Transplant Int (1990) 3: 234–237

TRANSPLANT
International

Transplantation in patients with diabetic nephropathy

Outcome of combined pancreas and kidney transplantation compared with kidney transplantation only

G. Nordén[1], G. Nyberg[1], L. Hedman[2], M. Olausson[2], and B. Frisk[2]

[1] Department of Nephrology and [2] Transplant Unit, Sahlgrenska Hospital, University of Göteborg, S-413 45 Göteborg, Sweden

Received May 7, 1990/Received after revision July 13, 1990/Accepted July 30, 1990

Abstract. Detailed results of 12 combined pancreas and kidney transplantations (Comb) were compared with those of two matched diabetic controls per patient – one living donor kidney recipient (LD) and one cadaveric donor kidney recipient (CD) – who, though eligible for pancreas transplantation also, preferred kidney transplantation only. Mean follow-up was 22, 23, and 21 months in the three groups. There was no mortality in the LD group, but two CD and one Comb patient died from cardiovascular disease. Two kidneys were lost in both the Comb and the LD group, compared to five in the CD group. Ten major vascular events occurred and three of them were lethal. The only LD case was one below-knee amputation; the other nine were equally distributed in the Comb and CD groups. The time spent in the hospital was shorter for the LD group. Thus, in the short run, LDs confer the best results, whereas in the long term the better metabolic control in the Combs may prove favorable.

Key words: Pancreatic transplantation – Diabetic nephropathy, kidney or pancreas-kidney transplantation – Combined pancreas and kidney transplantation

Kidney transplantation is an established treatment for end-stage renal failure, with a high success rate also in patients with diabetic nephropathy [10]. The introduction of cyclosporin as an immunosuppressive agent in the early 1980s further improved the results. Most large transplant centers now report 1-year patient survival rates around 95% and graft survival rates around 90% with living kidney donors versus 70% with kidneys from cadaveric donors [4, 6, 13]. During these last years, the results of combined pancreas and kidney transplantation have also improved, and its use has spread to many transplant units. The 1-year pancreas graft survival is 70%–80% in many units [1, 3, 5, 9, 11, 14]. Comparison of the two procedures as regards success rate, risks, and other consequences is difficult because in many transplant centers with a pancreas program, combined pancreas and kidney transplantation is proposed to all uremic diabetic patients, except those with very advanced complications. No controlled, randomized studies have been carried out. Our policy has been to advise patients with a living kidney donor to accept this offer and to warn recipients of cadaveric grafts that combined transplantation may confer additional risks without having any documented effect on further progression of diabetic complications, at least in the short term. A number of patients eligible for pancreas transplantation have, as a result, preferred to receive a kidney transplant only. This made it possible to analyze the outcome of combined pancreas and kidney transplantation with that of cadaveric donor kidney transplantation or living donor transplantation in similar patients matched for age and for diabetes duration.

Offprint requests to: G. Nordén

Patients and methods

From June 1986 until November 1988, 71 diabetic uremic patients underwent 73 kidney transplantations in our unit. Sixty-three of these patients had type I diabetes. Eighteen type I patients were recipients of primary combined pancreas and kidney grafts from cadaveric donors. The surgical technique was identical in all cases. A segmental pancreatic graft was anastomosed to the iliac vessels and the pancreatic juice was drained to the urinary bladder [8]. A sequential quadruple drug immunosuppressive protocol was used, based on antithymocyte globulin (ATG; Fresenius, Bad-Hamburg, FRG) for 7–10 days, steroids, azathioprine, and cyclosporin, the latter introduced during the 1st week [7]. The recipients of combined grafts comprised the Comb group. During the same period of time, 21 type I diabetic patients received primary kidney grafts from cadaveric donors. Fourteen of these patients were eligible for the combined procedure but preferred to receive a kidney transplant only (CD group). Seventeen diabetic patients received primary kidney grafts from living donors, 16 of them from living related donors and 1 from her spouse (LD group). Recipients of kidney grafts alone received triple drug immunosuppressive therapy starting on the day of transplantation. All recipients of kidney grafts alone took 3–5 injections of insulin daily and were encouraged to monitor their blood glucose.

Table 1. Pretransplant characteristics of recipients of combined pancreas and kidney transplantations (Comb), of diabetic recipients of cadaveric kidneys (CD), and of diabetic recipients of kidneys from living donors (LD)

	Comb ($n = 12$)	CD ($n = 12$)	LD ($n = 12$)
Age (years)	36 ± 6	38 ± 7	38 ± 7
Sex (M/F)	11/ 1	6/ 6	5/ 7
Diabetes duration (years)	24 ± 7	26 ± 7	24 ± 7
Time on dialysis treatment (months) (Range)	5 ± 6 0–17	13 ± 13* 0–45	3 ± 4 0–10
Predialytic transplantation	4	4	5
No. of patients with severely impaired vision	1	7	2

* $P < 0.05$ vs Comb and vs LD

Table 2. Characteristics of donors and the donor kidneys in the three groups of diabetic patients, recipients of combined pancreas and kidney transplants (Comb), recipients of CD, and recipients of kidneys from LD

	Comb ($n = 12$)	CD ($n = 12$)	LD ($n = 12$)
Age of donor (years)	32 ± 15*[1]	51 ± 12	50 ± 11
Cold ischemia time (hours)	7.8 ± 1.7*[2]	17.0 ± 4.6	< 1
No. of mismatches			
HLA A + B	3.1 ± 0.8*[3]	2.4 ± 1.0*[4]	1.5 ± 1.0
HLA DR	1.4 ± 0.6*[5]	1.0 ± 0.7	0.6 ± 0.4

*[1] $P < 0.005$ vs CD and vs LD
*[2] $P < 0.001$ vs CD
*[3] $P < 0.001$ vs LD
*[4] $P < 0.05$ vs LD
*[5] $P < 0.01$ vs LD

Table 3. Results of transplantation in recipients of combined pancreas and kidney grafts (Comb), in diabetic recipients of CD, and in diabetic recipients of kidneys from LD

	Comb ($n = 12$)	CD ($n = 12$)	LD ($n = 12$)
Patient survival	11/12	10/12	12/12
Kidney graft survival	10/12	7/12*	10/12
^{51}CrEDTA clearance (ml/min per 1.73 m^2 BSA)	48 ± 22	48 ± 17	50 ± 13
Pancreas graft survival	9/12	–	–
HbA_{1c}(%)	6.2 ± 0.9**	8.7 ± 1.4	8.5 ± 1.4

* NS vs Comb and LD
** $P < 0.001$ vs CD and vs LD

The three groups of patients (18 Comb/14 CD/16 LD) were matched for age (± 7 years) and diabetes duration (± 7 years), resulting in 12 triplets with one representative of each category. For six patients with combined pancreas and kidney grafts, no matched controls were available. This group consisted of males with a mean age of 37 ± 9 years. The observation time was 18 ± 4 months. Patient survival was 6/6, kidney graft survival was 6/6, and pancreas graft survival 5/6.

Pretransplant clinical data are listed in Table 1. As a consequence of the selection principles and matching, the groups were similar with regard to age, diabetes duration, and the extent of macrovascular disease. Present and past smoking habits were also similar. However, the groups differed in that the patients receiving cadaveric kidneys (CD group) had waited longer before undergoing transplantation and were under dialysis treatment for a longer time than the other groups. Severe visual impairment was also more frequent in this group. There was a sex dissimilarity as more males than females preferred combined transplantation. Table 2 presents data on the donor organs. The Comb group received organs from significantly younger donors than either the LD or CD groups and with a shorter cold ischemia time. On the other hand, HLA matching was poorer in the Comb group. The mean follow-up time was 22, 21, and 23 months in the Comb, CD, and LD groups, respectively, and ranged from 6 to 38 months. In three LD patients, follow-up was limited by a pancreas after kidney transplantation at 6, 15, and 19 months, respectively.

Student's *t*-test and the chi-square test were used for the statistical analyses.

Results

Patient survival

One patient in the Comb group and two in the CD group died during the observation period, all three from cardiovascular disease and with functioning grafts (Table 3). There was no mortality in the LD group.

Kidney graft survival

Two kidneys were lost in both the Comb group and the LD group, compared to five in the CD group (Table 3). Causes of graft loss were the patient's death (1 Comb, 2 CD), acute rejection (3 CD), chronic rejection (1 Comb, 1 LD), and technical failure (1 LD). The glomerular filtration rate of functioning kidneys did not differ between the groups (Table 3).

Metabolic control

In the Comb group, three pancreatic grafts were lost, one due to the patient's death, one due to early graft thrombosis, and one following rejection. Nine patients were independent of exogenous insulin at follow-up, but only two had HbA_{1c} values within the normal range (3.7%–5.1%). The mean HbA_{1c} values at the last evaluation of all patients alive in each group are presented in Table 3 and show much lower values for patients in the Comb group ($P < 0.001$). Figure 1 illustrates individual data and shows an overlap between the groups, even when those Comb patients who lost their pancreas grafts were excluded.

Major vascular complications

Ten major vascular events occurred during follow-up and three of them were lethal. The only case in the LD group was one below-knee amputation; the other 9 were equally distributed between the Comb and the CD groups (Table 4).

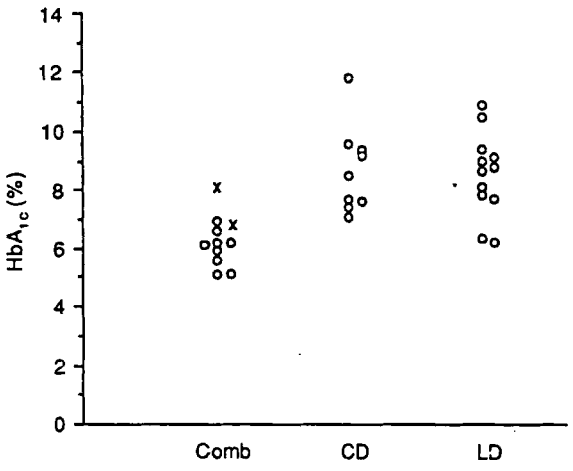

Fig. 1. Degree of metabolic control, measured as HbA_{1c}, in surviving diabetic recipients of combined pancreas and kidney grafts *(Comb)*, cadaveric kidneys (*CD;* one missing value), and kidneys from living donors *(LD)*. x Pancreas graft lost

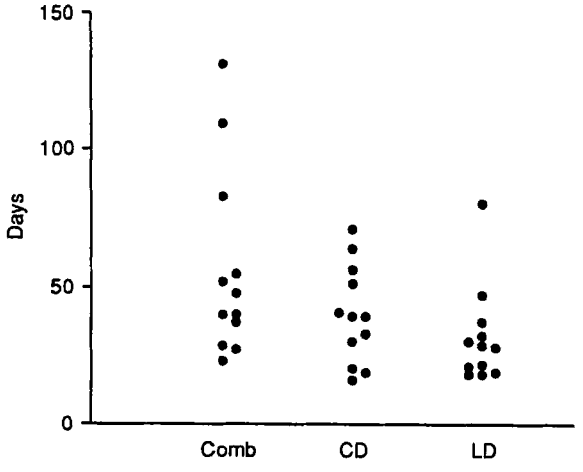

Fig. 2. Time (days) spent in hospital during the first 6 months after transplantation by recipients of combined kidney and pancreas grafts *(Comb)*, diabetic recipients of *CD* and diabetic recipients of kidneys from *LD*

Hospitalization

Time spent in the hospital during the first 6 months post-transplantation varied widely within each group (Fig. 2). The mean value was significantly higher for the Comb group than for the LD group ($P < 0.05$; Table 4). This was due both to vascular complications and to technical complications related to the pancreas transplantation.

Working capacity

Rehabilitation was related to patient and graft survival. Only five patients in the CD group worked 20 h per week or more versus 8 and 7 in the Comb and LD groups.

Discussion

Beneficial effects of successful pancreatic transplantation on late complications have now been reported in terms of improved microcirculation [2] and reduced signs of neuropathy [12]. In addition, the automatic regulation of blood glucose levels permits a more relaxed lifestyle with regard to physical exercise and diet, without the threat of hypoglycemic events. Patients in the Comb group had significantly lower HbA_{1c} values than patients in either kidney transplant group. Although some CD and LD patients managed to reach near normoglycemia, severe hypoglycemic symptoms sometimes occurred. The degree of metabolic control in the Comb group is superior.

The price for this better control was a prolonged hospital stay, sometimes as a result of technical complications related to the pancreas grafting but also for patients with an uncomplicated course. Compared with nondiabetic renal transplant recipients, the average hospital stay was, however, prolonged for patients in all three groups, mainly due to major vascular complications.

Comparing patient survival and kidney graft survival between the groups, recipients of cadaveric kidney grafts alone tended to have a poorer outcome than either recipients of combined pancreas and kidney grafts or recipients of living donor kidneys. The same finding has been reported from Oslo [3] and Munich [1]. The differences in those studies may have been an effect of patient selection, however, because high-risk patients have sometimes been excluded from combined transplantation. In our series, such patients were excluded before the matching procedure. The poorer outcome for patients subjected to the lesser procedure is, therefore, surprising. A higher number of patients with severe visual impairment in the CD group might indicate more pronounced late complications, but all patients in each group had proliferative retinopathy, and it is questionable whether the extent to which this caused visual impairment reflects vascular complications in general. The degree of nephropathy probably reflects microangiopathy in a more direct way and all patients were uremic. Macrovascular events before transplantation were equally distributed among the three groups.

If the prerequisites were the same for patients in the Comb and CD groups at the time the patients made their choice, it did, however, differ afterwards. Comb patients were granted a shorter waiting time, younger donors, a shorter cold ischemia time, and prophylactic treatment with ATG. This appears to reduce the number of rejection episodes and to improve kidney graft survival, at least in recipients of combined pancreatic and kidney grafts [9].

Table 4. Major vascular complications and rehabilitation after transplantation in the three groups of diabetic patients, recipients of combined pancreas and kidney grafts (Comb), recipients of CD, and recipients of kidneys from LD

	Comb ($n = 12$)	CD ($n = 12$)	LD ($n = 12$)
Myocardial infarction	1 (lethal)	3 (1 lethal)	0
Stroke	1	1 (lethal)	0
Amputation	2	1	1
Time in hospital (days)	56 ± 34*	40 ± 18	32 ± 18
Working ≥ half-time	8/12	5/12	7/12

* $P < 0.05$ vs LD

Whether these differences explain the better outcome in the Comb group is not clear. Alternatively, it has been suggested that the functioning pancreatic graft, by way of an unknown mechanism, might cause better patient survival [3].

From a practical standpoint, it may be concluded that, with the existing protocols, abstaining from a pancreas transplant and limiting the procedure to a cadaveric renal transplant does not reduce the short-term risks. Our policy, as described initially, has thus been changed.

Uremic diabetic patients with potential living related donors have a different risk/benefit pattern to consider when choosing between this option and the combined transplantation of grafts from cadaveric donors. The waiting time, patient survival, and kidney graft survival are the same with both options, but the time spent in the hospital is much shorter for LDs and less immunosuppressive therapy is required. In addition, there are data suggesting that long-term kidney graft survival will be better with the better matching obtained with living related donors [15]. Furthermore, if the indications for pancreas transplantation remain strong after successful LD kidney transplantation, a cadaveric pancreas may then be transplanted. Pancreatic graft survival is lower in that case [14]. However, three patients in our LD group later underwent pancreas transplantation. Two retained their first pancreatic grafts and the third has been successfully retransplanted. As a rule, we therefore still recommend the acceptance of living related donor kidneys, when offered.

Regardless of the mode of treatment, the clinical course is highly unpredictable in the individual case. Before choosing, the patients must therefore be thoroughly informed about the risks and options, as far as they are known.

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