

# Renal replacement treatment for diabetic nephropathy in Northern Ireland 1979-1987

A P Maxwell, J F Douglas, C C Doherty, W E Nelson,  
R A Donaldson, Mary G McGeown

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## SUMMARY

*Twenty-three patients with end-stage renal failure due to diabetic nephropathy received renal replacement treatment. All patients had insulin-dependent diabetes mellitus. Nineteen transplants were performed in seventeen patients. Two-year graft survival for all transplants was 74% with a two-year patient survival post-transplantation of 81%. Overall two-year patient survival was 73%, compared with 82% in non-diabetic patients receiving renal replacement treatment. In diabetic patients accepted for treatment there was a high incidence of non-renal complications, particularly vascular disease. An aggressive approach to the treatment of vascular disease in these patients may improve overall survival rates.*

## INTRODUCTION

The diagnosis of diabetic nephropathy in an individual diabetic patient is usually presumed in the presence of proteinuria and impaired renal function in association with diabetic retinopathy. Hypertension is almost invariably present at some stage and common histological features are diffuse and nodular glomerulosclerosis. The nephropathy may be compounded by other diabetic renal complications such as atheromatous renovascular disease, pyelonephritis, papillary necrosis and neurogenic bladder.

The prevalence of diabetic nephropathy increases with the duration of diabetes to a peak of around 20% after 20–25 years.<sup>1</sup> After 25 years the annual incidence declines, indicating that the development of nephropathy is not solely dependent on the duration of diabetes.<sup>2</sup> Renal failure secondary to diabetic nephropathy was responsible for over one quarter of the deaths in one study<sup>3</sup> of patients in whom insulin-dependent diabetes mellitus was diagnosed before 31 years of age. This and other similar studies<sup>4, 5</sup> emphasised the need for more liberal extension of renal replacement programmes to diabetic uraemic patients. The proportion of new patients with end-stage renal failure due to diabetes mellitus referred for renal replacement treatment is rising in Northern Ireland. To date, all patients have had insulin-dependent (type 1) diabetes mellitus. In the United Kingdom

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Renal Unit, Belfast City Hospital, Belfast, Northern Ireland, BT9 7AB.

A P Maxwell, MB, BCh, MRCP, Registrar.

J F Douglas, MA, BCL, MB, BCh, FRCP, Consultant Nephrologist.

C C Doherty, MD, MRCP, Consultant Nephrologist.

W E Nelson, MD, MRCP, Consultant Nephrologist.

R A Donaldson, BSc, MB, BCh, FRCS, Consultant Urologist.

Mary G McGeown, CBE, DSc(Hon), MD, PhD, FRCP, FRCPEd, FRCPI, Consultant Nephrologist, Physician in Administrative Charge.

Correspondence to Dr Maxwell.

overall, the proportion of diabetics with end-stage renal failure accepted for treatment had risen to 11.1% in 1984,<sup>6</sup> a figure still well below those of 25% in the USA<sup>7</sup> (although more elderly non-insulin dependent diabetic patients are treated there) and over 15% in some European countries;<sup>6</sup> this may reflect a lower prevalence and/or under-referral of diabetic renal failure. In diabetic patients with end-stage renal failure who receive renal transplants, the outcome compares favourably with that of non-diabetic patients in some centres.<sup>8</sup> However, sub-groups of diabetic patients with severe vascular disease have shown a clear excess of graft failure and patient mortality.<sup>9</sup>

This paper outlines the experience of the Renal Unit at the Belfast City Hospital in treating diabetic nephropathy between April 1979 and May 1987.

## PATIENTS

Twenty-three patients (14 male, 9 female) were accepted for renal replacement treatment. Their ages ranged from 23 to 62 years (mean 37.3) at time of referral. Renal replacement treatment commenced at a mean age of 38.3 years. The duration of diabetes ranged from 8 to 38 years (mean 21.7). Assessment for renal replacement treatment was generally late in the progression of renal failure: the mean serum creatinine was 773  $\mu\text{mol/l}$  at referral, and mean creatinine clearance 10 ml/min. Twenty-one percent of patients were referred as an emergency with life-threatening illness including pulmonary oedema. Diabetic nephropathy was a presumptive clinical diagnosis in all patients based on the presence of diabetic retinopathy, heavy proteinuria and impaired renal function. Nephrectomy and post-mortem pathological evidence confirmed the presence of diabetic nephropathy with typical histological features of diffuse and nodular glomerulosclerosis, arteriosclerotic lesions and interstitial fibrosis in all five cases examined; atheromatous renovascular disease was present in addition in three of these cases.

TABLE

*Complications present at renal referral in 23 insulin-dependent diabetic patients*

	<i>Number</i>	
EYES		
Retinopathy	23	100%
Proliferative retinopathy requiring laser therapy	16	70%
Blindness	5	22%
CARDIOVASCULAR		
Abnormal ECG	18	78%
ECG criteria for myocardial infarction	7	30%
Hypertension (BP > 150/90)	22	96%
Angina	5	20%
CEREBROVASCULAR		
Previous stroke	2	9%
PERIPHERAL VASCULAR DISEASE		
Intermittent claudication/ischaemia	8	34%
Amputation	2	8%
PERIPHERAL NEUROPATHY	13	57%

There was a high prevalence of non-renal diabetic complications in patients at the time of referral (Table). Retinopathy was present in all and 70% had received laser photocoagulation for proliferative retinopathy; 22% were registered blind. Cardiovascular disease was common: ECG recordings were reviewed by one investigator (APM) — 78% had an abnormal ECG, and 30% had the electrocardiographic criteria for a previous myocardial infarction. Angina pectoris was present in 22%, and hypertension (BP >150/90) in 96%. The prevalence of cerebrovascular disease was lower, 9% having had a completed stroke while carotid bruits were heard in 9%. Evidence of peripheral neuropathy was found in 57% based on clinical symptoms and signs, and nerve conduction studies in 13% of these patients confirmed the clinical diagnosis. Peripheral vascular disease had produced considerable morbidity in 34% of patients, and above-knee amputations had been required in 8% (two cases). Three further patients had above-knee amputations shortly after commencing renal replacement treatment.

### RENAL REPLACEMENT THERAPY

The mean age for commencing treatment was 38 years. Dialysis therapy was started in 60% of patients for refractory pulmonary oedema or hypertension, and in a further 30% for uraemic symptoms. Initial treatment was haemodialysis for the majority (61%), peritoneal dialysis in 30% and transplantation in 9%.

*Haemodialysis.* Fourteen patients initially started treatment with haemodialysis. Three patients had been commenced on intermittent peritoneal dialysis and were later changed to haemodialysis for reasons of infection and availability. Two patients changed from haemodialysis to chronic ambulatory peritoneal dialysis following assessment of chest pain. Both patients underwent coronary artery bypass grafting for multi-vessel coronary artery disease and were managed post-operatively by peritoneal dialysis. Vascular access has proved difficult in several patients.

*Intermittent peritoneal dialysis.* Five patients began intermittent peritoneal dialysis: one was subsequently transplanted, one was trained for chronic ambulatory peritoneal dialysis and three patients were transferred to haemodialysis.

*Chronic ambulatory peritoneal dialysis.* Two patients started this as their initial treatment and three are currently maintained on this mode of dialysis. Two of these patients manage the technique successfully despite being registered blind.

*Transplantation.* Nineteen renal transplants have been performed on 17 patients. Eighteen transplants were cadaver grafts, and one patient received a graft from a living related donor which never functioned because of intra-operative hypotension. The mean duration of dialysis pre-transplant was 9.9 months. Thirteen patients survive (11 with functioning grafts and two having returned to dialysis). Two-year graft survival is 74% including one operative death and two cases of primary non-function due to graft artery thrombosis. Comparable results in this unit for two-year graft survival in non-diabetics was 81%, and two-year patient survival 82%.

Operative problems encountered included atheromatous pelvic vessels in five recipients, in one case necessitating formal revascularisation at the time of transplant. Wound infections occurred in 38% post-operatively. Early transplant rejection (within three months) occurred in 10 grafts and required treatment with

high dose oral prednisolone. In three cases plasma exchange was included in the management of rejection. Eight of the 10 grafts continued to function. Diabetic transplant recipients were treated with a combination of low dose prednisolone (20 mg daily reduced in stages over 18 months to 10 mg daily) and azathioprine (3mg/kg).

*Mortality.* Seventeen of the 23 patients accepted for treatment survived to May 1987. Four transplant recipients died and post mortem examinations were obtained in three cases. One patient died from a combination of bacterial infection and transplant rejection; the other two suffered myocardial infarctions. The fourth transplant patient died suddenly at home after recent onset of atrial fibrillation, presumably also on the basis of ischaemic heart disease. The two deaths in non-transplanted patients occurred during haemodialysis, one from a myocardial infarction (confirmed by post-mortem examination revealing extensive triple vessel coronary artery disease which had been clinically silent), the other due to a cerebrovascular accident. Overall the two-year patient survival for all modalities of treatment during the period studied was 73.5%.

## DISCUSSION

In Northern Ireland the incidence of new cases of diabetic renal failure has been estimated at 7.6 cases/million/year, which is lower than in other UK regions reported.<sup>10</sup> The number of patients who have received treatment to date is less than the estimated number for a variety of reasons including limited resources and under-referral. The absence of older patients with non-insulin-dependent diabetes mellitus in our treatment group probably represents under-referral of such patients because of perceived bias towards treatment of younger patients with end-stage renal failure — a policy initially reflecting medical opinion<sup>11</sup> but latterly reflecting constraints on the expansion of the renal failure service. From 1979 the rate of referral of patients with diabetic nephropathy to the Renal Unit has been rising, and many insulin-dependent and non-insulin-dependent diabetic patients will reach the renal replacement programme this year. In view of the expected increase in the number of diabetic patients for assessment we have reviewed our preliminary experience in treatment of end-stage diabetic nephropathy.

The diabetic patients reported in this paper represent 7.3% of the total number of new patients accepted for renal replacement therapy in Northern Ireland between 1979 and 1987. However, over the last two years (June 1985 to May 1987), diabetic patients accounted for 12% of the total treated, indicating that increasing numbers of diabetic patients are receiving renal replacement therapy. Some diabetic patients who were referred in the period reported were not treated for reasons of advanced age, dependency and overwhelming medical complications. These criteria were equally applied to non-diabetic patients referred for assessment and reflect earlier restrictions on the provision of care for patients with renal failure. The number of diabetic patients with renal impairment in Northern Ireland is unknown as the recent survey<sup>10</sup> only selected for study diabetics with advanced renal failure (serum creatinine > 500  $\mu\text{mol/l}$  and urea > 25 mmol/l). Most of the patients reported here were referred at a late stage of their renal disease and required renal replacement, on average, within a year. Pulmonary oedema and hypertension were the main indications for starting treatment. A high incidence of non-renal diabetic complications was evident which posed many management problems. While vascular disease did not prove a contraindication to renal replacement treatment, our experience suggests that an aggressive approach to

this frequently co-existing problem is essential. Myocardial infarction was implicated in 50% of the deaths in diabetic patients in the period reported. Significant ischaemic heart disease may be present<sup>12</sup> without symptoms, often declaring itself only after treatment for end-stage renal failure has commenced. Two patients with multi-vessel coronary artery disease, which became symptomatic on haemodialysis treatment, underwent coronary artery bypass grafting procedures. These patients were managed post-operatively by peritoneal dialysis and later trained for continuous ambulatory peritoneal dialysis. Some centres have recommended coronary artery angiography as a routine pre-transplant screening procedure in diabetic uraemic patients<sup>13</sup> and others have reported that diabetic patients with significant coronary artery disease had a worse prognosis for all modalities of treatment but a trend to better survival following transplantation.<sup>14</sup> In those patients with significant peripheral vascular disease transplantation may worsen lower limb ischaemia by a 'vascular steal' phenomenon resulting in amputation in some cases shortly after a transplant procedure. Rimmer and colleagues<sup>9</sup> found higher mortality and graft loss following transplantation in patients with pre-existing atherosclerotic vascular disease and concluded this should influence the choice between therapeutic alternatives in diabetics with end-stage renal failure. Revascularisation procedures might favourably alter the survival characteristics of this group following transplantation. The vascular disease may lead to difficulty with vascular access.<sup>11</sup> Other problems encountered include autonomic neuropathy (urinary retention, hypotension), gastrointestinal symptoms and a wasting syndrome.<sup>15</sup> The two-year graft survival of 74% and two year patient survival of 81% post transplantation must in this series be interpreted with caution in view of the relatively small numbers of patients involved and the relatively short period of follow-up. Diabetic transplant recipients were treated with conventional immunosuppressive therapy (azathioprine and low dose prednisolone) and it is still our policy to reserve cyclosporin therapy for patients (diabetic or non-diabetic) who are intolerant of azathioprine.

The treatment of diabetic patients with end-stage renal failure by dialysis<sup>16, 17</sup> and transplantation<sup>8</sup> improves patient survival. The cost of renal replacement treatment for diabetic patients is higher than that for non-diabetic patients, one estimate suggesting transplantation is one-third more expensive.<sup>18</sup> New patients with end-stage renal failure due to diabetic nephropathy are now forming an increasing proportion of the numbers accepted for treatment in the United Kingdom,<sup>6</sup> and concern has been expressed that many patients who could benefit from treatment are probably not receiving it.<sup>19, 20</sup> The survey of diabetic renal failure for 1985 conducted by the Joint Working Party of the Renal Association, the British Diabetic Association and the Royal College of Physicians concluded that up to 40% of patients suitable for treatment were not receiving it.<sup>10</sup>

While prevention of diabetic nephropathy remains the ultimate goal, current aims are earlier referral and joint management of the patient by nephrologists and diabetologists, with stricter blood pressure<sup>21, 22, 23</sup> and metabolic control<sup>24</sup> attempting to reduce the rate of progression of diabetic nephropathy. End-stage renal failure in diabetic uraemic patients can be managed successfully with a combination of dialysis and transplantation. Vascular disease, whilst an important factor determining eventual outcome, has not proved a contraindication to treatment. The quality of life for the individual must also be considered in choosing between therapeutic alternatives in renal replacement treatment for diabetic patients.

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*Royal Victoria Hospital*

## FRIENDS OF THE ROYAL

The formation of a 'Friends of the Royal' group is currently under way. In order to explain the aims and object of the Friends and elect a Committee, an inaugural meeting is being held at 3.30 pm on Wednesday, 15 June, 1988 in Bostock House Ballroom, RVH. It is hoped that this organisation will promote the work of the Royal through the Ladies Committee, Working Mens Committee and Ex-Patients Guild and will in addition take on other projects to assist the Hospital. Anyone interested in our endeavours is welcome at this meeting. We look forward to your support and ideas.

*Ingrid Allen*