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Luis Carlos Feitosa Tajra
Marwan Dawhara
Mehdi Benchaib
Nicole Lefrançois
Xavier Martin
Jean Michel Dubernard

Effect of the surgical technique on long-term outcome of pancreas transplantation

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L.C. Feitosa Tajra · M. Dawhara
M. Benchaib · N. Lefrançois
X. Martin · J.M. Dubernard (✉)
Department of Urology and
Transplantation Surgery,
Hôpital Edouard Herriot,
Place d'Arsonval,
F-69437 Lyon cédex 03, France
Fax: + 33 4 7211 0582

Abstract To date there is no general consensus as to the best surgical technique for pancreas transplantation. Patients with a pancreas transplant functioning for 3 years or more were retrospectively investigated to compare three surgical techniques: segmental graft with duct obstruction (DO), whole graft with bladder drainage (BD), and whole graft with enteric drainage (ED). Several parameters were studied: patient and graft survival, rejection, long-term surgical and medical complications, and endocrine function. The best results in terms of graft survival and quality of metabolic control were obtained in the group that underwent whole graft transplantation with ED. At 3 years, overall pancreas graft survival was 65% for ED, 60% for BD, and 47% for DO. This surgical method has become the preferred technique in our unit.

Key words Pancreas transplantation, diversion · Enteric diversion, pancreas transplantation · Bladder diversion, pancreas transplantation

Introduction

Pancreas transplantation is the only treatment that is able to achieve insulin-independent euglycemia in type I diabetic patients. It is the procedure of choice in many transplant units for the management of end-stage renal disease type I diabetes [21]. Successful pancreas transplantation reduces the severity of secondary diabetic complications and improves the quality of life as compared to exogenous insulin therapy [13]. However, the most appropriate technique for vascular implantation and exocrine derivation has yet to be defined.

The pancreas transplantation program at the Hôpital Edouard Herriot was initiated in October 1976, and three different surgical techniques have been used: segmental grafts with duct obstruction by neoprene injection (DO), as described by our group in 1976 [6], whole grafts with bladder drainage (BD), and whole grafts with enteric drainage (ED). Previously, in prospective, randomized studies, we compared short-term results of pancreas transplantation with ED and DO, as well as with BD and DO [4]. In order to evaluate the long-term advantages of each technique, we have retrospectively studied patients with a pancreas transplant functioning for 3 years or more.

Materials and methods

Of the 280 pancreas transplantations performed in our unit between October 1976 and December 1996, 242 were performed before 1993. Pancreas grafts functioning well for more than 3 years were observed in 95 patients (49 men and 46 women). The mean age of the patients was 37 years (range 21–51 years). The mean duration of diabetes was 24 years (range 11–48 years). DO was carried out in 60 patients, whereas 26 patients received a pancreaticoduodenal graft with BD and 9 had a pancreaticoduodenal graft with ED. When a segmental graft was procured, revascularization was performed by anastomosis of the splenic pedicle to the recipient common iliac vessels. DO was achieved by injecting a synthetic polymer into the main pancreatic duct [6]. For whole pancreas transplants, arterial revascularization was done by end-to-side anastomosis to the common iliac artery using an iliac artery extension graft anastomosed to the superior mesenteric and splenic ar-

Table 1 Demographic information on the patient population

Age (years)	37.3 (21–51)
Sex	
Men	49 (49.9%)
Women	46 (51.1%)
Duration of diabetes (years)	23.6 (11–48)
Severe retinopathy	83 (93%)
Severe neuropathy	74 (83%)
Surgical techniques	
– Segmental	60 (65%)
– Bladder drainage	26 (25%)
– Enteric drainage	9 (10%)
Cold ischemia (min)	376.7 (105–1025)
Warm ischemia (min)	27.7 (16–45)
Retransplantation	4

tery of the pancreas graft. ED of the whole pancreaticoduodenal graft was established by end-to-side anastomosis between a Roux-en-Y intestinal loop and a small patch of duodenum encompassing the pancreatic duct, or by side-to-side duodenoenterostomy to a free intestinal loop [18]. BD of the whole pancreaticoduodenal graft was performed via a duodenocystostomy [11].

The immunosuppression protocols used in our unit have been described in detail elsewhere [4]. Since 1987, quadruple induction immunotherapy has been used combining cyclosporin, prednisone, azathioprine, and antilymphocyte globulins.

Demographic information on our patient population is shown in Table 1. The outcomes of these 95 patients were retrospectively studied with regard to patient and graft survival, rejection episodes, long-term surgical and medical complications, and endocrine function.

Data between groups were compared with a one-way analysis of variance (ANOVA). The Kaplan-Meier method was used to generate survival curves, which were compared with the log-rank test.

Results

Graft and patient survival

At 3 years, overall pancreas graft survival was 65% for ED, 60% for BD, and 47% for DO (P = NS, Fig. 1). Ninety percent of the grafts functioning at 3 years were expected to still be functioning at 5 years, and 65% at 10 years (Fig. 2). Of the 95 patients with pancreas grafts functioning for more than 3 years, 17 eventually lost their grafts (6 at 4 years, 4 at 5 years, 1 at 6 years, 1 at 7 years, 2 at 8 years, and 3 at 9 years). The cause of graft loss was death in 2 patients (myocardial infarction and cerebral hemorrhage), arterial thrombosis in 3 patients, and immunological causes (i.e., rejection) in 12. Better pancreas graft survival was observed after 1987, when quadruple immunosuppression was initiated. Before 1987, 3-year pancreas graft survival was 50%. With quadruple therapy, survival increased to 70%.

Metabolic evaluation

Metabolic evaluation performed annually in patients with currently functioning grafts included mean fasting

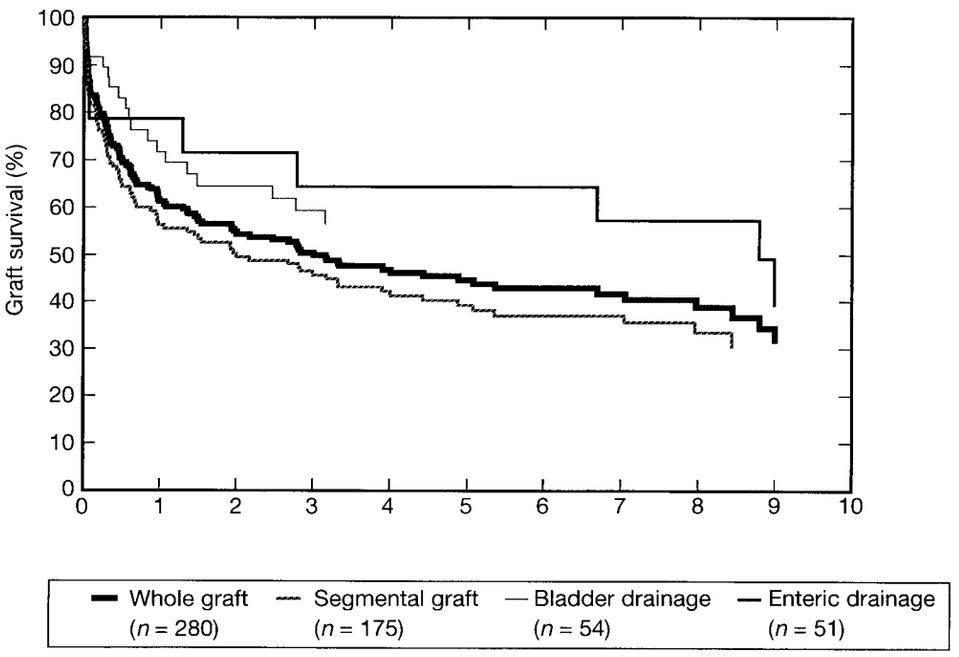

Fig. 1 Pancreas graft survival according to the type of surgical technique used

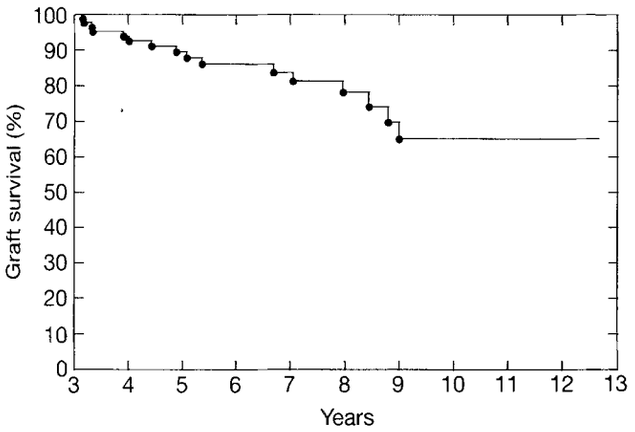

Fig. 2 Prognosis of graft survival in patients with a graft functioning for more than 3 years

blood glucose and oral glucose tolerance tests (OGTT), determination of insulinemia and C-peptide, and measurement of glycosylated hemoglobin. When we compared the whole grafts, no difference was observed in fasting blood glucose or OGTT. However, when we studied whole versus segmental grafts, significantly higher glucose levels and lower insulin and C-peptide levels were observed in DO pancreas. These differences were progressive with time and reached their highest levels at 5 years. Among the three groups, mean fasting blood glucose at 3 and 5 years were in the upper normal ranges and no differences were observed. However, at 3 years, OGTT was more elevated at 60, 90, and 120 min in the group of segmental grafts ($P < 0.05$). At 5 years, OGTT was higher in DO patients than in the whole pancreas groups, and this difference was significant ($P < 0.0001$, Fig. 3). The glycosylated hemoglobin values were more elevated during the first 2 years after transplantation in the ED group (6.9% and 8.6%, $P < 0.05$). However, no difference in glycosylated hemoglobin was observed for up to 9 years between whole and segmental grafts (Fig. 4). Insulin and C-peptide secretion were more significant in whole than in segmental graft recipients during fasting and oral tolerance tests. The fasting insulin and C-peptide concentrations were above normal levels in all transplant recipients, independent of the surgical technique. This elevation was never more than twice the normal levels, and no progressive difference with time was observed between the whole and segmental grafts. Otherwise, during oral tolerance tests, the elevations in insulin and C-peptide secretion were progressive with time in whole graft recipients. They reached their highest levels at 5 years, when elevation was six and four times the normal levels, respectively. Although more elevated than the normal levels, insulin and C-peptide secretion from segmental graft recipients were never more than twice the normal level. One patient with a DO graft maintained normal blood sugar and glycosylated hemoglobin for 13 years after transplantation.

Renal rejection episodes

Among the 95 patients with grafts functioning for more than 3 years, renal rejection was diagnosed at least once in 58 patients (61%). Sixty-nine episodes of rejection (an average of 1.15 rejection per patient) were observed in patients with segmental grafts. Patients with pancreaticoduodenal grafts experienced 48 episodes of rejection (an average of 1.36 rejection per patient). Although more episodes of rejection were observed with whole grafts, no significant difference was noticed in relation to the surgical technique. Furthermore, no difference in the incidence of rejection was observed between the 78 patients with a functioning graft and the 17 patients who lost their grafts after 3 years.

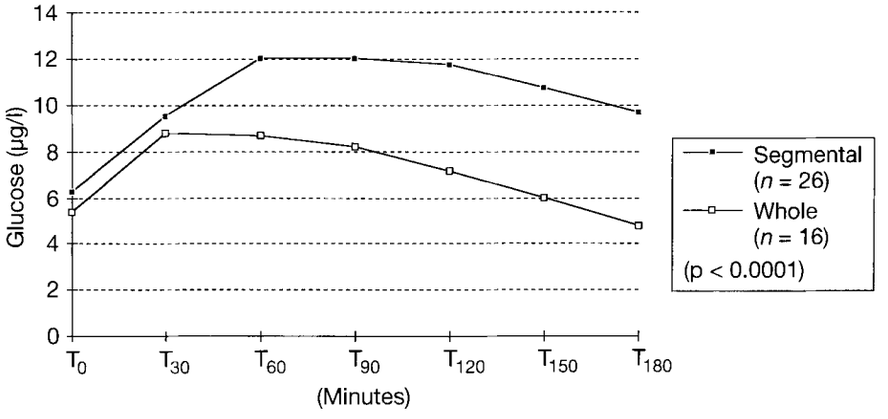

Fig. 3 Oral glucose tolerance test at 5 years —■— Segmental ($n = 26$); —□— whole ($n = 16$); $P < 0.0001$

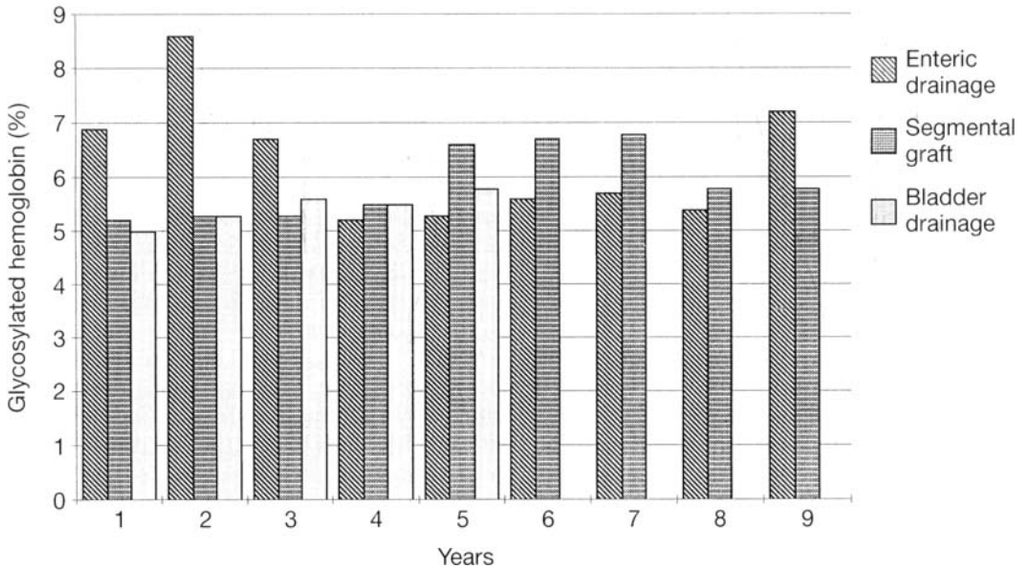

Fig. 4 Glycosylated hemoglobin according to the type of surgical technique used

Infectious complications

Of the 95 patients, 29 (30%) developed CMV infection with clinical signs and serum conversion and required acyclovir treatment. The incidence of CMV infection was not different in the 17 patients who lost their pancreas grafts after 3 years, nor did the surgical technique have any influence on the incidence of CMV (DO 22%, BD 38%, ED 33,%).

Urinary tract infection (UTI) was observed in 50 patients (52%). UTI was significantly more frequent in BD (66%) than in DO (44%) and ED (33%). BD patients presented more recurrent UTI (42%) than did DO (9%) and ED (33%) patients ($P < 0.05$). *E. coli* was identified, isolated, or associated with other bacteria in 70% of UTI.

Surgical complications

Two patients with BD developed urinary fistula with major reflux pancreatitis and urinary retention 3 years after transplantation. Despite initial conservative treatment, conversion from BD to DO was necessary. The duodenovesical anastomosis was freed and divided. The bladder opening was sutured and the duodenum was resected. Neoprene was injected after pancreas duct identification.

Four patients (19%) in the BD group developed dysuria associated with hematuria that required recurrent urethral catheterization. All patients with BD showed metabolic acidosis and required oral treatment with bicarbonate.

No long-term surgical complications were observed in patients with DO or ED.

Discussion

Although many efforts have been made to optimize insulin therapy, only pancreas-kidney transplantation can presently restore diabetic patients to a condition of normoglycemia that is compatible with a normal life [21]. In diabetic patients with end-stage renal disease who are candidates for kidney transplantation and immunosuppression, the addition of a pancreas graft is now recognized as the best treatment. Although morbidity is a consequence of pancreas transplantation, the long-term results in terms of patient survival are not affected. Furthermore, nearly the same immunosuppression is used for combined pancreas-kidney transplantation as for kidney transplantation alone.

Pancreas graft survival continues to improve with new protocols of immunosuppression and better reanimation support, but technical failure still is a major obstacle to successful pancreas transplantation. At 3 years, pancreas graft survival was 65% for ED, 60% for BD, and 47% for DO. However, in the 203 patients who underwent transplantation since 1987, the 3-year survival rate was 70%. This survival rate is comparable to what is observed in other organ transplantations, as 12% of the recipients in our series died of causes related to diabetes.

Causes of technical failure include allograft thrombosis, severe graft pancreatitis, and infectious complications, all of which may be responsible for graft pancre-

atectomy. Technical complications seemed to be more frequent with BD than with ED and segmental grafts. Previous prospective, randomized studies comparing DO with BD demonstrated that surgical complications might occur in the long run with BD [4]. BD is associated with more urological complications than other techniques. The presence of a duodenal segment anastomosed to the bladder may stimulate intestinal enteropeptidase secretion and activate the proteolytic enzymes trypsin and chymotrypsin. These activated enzymes may lead to debilitating symptoms and some autodigestion of the urinary system [12, 22]. This might explain the increased frequency of UTI and urinary fistula, sometimes resistant to conservative treatment. Conversion to duodenoenterostomy has been reported to be necessary in 15%–20% of the cases [19]. In 10 of 53 pancreatic grafts with BD, the conversion technique used duodenectomy and duct injection in 5 cases and conversion to ED in the other 5 cases [10].

Rejection is also an important cause of late graft loss (12 cases). In our patients, its frequency was the same in segmental and in whole grafts. The addition of a duodenal segment had no influence on rejection. Pancreas rejection is difficult to diagnose. There are no markers for endocrine pancreas rejection, and a biopsy of the graft is difficult to perform and to interpret. Antirejection therapy given for a kidney may mask or prevent concomitant pancreas rejection. Some centers attempt to make an early diagnosis of pancreas rejection based on an analysis of exocrine secretion. This interesting feature justifies BD as the urine pH and amylase content can be measured. In our experience, it has been of little help; the kidney remains the best marker of pancreas rejection. We have reported that features of kidney rejection occur earlier than those of pancreas rejection [7]. Thus, kidney rejection might appear to be the indicator of pancreas rejection. As in the case of coronary disease in cardiac grafts, arterial stenosis and thrombosis in pancreas grafts long after transplantation may be due to chronic rejection.

Several studies have shown that glucose control remains normal or near normal as long as patients have a functioning pancreas graft. Long-term functioning has been associated with all duct management techniques [3, 20]. However, even during the 1st year after transplantation, segmental grafts already show significantly higher glycemia levels than whole grafts [17]. In our study, these abnormalities increased during follow-up and reached their highest levels at 5 years. The differences observed in the oral glucose tolerance test at 5 years could be due to the smaller mass of tissue transplanted in this group. Later, a stabilization of endocrine function was observed, independent of the technique used.

Several hypotheses are plausible for the anormalities in meal-induced insulin and C-peptide secretion post-transplantation. As pancreas islet secretion normally drains into the portal vein, it has been suggested that peripheral venous hyperinsulinemia is the result of decreased insulin metabolism caused by insulin released from the transplanted pancreas into the iliac vein instead of the portal vein and, hence, avoidance of first pass hepatic insulin degradation [5]. However, insulin resistance caused by a primary defect in glycogen formation or secondary to immunosuppression may be another important cause of hyperinsulinemia in these patients [1, 2, 8, 16]. A third mechanism appears to be the failure of feedback inhibition of insulin secretion. This inhibition seems to be neurally mediated and, thus, is absent in the denervated, transplanted pancreas. Luzi et al. showed that, in pancreas transplant recipients, insulin secretion is inadequately suppressed by the infusion of exogenous insulin during both euglycemic and hypoglycemic conditions, suggesting the absence of negative feedback control on insulin secretion [9]. These hypotheses may explain the high peripheral insulin concentrations that may be sufficient to maintain euglycemia postprandially, but they do not explain why some of these patients present abnormal tolerance tests.

Most of the patients in the pancreas transplant unit are uremic and receive combined kidney-pancreas grafts. Changes in the C-peptide clearance would not be unexpected in these patients because of the dominant role of the kidney in the overall metabolic disposal of C-peptide. A minimal renal dysfunction that could result from either the transplant itself or the effect of cyclosporin or other factors could delay the clearance of C-peptide, complicating the interpretation of peripheral C-peptide concentration[14, 15]. This may explain our difficulty in interpreting the results and the absence of a correlation between insulin and C-peptide secretion in some patients.

Whole pancreaticoduodenal grafts are expected to exert better metabolic control than segmental grafts. Whole pancreaticoduodenal grafts seem to offer an optimal mass of tissue, and ED is more physiological than BD. Segmental pancreas transplantation is technically simpler, but the metabolic control after stimulation is less satisfactory. Glycosylated hemoglobin was more elevated in the ED group during the first 2 years, but the three groups later showed similar ranges.

In conclusion, pancreas transplantation is presently the only established method capable of achieving long-term normoglycemia in patients with type I diabetes. Secondary diabetic complications are fewer in the long run after successful pancreas transplantation. This contributes to improving the patient's quality of life. Chronic rejection is the most important cause of late graft loss, but incidence of late graft loss is low after 3 years as compared to in the early post-transplant period. We believe that whole pancreaticoduodenal grafting with ED is presently the best technique. In the long run, it yields

the best graft survival and excellent metabolic control. Although the best glucose control is achieved with pancreaticoduodenal grafts in the long run, we have seen that segmental grafts are also able to maintain normal blood sugar and glycosylated hemoglobin in patients for up to 13 years. Currently, the longest function reported in a pancreas graft is 16 years in a patient who received an open duct pancreas that resulted in atrophy of the exocrine tissue, as after DO [20]. Although the group of patients with ED was smaller than the other groups, this technique would appear to represent the method of choice. In our unit, it is now used for all patients. Forty-eight patients have received a whole pancreas graft with ED since 1994. At present, the results in terms of graft survival and early control of function are satisfactory.

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