Transplantation for diabetic nephropathy at Groote Schuur Hospital

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Abstract **Over a period of 6 years, 9 patients with diabetic nephropathy received renal allografts at Groote Schuur Hospital. This low figure represents 2,8% of the total number of renal transplants done at our institution, and is evidence of concern about the apparent poor results of transplantation in these patients. After 2 years, patients and graft survival rates in diabetics were 87% and 62% respectively. Vascular disease was a major problem. Six patients developed limb gangrene, and symptomatic coronary and cerebrovascular disease developed in 2 patients. Infections were common and included wound sepsis, cellulitis, candidiasis and urinary tract infections. Diabetes was poorly controlled after transplantation in 5 patients. Proliferative retinopathy was present in 6 patients but remained stable after transplantation.**

Despite very strict selection criteria, the results of renal transplantation in diabetic patients remain poor. Better treatment strategies are needed to justify acceptance of these patients for transplantation.

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Diabetic nephropathy is a major cause of renal failure world-wide and about 35% of type I diabetics develop this complication.[1] Care of the diabetic patient with end-stage renal disease (ESRD) presents a difficult problem because of the multisystem nature of the disease.[2] Management options include maintenance haemodialysis, continuous ambulatory peritoneal dialysis (CAPD) and renal transplantation. Early transplantation, before dialysis is needed, is generally considered to be the therapy of choice.[3] Improved survival and better rehabilitation of recipients and organs from living-related donors have been described over the past decade.[4] We examined the clinical course of patients who underwent transplantation for diabetic nephropathy at Groote Schuur Hospital over a 6-year period.

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Patients and methods

The records of all patients who had undergone renal transplantation for diabetic nephropathy at Groote Schuur Hospital from January 1985 to December 1990 were examined. All patients received standard immunosuppression after transplantation. Cyclosporin A 4 - 5 mg/kg was started intra-operatively and administered intravenously over 24 hours. Oral cyclosporin 10 mg/kg in two divided doses was commenced on the first postoperative day. The dose of cyclosporin was adjusted according to the whole blood levels and a trough level of 400 - 600 ng/ml was aimed for. Methylprednisolone 250 mg was given intravenously on day 1 after operation and 125 mg was given on day 2. A daily dose of oral prednisolone 24 mg was started as soon as the patient started taking food by mouth. Azathioprine was started at a dose of 1 mg/kg; adjustments in dosage were made according to changes in the white cell count. Rejection episodes were treated with daily bolus doses of methylprednisolone 500 mg, given intravenously on 3 successive days. When indicated, a second course of 3 bolus doses was given. Triple immunosuppressive therapy was given for 3 months after which cyclosporin was discontinued. Ophthalmological assessment of all patients was undertaken before and after transplantation.

Results

During the study period, only 9 patients received renal transplants for end-stage renal failure due to diabetic nephropathy (2,8% of total number of transplants performed). All were on dialysis at the time of transplanta-

tion (Table I). There were 6 men, and all but 1 of the patients had insulin-dependent diabetes mellitus (IDDM, type I). Histological evidence of diabetic nephrosclerosis was present in 1 patient. Mean age at transplantation was 37,6 years (range 30 - 46 years).

TABLE I.
Patients transplanted for diabetic nephropathy (*N* = 9)

Sex (M:F)	6:3
Race (C:W:B)	5:3:1
Diabetes	
IDDM	8
NIDDM	1
Age at transplant (yrs)	37,6 (± 5,81)
Interval to dialysis (yrs)	17,0 (± 8,76)
Time on dialysis (mo.)	10,2
Graft	CD 8
	LD 1
Daily medrol dose (mg)	
Start	22,6 (± 3,88)
Clinic	14,0 (± 5,41)
Total pulse medrol dose (mg)	
Start	2 300
Clinic	700

Duration of known diabetes before transplantation ranged from 6 to 30 years (mean 18,6 years). As shown in Fig. 1, there was an inverse relationship between age of onset of IDDM and interval to renal failure. The mean duration of dialysis before transplantation was 10,2 months. Eight patients received cadaver grafts and 1 patient received a graft from a living related donor. Rejection with return to dialysis occurred in 3 patients (acutely in 2), and all received a second cadaver graft. One patient lost his second graft because of chronic rejection. He was transferred to peritoneal dialysis, but died from severe limb gangrene and sepsis a few months later. At the end of the study, 8 patients were alive with a functioning graft (2-year patient and graft survival rates were 87,5% and 62,5% respectively). This compared with 2-year patient and graft survival rates of 83,8% and 57,9% in non-diabetics transplanted over the same period.

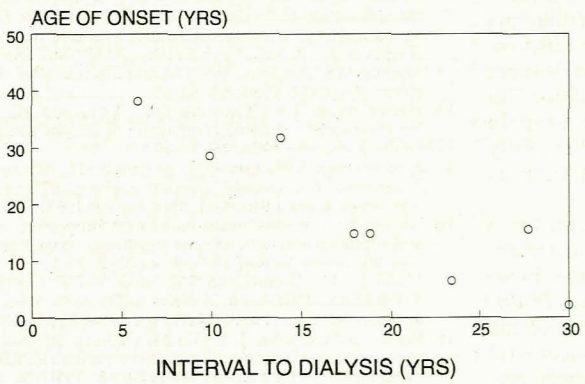

FIG. 1.
Age of onset of IDDM and interval to dialysis.

The mean daily dose of prednisolone (±SD) in the immediate post-transplantation period was 22,6 ± 3,88 mg, and this was eventually reduced to 14 ± 5,41 mg after discontinuation of cyclosporin (Table I). In addition, patients received an average total intravenous pulse methylprednisolone dose of 2 300 mg during the early post-transplantation period, and an average dose of 700 mg later. Glycaemic control after transplantation deteriorated in 6 patients, requiring increased insulin dosage.

Vascular and infective complications occurred most commonly (Table II). Hypertension was present in all patients before transplantation, and was uncontrolled in 1. Two patients developed symptomatic coronary artery disease — 1 suffered a non-fatal myocardial infarction soon after transplantation and the other developed angina with trifascicular block seen on an electrocardiogram. Neither had had stress testing or coronary angiography before transplantation. Two patients had evidence of symptomatic cerebrovascular disease. One had a transient neurological deficit suggestive of a transient ischaemic attack and the other had multiple cerebral infarcts causing major disability. Six patients developed limb gangrene — 3 of these had amputations; 1 patient was judged to be inoperable and subsequently died. Infective complications were very common (Fig. 2). Three patients developed tuberculosis before transplantation. The commonest infections post transplantation were wound sepsis, cellulitis, candidiasis and urinary tract infections. One patient developed severe pyonephrosis, requiring a nephrectomy; another 2 developed an opportunistic pneumonia, presumably bacterial. The infecting organisms were most commonly Gram-negative bacilli, Gram-positive cocci and candida.

TABLE II.
Complications after transplantation

Vascular*	
Symptomatic coronary artery disease	2
Cerebrovascular disease	2
Limb gangrene	6
Infective†	
Wound sepsis, cellulitis	8
Pneumonia	2
Urinary tract infection	2
Pyonephrosis	1
Candidiasis (local)	2
Septicaemia	1
Surgical	
Ureteric obstruction	1
Other	
Poor diabetic control	6
Duodenal ulcer	1
Demyelinating neuropathy	1
Worsening congenital ptosis	1
Cataract	1
Death	
Gangrene, sepsis	1

* All patients were hypertensive before transplantation.
† Three patients developed pulmonary tuberculosis before transplantation.

Proliferative diabetic retinopathy was present in 6 patients before transplantation and all received laser therapy. Two of these patients experienced vitreous haemorrhage and one required a vitrectomy. After transplantation 5 patients had stable 'burnt-out' retinopathy as assessed by an ophthalmologist; data are not available for 1 patient. Three patients had mild nonproliferative diabetic retinopathy before transplantation. In 2 patients the retinopathy has remained stable, while 1 patient developed disc vascularisation that required laser therapy.

Discussion

Patients with diabetic nephropathy comprised only 2,8% of those who underwent transplantation at Groote Schuur Hospital. This contrasts with approximately 20% in the USA and 11% in Europe,[5] and is evidence of concern about the apparent poor results of transplan-

tation in these patients. Despite strict criteria and a tendency to select younger, healthier patients with type I diabetes, the morbidity rate was distressingly high, particularly in respect of vascular and infective complications. Quality of life was not specifically examined in this study, and its quantification is fraught with error.[6] However, most patients spent much time in hospital as a result of their complications. Furthermore, rehabilitation was poor. Although only a small number of patients was examined in this study, patient and graft survival in diabetics was similar to that of other transplant groups at this centre. Problems were related to progressive extrarenal manifestations of diabetes not influenced by transplantation, especially vascular disease. Particularly distressing was the high rate of limb amputations, which has also been noted in other series.[7] Retinopathy, however, remained stable. The inverse relationship between age of onset of IDDM and interval to renal failure noted by previous investigators[8] was confirmed, and may affect co-morbid conditions such as hypertension.

Despite favourable reports elsewhere[9] there is still concern about transplantation in diabetic patients in the face of limited resources. Although a transplant from a living relative is the treatment of choice there is also some concern about future risk to the HLA-identical donor. Siblings with identical HLA subtypes (e.g. HLA-DQB1) may be at risk of developing subsequent diabetes themselves.[10]

How can results be improved? Very strict selection criteria should be applied. Potential candidates should routinely be referred to a cardiologist for stress testing and cardiac catheterisation, when indicated, before transplantation.[11] Surgically correctable coronary lesions should be attended to at this time. Similarly, evidence of peripheral vascular disease should be actively sought and bypass surgery performed where feasible. Patients with inoperable vascular disease should not be accepted for transplantation. Concomitant risk factors for vascular disease such as hypertension, dyslipidaemia and smoking should be managed aggressively.[12] Strict glycaemic control probably has little benefit at this stage and may cause dangerous hypoglycaemia in diabetic patients nearing ESRD. Early transplantation (i.e. before dialysis) may be beneficial. After transplantation, steroid-induced metabolic derangements and cyclosporin-related hypertension and hypercholesterolaemia may further aggravate vascular disease and predisposition to infection.[13] The smallest acceptable dose of these agents should be used. Results of transplantation in patients with NIDDM may well be better than in IDDM patients, even though patients are generally older and have concurrent medical diseases such as hypertension and obesity.

Other treatment options include maintenance haemodialysis or continuous ambulatory peritoneal dialysis (CAPD). Results of transplantation are, however, not strictly comparable with these because of different selection criteria.[14,15] Although the quality of life on haemodialysis is not as good as after a successful transplant, the recent use of recombinant human erythropoietin in dialysis patients has been associated with improved cognitive function as judged by neuropsychiatric testing, as well as improvements in physical tolerance and sexual potency.[16] Vascular access, hypotension and infections remain major problems and mortality from cardiovascular disease is high. CAPD avoids the episodic, rapid shifts of water and salt, and allows for 'physiological' administration of insulin.[17] Major disadvantages are the increased risk of obesity and infections such as peritonitis and catheter tunnel infections.[18]

The care of diabetic patients with ESRD remains problematic and costly. Better treatment strategies aimed at preventing ongoing diabetic complications, especially progressive vascular disease, are essential to justify acceptance of these patients for transplantation, particularly in countries where resources are limited. In this regard new drugs such as aldose reductase inhibitors may be of benefit.[19]

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