Prevention of Kidney Graft Diabetic Nephropathy by Pancreas Transplantation in Man

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SUMMARY

Kidney graft biopsies were performed 2–3 yr after transplantation in eight type I (insulin-dependent) diabetic patients who had previously been subjected to kidney transplantation (six patients) or combined kidney and segmental pancreas transplantation (two patients). In five of the six patients that had undergone only kidney transplantation, light microscopic examination of the graft biopsy revealed changes compatible with diabetic nephropathy, and electron microscopic morphometry showed a thickening of the glomerular basement membrane (GBM). In the two patients who had been subjected to combined pancreas and kidney transplantation, the kidney graft biopsy showed no light microscopic changes suggestive of diabetic nephropathy, and electron microscopy showed no thickening of the GBM. Thus, it appears to be possible to prevent the recurrence of diabetic nephropathy in human kidney allografts by simultaneous pancreas transplantation. DIABETES 1985; 34:306–308.

Pancreas transplantation for the cure of type I (insulin-dependent) diabetes is now being performed with increasing frequency and, according to the International Pancreas and Islet Transplant Registry, there are now more than 150 diabetic patients worldwide carrying pancreas grafts (August 1984). After successful transplantation, the patients become insulin independent and display normal glucose homeostasis, as reflected in glucose tolerance tests and measurements of glycosylated hemoglobin (HbA_1). However, to make the patient insulin independent is not, in itself, the purpose of the procedure, since the patient must instead take immunosuppressive drugs. The purpose of pancreas transplantation is to accomplish a regulation of glucose levels sufficiently good to avert the severe vascular complications of the disease. Whether such a beneficial effect does, in fact, occur has not been ascertained so far. We report here that two diabetic patients carrying well-functioning pancreas and kidney grafts showed no signs of recurrent diabetic nephropathy in their kidney graft, as determined at biopsy 2–3 yr after transplantation. Six diabetic patients who had carried only kidney transplants were similarly studied and all but one of their grafts were found to have signs of diabetic nephropathy, as observed by light and/or electron microscopy.

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MATERIAL AND METHODS

Eight type I diabetic patients were included in the study. Two patients had undergone combined kidney and segmental pancreas transplantation,[1] and six had been subjected to kidney transplantation only. The patients' characteristics are given in Table 1. Two to three years after transplantation, a percutaneous kidney graft biopsy was performed under local anesthesia, using a needle 2 mm in diameter (Tru-cut, Travenol, Deerfield, Illinois). The biopsy material was immediately cut into two pieces, one for light microscopy and the other for electron microscopy. The tissue for light microscopy was fixed in 4% buffered formalin, embedded in paraffin, and cut and stained according to standard techniques. With light microscopy the following lesions were blindly and semiquantitatively evaluated: nodular glomerulosclerosis, diffuse glomerulosclerosis, and hyaline arteriolosclerosis. The severity of each lesion was ranked from 0 to 3. The sum of these figures is referred to as the "diabetic nephropathy score."[2] The tissue for electron microscopy was embedded in LX 112 (Ladd Research Industries, Burlington, Vermont). The first nonsclerosed glomerulus found by light microscopy in each of two tissue blocks was cut for electron microscopy. Ten electron micrographs of each glomerulus were taken systematically, and the harmonic mean basement thickness was determined in the glo-

TABLE 1
Donor and recipient data, diabetic nephropathy score, and GBM thickness in kidney transplant biopsies performed in diabetic patients subjected to kidney transplantation only, or combined kidney and pancreas transplantation

Type of transplantation	Donor age/sex	Patient age/sex	Duration of diabetes (yr)	No. of mo. between transplantation and biopsy	HbA_1 at time of biopsy (reference value <8.5)	Diabetic nephropathy score (0–9)	GBM thickness	
							Transplanted kidney	Reference value*
Kidney only	59/M	41/F	20	24	16.4	1	409	343
Kidney only	33/M	31/F	27	27	11.1	0	309	387
Kidney only	50/F	30/M	16	30	13.1	3	466	315
Kidney only	44/F	37/F	21	30	9.4	2	519	326
Kidney only	48/M	44/M	30	30	13.1	1	545	374
Kidney only	60/M	31/M	27	36	12.7	4	462	339
Combined kidney and pancreas	39/M	25/M	19	25	7.7	0	291	386
Combined kidney and pancreas	14/F	40/M	29	28	5.3	0	324	297

*Individual reference values have been calculated with attention to donor age and sex, as suggested by Steffes et al.[6] Østerby reported the GBM thickness to be 306 ± 27 in normal kidney.[5]

merular capillaries.[3,4] About 200 measurements of the glomerular basement membrane (GBM) were used to calculate the mean membrane thickness for each patient.

At the time of study the patients received immunosuppressive therapy consisting of either azathioprine (1–3 mg/kg body wt/day) or cyclosporin (3–6 mg/kg body wt/day) in combination with prednisolone (10 mg/day). At the time of biopsy, all the patients had a stable kidney graft function without clinical, laboratory, or histologic signs of acute or chronic rejection.

RESULTS

As could be expected, the HbA_1 level was above normal in all six diabetic patients that had undergone kidney transplantation only (Table 1). Light microscopic examination of the kidney graft biopsies revealed slight or moderate changes compatible with diabetic nephropathy in five of the six patients (Table 1). In the same five patients electron microscopic morphometry showed a thickening of the GBM compared with the values found in normal subjects by Østerby[5] and by Steffes et al.[6] In the two patients that had undergone combined pancreas and kidney transplantation, the kidney graft biopsy material showed no light microscopic changes suggestive of diabetic nephropathy and the electron microscopic measurements revealed no thickening of the GBM (Table 1).

DISCUSSION

Despite the fact that there are now close to 500 patients that have undergone pancreas transplantation, it has not been shown whether this treatment influences the progress of diabetic macroangiopathy or microangiopathy. One reason for this is that the number of patients who have carried a pancreas graft for any length of time is still small. Furthermore, most of the patients have had severe diabetic vascular changes at the time of transplantation, changes that could perhaps be halted in the progress but not reversed.

In rodent experiments, it has been shown by several investigators that when pancreas grafts are given immediately after induction of diabetes, the glomerular lesions typical of the disease do not occur. If the transplantation is carried out soon after the induction of diabetes, some of the pathologic changes that have developed can indeed be reversed. Similar results have been obtained whether the euglycemia had been achieved by vascularized pancreas transplantation or by islet transplantation.[7–11]

We, as well as others, have found clear-cut, morphologic signs of diabetic nephropathy in the kidney graft of diabetic patients as early as 2 yr after the transplantation.[2,12] The use of combined kidney and pancreas transplantation in diabetic patients creates a unique opportunity to assess whether pancreas transplantation can prevent the development of the diabetic kidney lesions. Although this article is based on only a few patients and the period of observation is still relatively short, the observation that there were no light or electron microscopic signs of diabetic nephropathy in the kidney grafts of the patients that had received concomitant pancreas grafts indicates that pancreas transplantation may indeed prevent secondary diabetic lesions in man.

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