Rehabilitation and Effect on Secondary Complications

Effects of Pancreas Transplantation on Kidney-Allograft Glomerular Structure in Type I Diabetes

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Kidney-allograft biopsies were obtained before and at least 2 yr after successful pancreas transplantation in 9 insulin-dependent (type I) diabetic patients. Baseline biopsies showed mesangial volumes within normal limits and only minimal glomerular basement membrane (GBM) thickening. At follow-up, no significant changes were detectable in mean glomerular volume (1.28 ± 0.20 vs. 1.36 ± 0.30 × 10^6 μm^3), mesangial volume per glomerulus (0.20 ± 0.08 vs. 0.25 ± 0.10 × 10^6 μm^3), filtration surface per glomerulus (0.15 ± 0.04 vs. 0.16 ± 0.04 × 10^6 μm^2), and GBM width (440 ± 58 vs. 493 ± 123 nm). The rate of change of GBM thickening decreased in 3 of 4 patients in whom biopsies were performed at the time of kidney transplantation. The pancreas-transplant recipients had significantly less mesangial expansion (0.24 ± 0.10 vs. 0.55 ± 0.21 × 10^6 μm^3; $P < .01$) than a group of 11 diabetic patients matched for age of onset of diabetes, duration of diabetes before kidney transplant, and survival of the kidney allograft. Pancreas transplantation for >2 yr is associated with significantly less severe glomerulopathy in kidneys transplanted to diabetic patients. These data support the hypothesis that glycemic correction can prevent the development of nephropathy in kidney allografts in humans.

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Diabetic Retinopathy After Pancreas Transplantation for Type I Diabetes Mellitus

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We studied the effect of successful pancreas transplantation and consequent normoglycemia (mean total hemoglobin A_1 7.0%, range 5.8–8.3%) on visual function and diabetic retinopathy in 22 patients with type I (insulin-dependent) diabetes mellitus (study group). The control group consisted of 16 similar patients in whom pancreas transplantation was unsuccessful (mean total hemoglobin A_1 12.0%, range 8.0–18.0%). The majority of patients in both groups had advanced proliferative retinopathy. After a mean follow-up of 24 mo, we found no significant difference in the rate of progression of retinopathy score between the groups. Successful pancreas transplantation did not prevent progression of retinopathy across the range of retinopathy studied. Progressive retinopathy was observed more commonly in patients with low retinopathy scores (nonproliferative and mild proliferative retinopathy) at baseline in both the study group (13 of 17 eyes of 76%) and the control group (7 of 12 eyes or 58%). Further analysis suggested the possibility of less deterioration in the study group after 3 yr of euglycemia, particularly in eyes with advanced retinopathy. There was no difference in the rate of visual loss between the groups. This study provides evidence that normalization of blood glucose by pancreas transplantation neither reverses nor prevents the progression of diabetic retinopathy.

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Skin Microvascular Regulatory Responses in Diabetic Patients After Combined Kidney-Pancreas Transplantation

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The regulatory responses in the skin mircocirculation of fingers have been shown to be impaired in type I (insulin-dependent) diabetic patients compared with matched controls. It is also known that the blood glucose levels are closely related to the development and progression of microangiopathy in diabetic patients. A physiologic approach

to treatment of diabetes and maintenance of normoglycemia is pancreas transplantation. The aim of this study was to investigate whether there is any difference in skin microvascular reactivity between diabetic patients with vascular complications who had undergone combined kidney and segmental-pancreas transplantation (CKPT) compared with those waiting for transplantation and those with kidney transplantation (KT) only. Five groups were investigated: group 1 (n = 19, 29–44 yr old): long-standing diabetes, severe microangiopathy, CKPT 9 mo earlier, normalized blood glucose levels; group 2 (n = 20, 28–44 yr old): similar to patients in group 1 waiting for transplantation; group 3 (n = 7, 27–45 yr old): similar to patients in group 1 but had undergone KT 10 mo earlier; group 4 (n = 14, 20–47 yr old): diabetes duration <3 yr, no clinical signs of structural microangiopathy; group 5 (n = 19): healthy control subjects age- and sex-matched to group 1. Blood cell velocity in single capillaries (CBV) of the fingernail fold was evaluated by video photometric capillaroscopy. The total skin microcirculation immediately adjacent to the investigated capillary was evaluated by laser Doppler fluxmetry (LDF). The following variables were studied: CBV and LDF at rest and after arterial (200 mmHg, 60 s) and venous (50 mmHg, 30 s) occlusion performed with a miniature cuff at the base of the finger. Resting CBV was decreased in all groups ($P < .01$) except group 4 compared with the control group (1, 0.22 ± 0.16; 2, 0.18 ± 0.13; 3, 0.15 ± 0.14; 4, 0.28 ± 0.18; 5, 0.46 ± 0.35 mm/s). The peak CBV after arterial occlusion was decreased in all groups ($P < .05$) compared with the control group (1, 0.57 ± 0.30; 2, 0.48 ± 0.26; 3, 0.41 ± 0.23; 4, 0.56 ± 0.33; 5, 0.93 ± 0.45 mm/s). The time to peak CBV after arterial occlusion was significantly ($P < .05$ and $P < .01$) prolonged in groups 1 and 2 compared with the control group (1, 9.3 ± 2.5; 2, 10.4 ± 4.0; 3, 9.4 ± 2.3; 4, 8.8 ± 3.9; 5, 7.3 ± 3.0 s). During venous stasis, LDF decreased less ($P < .001$, .05) in groups 2, 3, and 4 but not in group 1 compared with the control group. No significant differences were found between the groups. This study shows a tendency to better regulatory responses of the skin microcirculation in diabetic patients who have undergone CKPT. However, the microvascular reactivity was still significantly impaired compared with healthy control subjects. The finding that patients who had isolated KT showed a marked impairment of the skin microcirculation may indicate that the pancreas transplantation per se and not the improved kidney function is responsible for the tendency toward better microvascular reactivity. To more properly investigate the effect of pancreas transplantation, we have started a prospective study on diabetic patients waiting for a pancreas graft.

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Long-Term Effects of Successful Pancreas-Allograft Transplantation

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Between June 1979 and November 1987, 26 pancreas transplants were performed on 22 patients (4 received 2 transplants). Twenty were uremic type I (insulin-dependent) diabetic patients, and the other two were type I diabetic patients without renal failure. There were 14 men and 8 women (aged 29–50 yr, avg 33 yr). In this group, 6 pancreas grafts are currently functional (from 4 to 76 mo). Long-term (>12-mo) graft survival occurred in 5 patients treated with the following surgical techniques: *1*) Segmental neoprene-injected grafts (total of 6); 1 is functional 72 mo posttransplantation. *2*) Grafts drained to the ureter (total of 9); 2 are functional at 65 mo (segmental) and 50 mo (whole organ). *3*) Enteric drainage (total of 1); 1 is functional at 34 mo. *4*) Whole organ drained to the bladder (total of 10); 1 is functional at 21 mo. Immunosuppression consisted of azathioprine and prednisone in 2 patients and cyclosporin, azathioprine, and prednisone in 3 patients. Normalization of glucose homeostasis by transplantation was achieved in 5 long-term recipients. These patients had been diabetic for an average of 21 yr before transplantation. In this group, the following observations were made: *1*) Glucose homeostasis: completely insulin free since time of transplantation. Serum C-peptide (normal 0.3 pmol/ml) 0.67–2.4 pmol/ml, mean 1.36 ± 0.21. Hemoglobin A_{1c} (normal 6–8%) pretransplant mean 11.04 ± 0.91; posttransplant mean 6.56 ± 0.17%. *2*) Diabetic retinopathy: 5 patients with functional pancreas grafts had complete ophthalmologic evaluations before transplantation and follow-up. Progression of the retinopathy occurred in all patients after pancreas transplantation. The nonuremic patient who originally exhibited only background diabetic retinopathy developed proliferative diabetic retinopathy despite achieving a euglycemic state for 3 yr. *3*) Macrovascular disease: serial evaluation of macrovascular disease by noninvasive hemodynamic parameters showed deterioration in 1 patient at 40 mo posttransplantaton. In the remaining patients there were no major hemodynamic changes. *4*) Peripheral neuropathy: stabilization of chronic neuropathy was documented by electrophysiological studies in the 4 uremic transplant recipients. Slight improvement was noted in the nonuremic recipient. Interestingly, this patient developed proliferative retinopathy. *5*) Nephropathy: acute rejection occurred in 1 and chronic rejection in 2 of 4 synchronously transplanted kidneys. A patient who lost a synchronously transplanted kidney underwent a second successful kidney transplant. One kidney in this group has normal function 72 mo posttransplantation, with no evidence of diabetic nephropathy on biopsy. Recipients of pancreas grafts can achieve a euglycemic state for up to 6 yr posttransplantation. Rejection rather than recurrent disease is a major threat to synchronously transplanted kid-

neys. In relation to systemic manifestations, we could not demonstrate significant improvement in either micro- or macrovascular disease. It appears from our limited study that pancreas transplantation neither protects nor improves diabetic retinopathy once microvascular changes have occurred. Early transplantation before systemic involvement may prevent development of some of the serious complications of diabetes mellitus.

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Improved Functional Status of Patients After Successful Pancreas Transplantation

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A patient survey and review of records were performed for 20 recipients of successful pancreas transplants. Sixteen patients received simultaneous kidney-pancreas transplants, and 4 patients received postrenal pancreas transplants. Patients were initially surveyed after at least 6 mo of satisfactory graft function and were surveyed 12 mo later for a total follow-up period of at least 18 mo. The initial survey showed that 18 of 20 patients (90%) had visual problems due to diabetic retinopathy before transplant; after 6 mo, 8 of 18 (44%) noted subjective visual improvement or stabilization; 12 of 18 noted improvement or stabilization after another 12 mo. Sixteen of 20 (80%) had symptoms of gastroenteropathy before transplant, and 15 of 16 (94%) improved or stablilized after 6 mo; 15 of 16 continued to show improvement or stabilization after another 12 mo. Thirteen of 20 (65%) had symptoms of neuropathy before transplant, and 13 of 13 (100%) improved or remained stable at 6 mo; 11 of 13 remained improved or stabilized after another 12 mo. Eighteen of 20 (90%) had pretransplant symptoms of fatigue and depression, and 16 of 18 (89%) were improved or stabilized after 6 mo; 12 of the 16 had improvement or stabilization after another 12 mo. All 20 patients stated that they were pleased with the transplant and would do it again. During the additional 12-mo follow-up period, 2 patients (10%) had pancreatic graft loss, with 1 death (5%). One patient had chronic rejection of the kidney and pancreas and died from a myocardial infarct after resuming dialysis. One patient had rejection of the pancreas with continued function of the kidney. Additionally, 3 patients had rejection of the kidney with continued function of the pancreas, 1 of whom rejected a second kidney and later received a successful third kidney transplant. Four patients had minor amputations, and another 5 patients required hospitalization during the 12-mo period. There was no mortality in patients with functioning pancreas transplants during the 18-mo study. All patients reported stabilization or subjective improvement of one or more functional aspects reviewed in the survey.

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Pancreas and Kidney Transplantation in Diabetic Patients: Effects on Metabolic Control and Degenerative Complications

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Twelve simultaneous kidney-pancreas transplantations were performed in uremic insulin-dependent diabetes mellitus patients (38 ± 7 yr old, duration of diabetes 24.8 ± 5 yr, duration of dialysis 20 ± 12 mo). The surgical approach was according to the segmental neoprene-injected technique, as previously described by Dubernard. Patients received steroids (1 mg · kg^{-1} · day^{-1}, tapered). Antilymphocyte globulin was administered during the first 10 postoperative days and was substituted by cyclosporin (9 mg · kg^{-1} · day^{-1}, tapered) when the function was stable. Intravenous heparin was administered during the first 10 postoperative days to prevent pancreatic thrombosis and was substituted in the following period by oral acenocoumarin. All patients but one are currently alive and were followed up for 6–33 mo. One patient died of myocardial infarction with a functioning pancreas. In two cases a venous thrombosis led to pancreas-graft failure. Eight patients are insulin independent, and only one receives 10 U/day insulin but with high C-peptide values. Metabolic investigations showed a good insulin peak (62 ± 11 μU/ml) after intravenous glucose (0.5 g/kg). An oral glucose tolerance test showed a normal glucose tolerance in four patients and an impaired tolerance in four patients. HbA_{1c} levels and a 24-h metabolic profile for blood glucose and free insulin showed a good metabolic control in all patients. A 120-min euglycemic-hyperinsulinemic insulin clamp (1 mU · kg^{-1} · min^{-1})

combined with indirect calorimetry showed total-body glucose uptake (M value) to be lower in transplanted patients than in control subjects (4.2 ± 0.3 vs. 7.8 ± 0.5 mg · kg^{-1} · min^{-1}) but higher than in nontransplanted uremic diabetic patients (1.9 ± 0.2 mg · kg^{-1} · min^{-1}), indicating a reduced insulin resistance, despite chronic immunosuppressive therapy. Long-term degenerative complications were followed up through regular assessment of funduscopy, fluorescein angiography, nerve conduction velocity (EMG), and autonomic neuropathy tests. EMG evolution showed an amelioration of nerve conduction velocity in all examined patients. In particular, an amelioration of nerve conduction velocity was observed in six of eight patients for the sural nerve, six of eight for the peroneal, seven of eight for the proximal median, and eight of eight for the distal median. In conclusion, pancreas transplantation restores glucose moneostasis in uremic diabetic patients and can reverse long-term degenerative complications of diabetes.

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Diabetic Retinopathy in Patients Submitted to Successful Kidney-Pancreas Allotransplantation

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The interrelationship between metabolic control and diabetic retinopathy was the object of several investigations without definite conclusions. Pancreas transplantation in diabetic patients represents the ideal model to investigate this aspect, because it can lead to normal glucose homeostasis in these patients. The aim of our survey was to study the effects on diabetic retinopathy (DR) of good metabolic control after kidney-pancreas allotransplantation. Nine insulin-dependent diabetes mellitus patients submitted to segmental neoprene-injected pancreas allotransplantation underwent complete ophthalmological examination and retinal fluorescein angiography before surgical intervention. The data collected showed DR in 13 eyes already panphotocoagulated, evolved neovascular glaucoma in 2 eyes, and secondary retinal detachment in the remaining 2 eyes. In 1 case the presence of vitreous hemorrhage did not allow completion of the panphotocoagulative treatment. Visual acuity ranged from L.P. to 10/10. Immunosuppressive therapy was based on antilymphocyte globulin, azathioprine, steroids, and cyclosporin. All patients achieved complete insulin independence within a few weeks from surgery. A good metabolic control was achieved in all patients, as demonstrated by normal HbA_{1c} levels. Metabolic investigation showed a good function of the transplanted pancreas: serum free-insulin levels after an oral glucose tolerance test reached a peak (40.7 ± 11.5 μU/ml) at 60 min. A good insulin release was observed after an intravenous glucose tolerance test. The assessment of clinical and fluorescein angiographic data did not evidence any significant difference between the data collected before and after transplantation (follow-up 5–32 mo). The only case showing a significant improvement of visual acuity was the patient with vitreous hemorrhage, which did not allow completion of panretinal photocoagulation before intervention. After surgery the endovitreous hemorrhage was absorbed, and visual acuity increased to 3.5/10, thus allowing completion of panphotocoagulative treatment. Patients submitted to pancreas and kidney transplantation are generally affected by end-stage degenerative diabetic complications, particularly microangiopathy; thus, the possibility to reverse retinal lesions is extremely limited. These preliminary results indicate that DR does not deteriorate in patients receiving a pancreas transplantation.

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