Treatment of renal failure from diabetic nephropathy with cadaveric homograft

Claude Beaudry, M.D., F.R.C.P.[C] and Louis Laplante, M.D., *Montreal*

Summary: We report two patients with terminal renal failure secondary to diabetic nephropathy treated with cadaveric kidney transplantation. Neither of these patients had peripheral vascular disease or peripheral neuropathy. There was a proliferative diabetic retinopathy with hemorrhages and exudates in one patient and only background diabetic changes in the ocular fundi of the other; there have been no significant changes in visual acuity or retinopathy in either patient following the transplantation. Both have good kidney function after 8 and 15 months and are completely rehabilitated.

The requirement for insulin decreased in both patients during the period of renal insufficiency and increased following transplantation; this seemed to be related to the large dose of steroids given because now that a maintenance level of steroids has been established, both patients require the same dosage of insulin as they did before the onset of renal insufficiency.

Chronic renal failure can be treated by either hemodialysis or kidney transplantation. The criteria used in selecting candidates for a kidney transplant can vary, but it is generally accepted that these patients must not be afflicted with systemic diseases, such as diabetes, amyloidosis or systemic lupus erythematosus.

In October 1970 a 31-year-old man with juvenile diabetes was referred because of terminal chronic renal failure. In spite of a diabetic retinopathy grade II/IV and because of the absence of peripheral vascular disease and peripheral neuropathy, it was decided to enter this patient in our cadaveric kidney transplant program and treat him with conservative measures in the meantime. In March 1971 he received a cadaver kidney transplant. Since then his condition has been excellent. His kidney function is good and rehabilitation is complete at 15 months. Since this experience seemed worth while another patient, aged 28, with juvenile diabetes and chronic renal failure without peripheral vascular disease was accepted on our kidney transplant program in November 1971. He received a cadaver kidney the next month. Eight months later his condition is also excellent.

In November 1971 at the meeting of the American Society of Nephrology in Washington, Comty and Shapiro[1] reported their results with chronic hemodialysis in 20 uremic diabetics. After one year the mortality rate was 37.5% and over the four years of the study it was 50%. The rehabilitation rate was disastrous. The survival rate was also far below what is seen with chronic renal failure in patients without diabetes. However, Simmons *et al*[2] reported at the same meeting their experience with 19 diabetic patients in chronic renal failure treated by cadaveric kidney transplants. Fourteen patients were doing very well after 6 to 30 months of follow-up. The rehabilitation rate was surprisingly high.

In view of the small number of studies of diabetic patients with chronic renal insufficiency, we report our experience with these two young patients who received cadaveric kidney transplants.

Case reports

Case 1

This 32-year-old man was known to have juvenile diabetes from the age of 19. In 1969 evident kidney involvement was associated with a serum creatinine of 3.2 mg./100 ml. and a proteinuria of 1.5 g. daily. A needle kidney biopsy showed diffuse and nodular glomerulosclerosis. Capsular drops were noted and afferent arterioles were hyalinized. Tubular atrophy was also present.

In October 1970 the serum creatinine was 8.3 mg./100 ml. The patient was complaining of nausea and vomiting. Because of the juvenile diabetes hemodialysis or kidney transplant was not considered at that time. For the next three months his condition continued to deteriorate. Because of the determination of the patient and his wife, and also because of the absence of peripheral vascular disease and peripheral neuropathy, we decided to put him on our cadaveric kidney transplant program and to complete his renal investigation. The cystoscopic examination and the voiding cystogram yielded normal findings. The urine culture was sterile. The 24-hour endogenous creatinine clearance was 5.7 ml./min., the urinary output approximately 1500 to 1800 ml./day and the 24-hour proteinuria about 4 to 5 g. Diabetic retinopathy was judged to be grade II/IV. The hemoglobin was 9.3 g. and hematocrit 29.5%. The barium meal showed a diminution of gastric motility confirmed by antral manometry and gastroscopy. The patient was receiving 42 units of lente insulin subcutaneously per day and alphamethyldopa 250 mg. twice a day.

He was given a cadaveric kidney transplant on March 11, 1971. The donor kidney was perfused with a solution of Ringer's lactate containing heparin and procaine at a pressure of 100 cm. of water. The two renal arteries from the donor were joined termino-laterally to the external iliac artery and the renal vein was joined in the same manner to the external iliac vein. The donor ureter was joined to the recipient's bladder by a neocystostomy. The warm ischemia time was five minutes and the cold ischemia time 200 minutes.

There was an immediate diuresis upon restoration of the renal circulation. During the first 16 hours the patient voided 5800 ml. He received prednisone 4 mg./kg./day and azathioprine 4 mg./kg./day. Nausea and vomiting ceased on the first postoperative day. The serum creatinine was 1.2 mg./100 ml. on the fourth postoperative day. On the seventh postoperative day the patient had a slight acute rejection episode characterized by nausea, a decrease in urinary output, fever and increased serum creatinine. The prednisone was increased

From the Department of Medicine, University of Montreal and the Service of Nephrology, Maisonneuve Hospital, Montreal, Quebec

Reprint requests to: Dr. Claude Beaudry, Maisonneuve Hospital, 5415, Blvd. l'Assomption, Montreal 410, P.Q.

from 120 mg. to 250 mg./day. In spite of these large amounts of steroids the diabetes proved to be fairly easy to control. The prednisone dosage was then progressively decreased until a maintenance dose of 15 mg./day was attained at six months post-transplantation. At that time the serum creatinine was 1 mg./100 ml. and the 24-hour endogenous creatinine clearance was 85 ml./min. There was no proteinuria. Even with continuous adjustment of the diet, the 24-hour glycosuria was averaging 60 g. and the glycemia 350 mg./100 ml.

At present, after 15 months, the patient is doing well. He was able to resume his normal work rapidly. His kidney function is good with a serum creatinine of 1.0 mg./100 ml. and a 24-hour endogenous creatinine clearance between 60 and 95 ml /min. Proteinuria is still absent and glycosuria has decreased to 35 g./24 hrs. with a glycemia averaging 200 mg./100 ml. He is receiving 80 units of lente insulin subcutaneously per day. He is also taking 20 mg. of prednisone every other day and 125 mg. of azathioprine daily. His blood pressure has been normal since the kidney transplantation without alphamethyldopa. The patient's own kidneys have not been removed.

The patient had been taking 80 units daily of lente insulin from 1960 until 1966. Then the dosage was gradually lowered until by January 1971 (two months before the kidney transplantation) the dosage was 40 units per day. It was increased to 110 units during the post-transplantation period and since that time has been gradually reduced to 80 units.

In December 1970 the visual acuity was 20/40 O.D. and 20/25 O.S. There were only background diabetic changes, i.e. no proliferative lesions. In May 1972 the visual acuity was 20/20 O.D. and 20/25 O.S., and the background changes, though still present, had not progressed.

Case 2

This 28-year-old man was known to have juvenile diabetes from the age of 12. He was admitted to Maisonneuve Hospital on November 8, 1971 in severe acidosis and with generalized edema. A few days earlier he had been discharged from another hospital where no treatment had been offered for his chronic renal failure owing to the diabetes. On admission the patient was very pale and had bilateral pleural effusions. The blood pressure was 170/110 mm. Hg. The serum creatinine was 20.6 mg./100 ml. A kidney biopsy done at the other hospital showed nodular and diffuse diabetic glomerulosclerosis, severe arteriolosclerosis and signs of probable chronic pyelonephritis. The hemoglobin was 6.2 g./100 ml. and the hematocrit 20%. Serum proteins were 5.4 g./100 ml. with 2.99 g. of albumin. Daily urinary output was averaging 1200 ml. with proteinuria of 4 g. Peritoneal dialysis proved very useful and the patient lost 19 pounds. He was accepted into the renal transplantation program and a complete investigation disclosed satisfactory findings. Results of cystoscopic examination, a voiding cystogram and a complete digestive tract investigation were normal. Specimens taken from multiple sites for bacteriological study (blood, urine, sputum) gave negative findings. Hemodialysis was performed on seven occasions during this hospitalization. No blood tranfusions were given.

On November 30, 1971 the patient received a cadaver kidney transplant. The warm ischemia time was one minute and the cold ischemia time was 94 minutes. The donor kidney was perfused with a solution of Ringer's lactate containing procaine and heparin, and was placed in the left iliac fossa. The renal artery was joined termino-terminally with the hypogastric artery and the renal vein termino-laterally with the external iliac vein. The ureter was joined to the bladder by a neocystostomy.

The immunosuppression treatment consisted of prednisone 4 mg./kg./day and azathioprine 4 mg./kg./day. In addition the patient received antilymphocyte globulin (ALS*) 20 mg /kg./day for 10 days through a central venous catheter. The immediate postoperative period was uneventful except for acute tubular necrosis. Only one additional hemodialysis was necessary, on the second day post-transplantation, after which adequate diuresis became evident. On the 24th day post-transplantation, the patient had a questionable acute rejection episode characterized only by a rise in serum creatinine of 0.2 mg./100 ml. This episode was easily controlled by an increase of prednisone from 60 to 100 mg. per day. Since then the patient has done very well. His kidney function is good at seven months post-transplantation, with a serum creatinine of 1.1 mg /100 ml. and a 24-hour endogenous creatinine clearance of 68 ml./min. He is taking presently a daily dose of 20 mg. of prednisone and 150 mg. of azathioprine. He is also receiving lente insulin subcutaneously, 60 units in the morning and 10 units in the evening. His blood pressure has remained moderately elevated since the kidney transplantation. The patient's own kidneys have not been removed. Proteinuria is absent and glycosuria is averaging 20 g./day; glycemia averages 200 mg./100 ml./day. Work has been resumed and rehabilitation is complete.

This patient was taking 60 to 70 units of lente insulin around the year 1964. Starting in 1969 the dosage was gradually reduced to 45 units by October 1971 when the patient was in terminal renal failure. In the post-transplantation period the dosage was increased to 100 units and then was gradually reduced to 70 units per day.

On admission to our hospital the patient was noted to have a proliferative diabetic retinopathy but he was not seen by the ophthalmologist. Four months after transplantation the visual acuity was 20/20 O.D. and 20/50 O.S. There were bilateral proliferative lesions limited to the retinal plane, and some exudative and hemorrhagic lesions. Photocoagulation with the xenon arc was done on the left eye on March 29, 1972 and on the right eye on May 31, 1972.

In July 1972 visual acuity was 20/20 O.D. and 20/60 O.S. The diabetic process was described as arrested.

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Discussion

The treatment of chronic renal failure secondary to diabetic nephropathy or associated with diabetes has been very disappointing until lately. Peritoneal dialysis or hemodialysis was available for only short periods. Chazan *et al*[3] describe their experience with 44 patients including five diabetic patients treated by chronic hemodialysis and report several complications, particularly hyperosmotic coma and increased requirement for insulin. Comty and Shapiro[1] have reported their experience with long-term hemodialysis in 20 nonselected diabetics. The incidence of complications is extremely high and includes fluid excess, difficulty in controlling the diabetes, gastrointestinal problems, blindness, orthostatic hypotension, infection, poor access to blood vessels, adrenal insufficiency, psychological and neurological problems and poor rehabilitation results. The survival rate of these patients compared to non-diabetic patients is very poor. They conclude that hemodialysis must be reserved for diabetics without such complications. Baskin, McNichol and Iledan[4]

suggested that home dialysis would be a fair alternative treatment.

The report of Simmons *et al*[8] suggests that the treatment of chronic renal failure secondary to diabetic nephropathy is much more satisfactory with kidney transplant. Among 19 patients who received such a transplant, 14 had normal kidney function after periods of 6 to 30 months; seven had a follow-up of over one year. The authors report decreased insulin requirement after kidney transplantation. Steroid therapy is given according to the usual schedule. Treatment of the diabetes tends to maintain the blood sugar at a level lower than 200 mg./100 ml. and the glycosuria at less than 50 g./24 hrs. Our experience with two patients shows a similar pattern for both: the need for insulin had decreased with progression of the renal insufficiency and has increased following the transplantation. This change seems related to the high dosage of steroids: the need for insulin decreased when the dosage of steroids was gradually lowered. Now that both patients have reached a maintenance level of steroids (10 to 20 mg. of prednisone per day), they require the same dosage of insulin that they were taking before the onset of renal insufficiency. It is possible that, with time, the insulin requirement may decrease further. Maintenance of acceptable levels of glycosuria and glycemia has also been a major problem in these patients who have increased appetite associated with steroid treatment.

The visual acuity and diabetic retinopathy have not shown any striking changes following the kidney transplantation. Our consultants in ophthalmology think that there has been possibly a slight improvement.

In the 1971 Fall Newsletter of the ACS-NIH Organ Transplant Registry, 29 patients were reported with chronic renal insufficiency secondary to diabetic nephropathy who received kidney transplantations. There were 23 men and 6 women aged 23 to 51 with a mean age of 37.1 years. Fourteen kidneys were transplanted from living related donors. Eleven patients were alive with functioning grafts at 5 to 25 months; there were three failures. Fifteen kidneys were transplanted from cadaver or unrelated living donors. Six patients were alive with functioning grafts at 2 to 26 months; there were failures in seven cases. No follow-up data were available in two cases. There is no mention of any associated peripheral vascular disease or peripheral neuropathy.

Our two patients have good kidney function with good endogenous creatinine clearance. It is a little surprising to notice disappearance of the proteinuria in both patients who had good urinary output and marked proteinuria prior to kidney transplantation.

The increased glomerular filtration rate reported in juvenile diabetes of short duration is now believed to be attributable to the high serum growth hormone level.[5-9] However, in diabetics who have kidney involvement, especially with proteinuria, there is usually a decrease in glomerular filtration rate. Ditzel and Junker[10] believe that the increased glomerular filtration rate in recent-onset and short-term diabetes may be due to constriction of the vas efferens causing an increase in the filtration pressure. They found no correlation between the average levels of growth hormone during the clearance determination and the glomerular filtration rate. Although our two patients have juvenile diabetes of several years' duration, it is very likely that the new kidneys do not show any diabetic involvement as yet. They could be considered as behaving like kidneys of patients with short-term diabetes.

In juvenile diabetics without peripheral vascular disease, severe blindness or peripheral neuropathy, the success of treatment by cadaver kidney transplantation of chronic renal insufficiency has been so far sufficiently rewarding as to encourage us to continue this form of management.

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Résumé

Nous avons présenté deux malades porteurs d'une insuffisance rénale terminale secondaire à une néphropathie diabétique et traitée par greffe rénale cadavérique. Aucun de ces malades n'avait d'atteinte vasculaire périphérique ou de neuropathie périphérique. Tous deux ont une bonne fonction rénale 8 et 15 mois après leur greffe rénale et ont repris leur travail habituel. Les auteurs, tout comme cela est rapporté dans la littérature, insistent sur l'efficacité de ce traitement chez de tels malades. Le succès de la greffe rénale dépend en grande partie de l'absence d'atteinte vasculaire périphérique ou de neuropathie. Il n'y a pas eu de changements significatifs de l'acuité visuelle et de la rétinopathie diabétique chez aucun de nos patients. Les besoins en insuline ont diminué avec la progression de l'insuffisance rénale, augmenté après la greffe rénale puis diminué graduellement à mesure que les doses de stéroides ont été abaissées, pour atteindre le niveau de la période pré-insuffisance rénale.

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