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Simultaneous pancreas/kidney transplantation – the optimal therapy for type I diabetics with end-stage renal disease in Europe, too?

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Abstract Contrary to the situation in the USA, the number of pancreatic transplantations declined during the last year in the Eurotransplant region. Whether the high postoperative morbidity and unsatisfactory graft function rates reported by many European centres can be overcome was investigated in a single centre study. In a consecutive series of 80 patients with simultaneous pancreas/kidney transplantations, postoperative morbidity due to graft pancreatitis and recurrent rejections was significant. Both of these complications, however, were treated successfully in the vast majority of patients. Graft thrombosis was almost completely prevented. Excellent function rates of the pancreatic grafts of 88% after 1 year and 83% after 5 years were achieved. Thus, simultaneous pancreas/kidney transplantation can be recommended as the optimal therapy for type I diabetics with end-stage renal disease in Europe, too.

Key words Pancreas transplantation · Perioperative morbidity · Rejection · Endocrine function · Graft function rate

Introduction

Contrary to the situation in the USA the frequency of pancreatic transplantations has markedly declined in the Eurotransplant region. In Germany, the number of pancreatic transplantations performed dropped from 45 in 1991 to 31 in 1992. The reasons for this problematic development are certainly multifactorial. Besides a high postoperative morbidity imposing marked strain on patients as well as on their physicians, the overall success rate in respect to insulin independence seemed to be unsatisfactory. Many centres in Europe have reported 1-year graft function rates of only 60–70%, which is significantly lower than those of the leading centres in the USA [1, 2]. In addition, completely normal glucose tolerance after a standardized oral glucose load has been reported in about 50% of insulin-independent patients only [3]. Considering these results, the question arises of whether combined pancreas/kidney transplantation can be regarded as optimal therapy for type I diabetic patients in Europe, too. Thus, the aim of the following study was to investigate whether, by strict standardization of the perioperative treatment protocol, the limitations of pancreas/kidney transplantation in our region could be overcome.

Patients and methods

From January 1987 to July 1992, simultaneous pancreas/kidney transplantation was performed in 80 patients with diabetes mellitus type I and end-stage renal disease. The mean age was 39 years, ranging from 22 to 56 years. All patients had a thorough medical check-up before transplantation. Moderate to severe extrarenal diabetic complications were found in all patients. The only exclusion

criteria for transplantation, however, were severe coronary heart disease or cardiomyopathy. All pancreatic grafts were placed intraperitoneally and connected to the right iliac vessels; the kidney grafts were placed either extra- or intraperitoneally and connected to the left iliac vessels. The pancreatic grafts were drained via the duodenal segment into the urinary bladder ($n = 73$) or the small intestine ($n = 7$). Cold ischaemia time was limited to 16 h, mean cold ischaemia time was 11 h. In all patients, a closed continuous peritoneal lavage was started 2–24 h after transplantation. The lavage was performed until disappearance of clinical abdominal symptoms and normalization of leucocyte count and enzyme levels in the lavage fluid. All patients recieved low molecular weight dextran and low dose heparin. Antithrombin III was substituted whenever serum levels fell below 70%. Immunosuppression was started with quadruple therapy using ATG (Fresenius) for the first 14 days. Later on, triple drug therapy was used as described previously. OKT III was used as a first-line therapy for rejection. In case of recurrent rejection, antithymocyte or antilymphocyte globulin or bolus corticoid therapy was used.

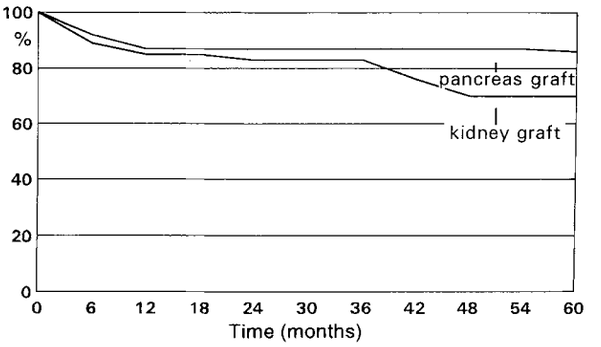

Fig. 1 Graft function rate after simultaneous pancreas/kidney transplantation in 80 consecutive patients

Results

All pancreaticoduodenal grafts showed primary function immediately after reperfusion. In six patients, however, different amounts of exogenous insulin were necessary in the early postoperative period in order to achieve normoglycaemia.

In all patients, high amounts of pancreatic enzymes such as amylase and lipase were detected in the peritoneal lavage fluid immediately after transplantation. This enzyme leakage disappeared rapidly in grafts without graft pancreatitis. In 18 patients, however, oedematous graft pancreatitis was seen, characterized by moderate abdominal symptoms, prolonged enzyme leakage into the abdomen, reduced secretions via the pancreatic duct and a typical morphological picture [4]. Prolonged peritoneal lavage was the only therapy necessary in these patients. In eight patients necrotizing graft pancreatitis developed within the 1st postoperative week. In all of them aggressive and, if necessary, repeated necrectomies were performed and the peritoneal lavage continued for a prolonged time. Using this approach, all of these grafts were saved. While exocrine function declined or disappeared completely, endocrine function was preserved in all grafts.

In spite of 115 arterial or venous reconstructions performed in these pancreas grafts, early postoperative graft thrombosis was seen only once in a patient with protein C deficiency. Dramatic coagulation disorders were seen in the early postoperative period, especially in patients with graft pancreatitis [5]. A rapid and dramatic drop in antithrombin III levels were found in some of the patients. Because pancreatic transplantation induces a state of hypercoagulability in the early postoperative period in many of the patients, low dose heparin and low molecular weight dextran were given. In addition, we believe that correction of low serum levels of antithrombin III is essential in order to reduce the risk of early postoperative graft thrombosis.

Almost 70% of patients developed acute rejection episodes of the kidney or pancreas or both. Markers of rejection were an increase in serum levels of creatinine or different pancreatic enzymes and a drop in amylase excretion via the pancreatic duct. Besides numerous percutaneous kidney biopsies, open pancreatic biopsies, which can be done under local anaesthesia, were performed with no complications in ten patients. OKT III, which was used as a first-line therapy for acute cellular rejection episodes, reversed all primary rejections except two. Recurrent rejections were seen in 35% of patients and treated with polyclonal antilymphocyte or antithymocyte antibodies or bolus corticoid therapy.

Graft function rate of the pancreatic graft, i.e. independence of exogenous insulin, was 88% in our series after 1 year and 83% after 5 years (Fig. 1). HbA1 was normal in all of these patients. When studying the insulin and C-peptide secretion after a standardized oral glucose load, more than three-quarters of these patients showed completely normal endocrine function of the pancreatic graft.

Discussion

Pancreatic transplantation is performed only by a minority of transplant centres in Europe. Due to a high perioperative morbidity and unsatisfactory overall results, the number of pancreatic transplantations performed has declined markedly the last year in the Eurotransplant region. This is in sharp contrast to the

situation in the USA. The results of this study, however, clearly demonstrated that pancreatic transplantation can be performed in Europe, too, with a remarkably high success rate.

The perioperative morbidity is certainly significantly higher after simultaneous pancreas/kidney transplantation than after isolated kidney transplantation. Graft pancreatitis, graft thrombosis, recurrent rejection episodes and a high frequency of bacterial and viral infections are most crucial in this respect [6]. By using our treatment protocol, almost all of these potential complications can be overcome.

The frequency of graft pancreatitis was rather high in this series. It was closely related to the donor selection criteria used. Thus, the incidence, as well as the severity of graft pancreatitis, could be significantly reduced by using only grafts from haemodynamically stable donors. In the case of graft pancreatitis, however, endocrine function of the grafts can be preserved in nearly all cases when using the therapeutic regimen developed in our centre. While continuous peritoneal lavage is an excellent tool for treatment of oedematous graft pancreatitis, in necrotizing graft pancreatitis, aggressive and, if necessary, repeated local necrectomies have to be done in addition.

In spite of the high frequency of vascular reconstructions performed in the pancreatic grafts, early postoperative graft thrombosis disappeared almost completely [7]. A meticulous surgical technique is important. In addition, it was clearly demonstrated that a strong activation of the coagulation cascade takes place in some of the patiens after reperfusion of the pancreatic graft [5]. It is tempting to assume that factors arising from the pancreas, such as activated trypsin etc., are responsible for these findings. Thus, we still believe that some kind of anticoagulation therapy should be used in the early postoperative period. Correction of low antithrombin seems to be important in this respect.

The incidence of rejection episodes in our series was rather high in spite of quadruple therapy for immunosuppressive induction. Similar findings have been reported by others [8]. By using mono- or polyclonal antilymphocyte antibodies, almost all rejection episodes were reversed. In addition, all patients were immunologically stable after 3–4 months. Late rejections were extremely rare.

The lack of technical graft failures and the effective immunosuppressive therapy were responsible for the excellent graft function rate in our series. The 1-year graft function rate of the pancreas, for the first time, equaled that after isolated kidney transplantation. In addition, graft function of the pancreas remained remarkably stable in the following years. To date, only one pancreatic graft of our series was lost due to chronic rejection. Thus, the results of our series clearly demonstrated that, in spite of a significant perioperative morbidity, excellent graft function rates can be achieved after pancreatic transplantation when using our protocol. Considering the enormous gain in well-being and quality of life, simultaneous pancreas/kidney transplantation should be regarded as the optimal therapeutic modality for patients with type I diabetes and end-stage renal disease in our region, too.

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