Occasional Survey

Renal transplantation in diabetic nephropathy

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Abstract

Forty diabetics who had developed end-stage renal failure from diabetic nephropathy and underwent renal transplantation have been followed up from one to six years. After one and two years 63% and 42% survived (45% and 33% respectively with functioning kidneys). Older patients, those with coronary and peripheral vascular disease, and those with severe neuropathy are prone to higher postoperative morbidity and mortality. The presence of advanced retinopathy, on the other hand, does not appear to influence the outcome.

Introduction

Diabetic nephropathy is a common complication of long-term diabetes, especially when diagnosed in those under 30 years of age.¹ Renal failure from nephropathy is the cause of death in about one-fifth of these diabetics, and is a cause of morbidity in many more dying from other disorders, chiefly cardiovascular disease^{2,3} (A Moloney *et al*, unpublished observation). In the United States it has been predicted that during the 1980s renal failure from diabetes will become the fourth commonest source of new patients on dialysis.⁴

End-stage renal failure in diabetics is complicated by the many sequelae of long-term diabetes affecting the eyes, arteries, and

peripheral nerves, and some patients are incapacitated by these problems. Many centres have therefore been reluctant to undertake renal transplantation in diabetics especially where resources have been limited. Since 1966, however, patients with diabetic nephropathy attending the University of Minnesota have been accepted into the transplant programme, and this centre has now the world's greatest experience in treating this disease. The results, although less satisfactory than in non-diabetics, have been very encouraging.⁵⁻¹¹

Patients

Between January 1974 and December 1980, 44 renal transplants were performed in 40 diabetics with end-stage renal failure from diabetic nephropathy, and these have been followed up from 12 months to six years. Diabetics with other forms of renal disease received transplants during the same period but are not considered in this study. Patients with diabetic nephropathy were defined as those in whom proteinuria had been present for several years (known minimum two years), renal failure was gradual in its development (more than one year), and in whom retinopathy was also present. Biopsies were not routinely performed.

There were 33 men and seven women. The mean age at diagnosis of diabetes was 15.2 years (range 2 to 48 years) and duration of diabetes 22.8 years (range 10 to 43 years) at the time of transplantation. Their mean age at transplantation was 38 (range 24-61); 13 were over 40 (fig 1). Thirty-five were insulin-dependent diabetics who had taken insulin since the onset of their diabetes; there were five non-insulin-dependent diabetics, who were generally older at diagnosis of diabetes (mean 40 years) and at transplantation (mean 53 years).

DIABETIC AND VASCULAR COMPLICATIONS

Retinopathy

All the patients had diabetic retinopathy, and 33 had proliferative changes. Nine patients were blind and a further five saw only 6/60 in the better eye. Twenty-one patients had received photocoagulation before transplantation.

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FIG 1—Age distribution at transplantation of 40 patients with diabetic nephropathy. White columns show survivors, black columns show those who have died.

Hypertension

Hypertension was often present, with diastolic pressure persistently greater than 95 mm Hg in 35 cases and greater than 100 mm Hg in 17. Twenty-four had been treated with hypotensive drugs before transplantation. After transplantation fewer required hypotensive treatment (seven of 27 survivors at six months), although of six patients surviving with functioning grafts for more than three years, five developed hypertension and once again needed treatment. Three patients required bilateral nephrectomy to control hypertension.

Vascular disease

Coronary artery disease is common in end-stage nephropathy: 15 of 28 electrocardiographs showed definite ischaemic changes, five minimal changes—that is, T-wave inversion in lead aVL only—and only eight were entirely normal. Two had had myocardial infarcts before transplantation; one of these died soon after transplantation from heart disease and one has survived over 18 months. Eight of the 20 deaths after transplantation were from ischaemic heart disease.

Peripheral vascular disease was also common. Eight of 35 patients examined had ischaemia in one or both legs—that is, no pulses in one or both feet: after transplantation two of these eight patients lost three legs from gangrene, one developed gangrene of two fingers, one gangrene of both hands (he also lost both legs), and one developed a foot ulcer. Of 27 patients in whom one or both pulses were palpable in both feet, none needed amputations and two developed neuropathic foot ulcers.

Medial arterial calcification is usual in patients with advanced diabetic nephropathy: of 33 foot radiographs, calcification was present in 27 and was sometimes extensive in both hands and feet (fig 2).

FIG 2—Medial arterial calcification in a 31-year-old man with end-stage renal failure from diabetic nephropathy.

Neuropathy

Ankle jerks were present in only five cases, but absent in all the others, signifying peripheral neuropathy in this predominantly young group of patients. The clinical severity of neuropathy before transplantation ranged considerably from those with no signs or symptoms of neuropathy to very severe sensory neuropathy with ulceration of feet (2), heels (1), and toe amputation (1). Autonomic symptoms were also present and included postural giddiness (10) and commonly gustatory sweating (21).¹²

SELECTION OF DONOR

Live related donors were the source of eight kidneys, and 36 were from cadavers, four of which were used for second grafts. There was a negative lymphocytotoxic cross-match in all cases. Tissue typing was undertaken but matching was not used as a criterion in donor-recipient selection. During the seven-year period various immunosuppressive regimens were used, all based on steroids and azathioprine. Antilymphocytic globulin (Pressimmune) was used in some cases. Episodes of acute rejection were all treated intravenously with methylprednisolone daily for three days. Chronic rejection was treated with an increased dose of oral steroids.

Only half the patients received regular dialysis for more than one month before transplantation. Three patients underwent bilateral nephrectomy at the same time as transplantation.

MANAGEMENT OF DIABETES

At transplantation

Continuous intravenous insulin infusion is always used, using soluble insulin diluted in physiological saline at a concentration of one unit per millilitre. Infusion rates vary considerably, usually in the range 2 to 20 units an hour; during treatment with high doses of steroid the higher infusion rates are often needed.

Intravenous insulin infusion is continued until drips have been taken down and the patient is able to eat. Soluble insulin is then given subcutaneously three times daily before meals, with an optional fourth dose at midnight if required. The daily dose is started about 20% above the pretransplant dose, and adjustments thereafter are made by trial and error.

Once reasonable stability has been achieved, twice daily insulin is resumed, usually with a mixture of short- and medium-acting insulins.

During haemodialysis

During haemodialysis at any stage before or after transplantation the normal insulin regimen is maintained. If there is any tendency towards hypoglycaemia glucose is added to the dialysate at a concentration of 11.1 mmol/l (200 mg/100 ml).

During peritoneal dialysis with solutions of low glucose content (usually 1.36% glucose) no adjustment to the normal insulin regimen is needed. Solutions of high glucose content, however, severely disrupt diabetes: in these circumstances normal daily subcutaneous insulin is continued and soluble insulin added to every bag containing 4.5 or 6.36% glucose at a rate of about 20 or 30 units/litre respectively.

Rejection

High doses of steroids always upset diabetics within 12 hours. We anticipate this problem by increasing the first insulin dose given after administration of steroids. We increase the soluble component by about 20%, but the exact amount varies greatly.

If severe hyperglycaemia develops at any stage (and it often does) this may be quickly rectified either by intravenous insulin infusion or hourly intramuscular insulin (roughly four units an hour) given for a few hours as a supplement to the normal subcutaneous insulin until a satisfactory blood glucose concentration (under 10 mmol/l) is restored.

Results

Table I shows the outcome of the 40 patients receiving primary renal transplants. After one and two years 63% and 42% respectively were alive, 45% and 33% with functioning kidneys. Of the eight who

received live related transplants, four are well and working after three to six years, one with a functioning kidney died suddenly after two and a half years, two are on haemodialysis, and one died on haemodialysis 15 months after his second transplant.

Successful operations were more likely to be achieved in younger patients (table II). Eleven of 24 patients transplanted under 40 years are alive with functioning kidneys after a mean of 25 months, while only three of 16 patients aged over 40 were alive after two years.

Table III shows the causes of the 20 deaths. Sepsis (8 cases) and cardiovascular disease (8) were the commonest. Four deaths occurred within one month of transplantation, eight within three months, and eight after this period. Eight patients died with functioning kidneys, and in the 12 others the graft had already failed.

TABLE I—Survivors of 40 diabetic renal transplants

	1 year	2 years	3 years	4 years	5 years	6 years
Total No of survivors	25/40	10/24	6/19	3/12	1/10	1/9
With functioning kidney	63%	42%	32%	25%	10%	11%
	18/40	8/24	5/19	3/12	1/10	1/9
	45%	33%	26%	25%	10%	11%

TABLE II—Age and survival after transplantation in diabetics

Age (years)	No	Deaths	Survivors with functioning kidneys	Survivors without functioning kidneys
< 40	24	10	11	3
≥ 40	16	10	3	3

TABLE III—Causes of death (20 cases)

Sepsis	8
Pseudomembranous colitis	2
Pneumonia	4
Urinary tract	1
Unknown source	1
Ischaemic heart disease	8
Pulmonary embolism	1
Haemorrhagic gastritis	1
Vessel haemorrhage	1
Gangrene	1

Four patients have received second transplants; three had received the first transplant from a cadaver donor and one from a live related donor. All four died between three days and 15 months after retransplantation; of the three surviving more than a few days, only one still had a functioning kidney at death.

REHABILITATION

The quality of rehabilitation is often satisfactory in long-term survivors. Of 20 patients alive up to a maximum of six years, 13 were working, two were active at home (both blind), and five were inactive with chronic foot ulceration (one), bilateral amputation (one), and poor general health in the oldest patients to receive transplants.

Discussion

Renal transplantation as a treatment of end-stage renal failure from diabetic nephropathy has been reported since the beginning of the last decade. Patient survival, frequency of complications, and degree of rehabilitation for diabetic recipients have been inferior to those for non-diabetics yet the results are encouraging. Just under half our patients are alive after two years, one-third with satisfactory renal function. These results are similar to those of others overall¹¹ although less satisfactory than the outcome in Minneapolis.⁶ Age and severity of diabetic complications in our relatively unselected patients may to some extent have influenced our results adversely. Transplants in older diabetics are pro-

gressively less successful, with a decrease in survival over 40 and 50 years of age, while survival of those aged under 30 is similar to those of non-diabetics. The outcome is better after transplantation of kidneys from live related donors, which formed only a minority of our own series. The sex of the patients should not affect the outcome: the heavy bias towards men in our series is unexpected and presumably reflects a bias of referral, since nephropathy is only slightly commoner in men than women.¹³

Several unfavourable features influence both survival and morbidity after transplantation. One of the most serious is the presence of cardiovascular disease. This is common in long-term diabetics, probably almost universally present if sought by coronary angiography.¹⁴ Myocardial infarcts after transplantation are much commoner in diabetics than non-diabetics, and altogether cardiovascular disease accounts for about one-third or more of the deaths.⁶ Cardiomegaly and cardiac failure were such ominous features in the major Scandinavian study that they were considered to be a contraindication to transplantation.⁸ Minor electrocardiographic changes alone, however, serve as a relatively poor guide to prognosis, at least in the short term.

The presence of peripheral vascular disease is also serious. In addition to atheroma, medial calcification is usually present as well. Arterial disease leads to difficulties in obtaining adequate access for haemodialysis.¹⁵ Amputations are needed with distressing frequency, and were reported in 17% of 373 patients from Minneapolis,¹⁶ patients often losing one or sometimes both legs. Gangrene of fingers also occurred in one of our patients even in the absence of fistula insertion in the same arm, and this too was not uncommon in the patients in Minneapolis. Duration of survival among amputees appears to be shorter than among non-amputees.¹⁶

Peripheral neuropathy is usually present in advanced diabetic nephropathy and autonomic neuropathy frequently so. Its severity varies considerably, however. Neuropathic ulceration of the feet increases postoperative morbidity and sepsis. Neuropathic patients are prone to develop ulceration of the heels, and this serious complication must be prevented by raising the heels during the whole postoperative period while the patient is in bed. The presence of a neurogenic bladder with a large residual urine volume, though uncommon, is ominous because of the grave risk of postoperative infection, which may jeopardise the whole operation. Careful preoperative assessment by cystometrography is needed. Postural hypotension can be an added hazard. Transplantation has little effect on diabetic neuropathy with only slight improvement in sensory responses¹⁷; any motor weakness present may improve postoperatively.

Retinopathy, usually proliferative, is a constant feature of end-stage diabetic renal disease, and about one-quarter of patients are blind.¹⁸ Although blind patients are obviously handicapped in managing dialysis procedures, the results of transplantation do not seem to be adversely affected, and blindness alone is not a contraindication to surgery. Retinopathy may accelerate during the year or two before transplantation,¹⁷ and it has been suggested that its progression is to some extent reduced after transplantation compared with its course during haemodialysis.¹⁸ Retinopathy must be constantly reviewed during all forms of treatment for renal failure, and photocoagulation given whenever appropriate.

The right time for transplantation in patients with diabetic nephropathy requires careful consideration. They should be assessed when serum creatinine concentration is roughly 500 $\mu\text{mol/l}$. At this time they are usually unwell, anaemic, and experiencing problems of fluid retention with peripheral and pulmonary oedema. Decline of renal function is inexorable, and the linear plot obtained by charting inverse of creatinine against time provides a useful indicator of prognosis.¹⁹ Patients are likely to need treatment within a few months after a serum creatinine concentration of 500 $\mu\text{mol/l}$, and in those selected for transplantation it may be advantageous to undertake this when the creatinine is 700–800 $\mu\text{mol/l}$, before they are seriously ill and before the need for dialysis arises. It must be accepted that some

diabetics are so overwhelmed by complications of their disease that only conservative treatment should be offered.

Although examination of the glomeruli and arterioles of kidneys transplanted into diabetics shows changes that appear to be characteristic of diabetes,^{20, 21} these may take many years to evolve, and no cases of renal failure from these abnormalities have yet been described. There is a real challenge in treating end-stage diabetic renal failure. The results are sufficiently rewarding to encourage further efforts in this field.

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References

- Deckert T, Poulsen JE, Larsen M. Prognosis of diabetics with diabetes onset before the age of thirty one. *Diabetologia* 1978;14:363-70.
- Marks HH. Longevity and mortality of diabetics. *Am J Public Health* 1965; 55:416-23.
- Tunbridge WMG. Deaths in diabetics under 50 years of age. *Lancet* 1981; ii:569-72.
- Rao TKS, Hirsch S, Arram MM, Friedman EA. Prevalence of diabetic nephropathy in Brooklyn. In: Friedman EA, L'Esperance FA, eds. *Diabetic renal-retinal syndrome*. New York: Grune and Stratton, 1980: 205-7.
- Goetz FC, Kjellstrand CM. The treatment of diabetic kidney disease. *Diabetologia* 1979;17:267-81.
- Najarian J, Sutherland D, Simmons R, et al. Ten year experience with renal transplantation in juvenile onset diabetics. *Ann Surg* 1979;190: 487-500.
- Sutherland DER, Fryd DS, Simmons RL, et al. Long-term diabetic renal transplants. In: Friedman EA, L'Esperance FA, eds. *Diabetic renal-retinal syndrome*. New York: Grune and Stratton, 1980:353-71.
- Joint Scandinavian Report. Renal transplantation in insulin-dependent diabetics. *Lancet* 1978;iii:915-7.
- Mitchell JC. End stage renal failure in juvenile diabetes mellitus: a 5 year follow-up of treatment. *Mayo Clin Proc* 1977;52:281-8.
- Zincke H, Woods JE, Palumbo PJ, Leary FJ, Johnson WJ. Renal transplantation in patients with insulin-dependent diabetes mellitus. *JAMA* 1977;237:1101-3.
- Kjellstrand CM, Goetz FC, Najarian JS. Transplantation and dialysis in diabetic patients: an update. In: Friedman EA, L'Esperance FA, eds. *Diabetic renal-retinal syndrome*. New York: Grune and Stratton, 1980: 345-51.
- Watkins PJ. Facial sweating after food: a new sign of diabetic autonomic neuropathy. *Br Med J* 1973;i:583-7.
- Andersen AR, Andersen JK, Christiansen JS, Deckert T. Prognosis for juvenile diabetics with nephropathy and failing renal function. *Acta Med Scand* 1978;203:131-4.
- Bennett WM, Norman DJ, Barry JM. Coronary artery disease in end-stage diabetic nephropathy. In: Friedman EA, L'Esperance FA, eds. *Diabetic renal-retinal syndrome*. New York: Grune and Stratton, 1980:219-27.
- Butt KMH, Ortega-Gaytan M, Shirani K, et al. Angioaccess in uremic diabetics. In: Friedman EA, L'Esperance FA, eds. *Diabetic renal-retinal syndrome*. New York: Grune and Stratton, 1980:209-18.
- Peters C, Sutherland DER, Simmons RL, Fryd DS, Najarian JS. Patient and graft survival in amputated versus nonamputated diabetic primary renal allograft recipients. *Transplantation* 1981;32:498-503.
- Barbosa J, Burke B, Buselmeier TJ, et al. Neuropathy, retinopathy and biopsy findings in transplanted kidney in diabetic patients. *Kidney Int* 1974;6, suppl 1:532-6.
- Ramsay RC, Cantrill HL, Kinyoun JL, et al. Visual status in diabetic renal failure. In: Friedman EA, L'Esperance FA, eds. *Diabetic renal-retinal syndrome*. New York: Grune and Stratton, 1980:309-15.
- Jones RH, Mackay JD, Hayakawa H, Parsons V, Watkins PJ. Progression of diabetic nephropathy. *Lancet* 1979;ii:1105-7.
- Mauer SM, Barbosa J, Vernier RL, et al. Development of diabetic vascular lesions in normal kidneys transplanted into patients with diabetes mellitus. *N Engl J Med* 1976;295:916-20.
- Mauer SM, Miller K, Goetz FC, et al. Immunopathology of renal extra-cellular membranes in kidneys transplanted into patients with diabetes mellitus. *Diabetes* 1976;25:709-12.

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Is a normally athletic man of 50 with arthritis in one hip and early arthritis in the other who wishes to continue playing tennis and squash a suitable candidate for arthroplasty?

A man of 50 with arthritis, but otherwise normally active, is not a candidate for total hip replacement. The problem with all the traditional implants is that they are worn out rapidly by heavy use and to undertake such a procedure to enable a person to continue his athletic achievements would be foolhardy. If he had sufficient pain to warrant such a procedure all vigorous sporting activity would have to stop. If a 50-year-old man had multiple joint disease or pain disturbing sleep and pain preventing work then he would be considered for such a procedure. In an active man an osteotomy of the proximal femur may relieve his symptoms, and if it did sporting activity could be resumed. These procedures, however, bring relief of symptoms in only about 70% of patients. If they fail, a total hip replacement can be undertaken later.—C R D LIGHTOWLER, consultant orthopaedic surgeon, London.

Most families use "hand hot" or "hot" water for washing their clothes either by hand or in a machine. It is presumed that hot water has some pasteurising effect. Cold-water washing powders are being or are going to be introduced. Is there any evidence that the detergents used in cold-wash powders have a disinfectant effect similar to those used in hot water?

The effect of all domestic washing procedures is primarily mechanical. This cleans and removes much infected material and bacterial cells but cannot be relied on to sterilise. This is particularly so for hand washing with "hand hot" water of uncertain temperatures. Machines incorporating heated cycles do disinfect, provided an appropriate temperature is maintained for a sufficient period. The temperatures stipulated for soiled and for fouled and infected linen in hospital laundries are 65°C for 10 minutes or 71°C for three minutes.¹ In many domestic machines with numbered cycles, however, the exact temperature is not known to the owner, and it is important to note that extra time is required for warming up and mixing the contents. Four minutes has been suggested for small machines and eight minutes for large ones,² but again in domestic machines this may be beyond the control of the operator. Absence of appropriate temperature for the

stipulated time or total absence of a heated cycle would inevitably result in failure of disinfection in those cases in the home where this is essential, notably for the washing of nappies if disposables are not used. For this purpose some machines incorporate a nappy cycle with a temperature in excess of 90°C. Otherwise boiling for at least three minutes is required. Detergents have a totally unpredictable antibacterial effect. In hospital practice where necessary they would be combined with a compatible disinfectant, but heat treatment would always be preferred. Domestic machines using cold-water cycles with cold-wash powders will not sterilise, though prolonged washing will greatly reduce bacterial numbers. A final sterilising stage occurs when linen is ironed but this is open to recontamination on storage, though with largely benign organisms. The old recommendation that in an emergency the inner folded surface of freshly laundered and pressed material may be used as a dressing is reasonably sound.—J H DARRELL, reader in clinical bacteriology, London.

¹ Kelsey VC, Wagg RE. The disinfection of textiles in laundering in hospitals. *British Launderers Research Association Bulletin* 1969;9:231-9.

² Maurer IM. *The best method of disinfection in hospital hygiene*. London: Edward Arnold, 1978.

What is the statistical chance of a couple having a diabetic child when the father developed the disease before he was 40?

Diabetes mellitus is genetically heterogeneous. The diabetes in the patient is probably to the insulin-dependent "juvenile type," and if so the risk to children of developing diabetes is probably about 4%.^{1, 2} This estimate is confirmed, by recent work with HLA typing, for the parents and haploidentical siblings of patients.³ If the diabetes is of non-insulin-dependent "maturity onset" type the risk is probably higher, about 10% for children, but is then likely to be of later onset and less serious.—C O CARTER, professor of clinical genetics, London.

¹ Simpson NE. Diabetes in the families of diabetics. *Can Med Assoc J* 1968;98: 427-32.

² Harper PS. *Practical genetic counselling*. Bristol: John Wright, 1981.

³ Gorsuch AN, Spencer KM, Lister J, Wolf E, Bottazzo GF, Cudworth AG. Can future type 1 diabetes be predicted? A study in families of affected children. *Diabetes* (in press).