several large membrane-bound vacuoles and different

steps of fusion figures with zymogen granules were demonstrable. Later, the autophagic activity was increased and, 5 hours after reperfusion, necrosis of single acinar cells were found.

### Blood Chemistry

Within the first hours after reperfusion, all patients showed a steady increase of pancreatic enzyme serum levels. The average peak levels were measured during the first 24 hours. Amylase levels were increased three- to ten-fold and lipase four- to 40-fold of normal values (amylase < 53 U/L, lipase < 190 U/L). Two thirds of patients reached normal pancreatic enzyme levels within the first 7 days after transplantation.

Antithrombin III plasma levels and  $\alpha$ -2 macroglobulin plasma levels dropped from normal values prior reperfusion to less than 60%, in most of the patients, within a few hours after reperfusion of the pancreatic grafts (Fig 1). High doses of antithrombin III were necessary during the following days (mean = 3500 U/d) to keep plasma levels at >80%. In nine of ten patients, no insulin adjustment was necessary after reperfusion of the pancreatic grafts. Blood glucose levels were in normal range in spite of IV or oral glucose intake. One patient required exogenous insulin until day 14 after operation.

### Peritoneal Lavage Parameters

High amounts of pancreatic enzymes were measured in the first effluents of CCAL. Lipase values ranged from 386 to 38,900 U/L and amylase values from 230 to 2210 U/L. Enzyme levels decreased drastically during the following days.

### Pancreatic Juice Parameters

The secretion of pancreatic juice differed from 0 to 30 mL/h within the first 24 hours after reperfusion. During the following postoperative days, the secretion increased and reached a plateau of about 15 to 60 mL/h in five of six patients. In one patient, the pancreatic secretion was less than 2 mL/h until removal of the pancreatic duct catheter. The qualitative analysis of proteins in the pancreatic juice

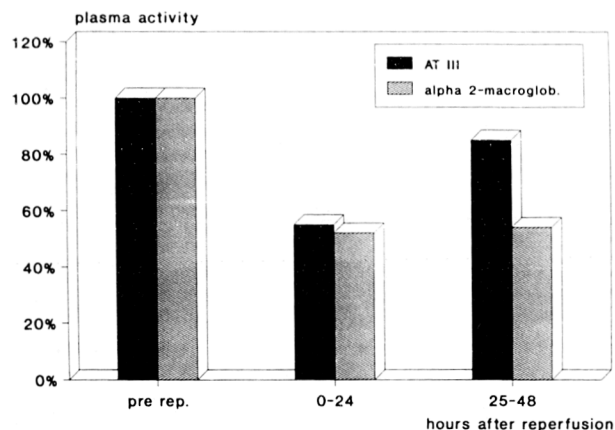
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**Fig 1.** Changes of antithrombin III and  $\alpha$ -2 macroglobulin before (100% plasma activity) and after reperfusion of pancreatic grafts. Immediately after reperfusion, a significant decrease of both parameters is evident (mean values). Antithrombin III was substituted to keep plasma levels at >80%.

showed high amounts of albumin in the juice secreted intraoperatively.

#### DISCUSSION

The results of our clinical study indicate that the early damage of vascularized pancreatic grafts is, in part, characterized by an inflammatory process of the exocrine pancreatic parenchyma. The morphological alterations of the reperfused grafts are very similar to the initial events of acute pancreatitis described in several animal models.<sup>2,3</sup>

In addition to these morphological alterations, the exocrine secretion of the pancreatic grafts is impaired. This

exocrine dysfunction is characterized by a decrease of the volume and an increase in albumin concentration in the pancreatic juice during the first days after transplantation. These observations are comparable to the impaired exocrine secretion during acute pancreatitis in experimental studies.<sup>4</sup>

Besides these morphological and functional characteristics of the pancreatic grafts themselves, different systemic parameters reflect the involvement of the plasma proteinase inhibitory system. In the early reperfusion period, antithrombin III and  $\alpha$ -2 macroglobulin activity dropped drastically to 50% of the initial values. Such a consumption of natural protease inhibitors is typical during the course of acute pancreatitis or hemorrhagic shock.<sup>5,6</sup> Therefore, in our opinion, a generous antithrombin III substitution is one of the most important factors to prevent early graft thrombosis.

Contrary to these local and systemic reactions, which are very similar to those in acute pancreatitis, the endocrine part of the gland seems to be less affected. Initial endocrine dysfunction after pancreatic transplantation occurred in only one of ten patients in our series.

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