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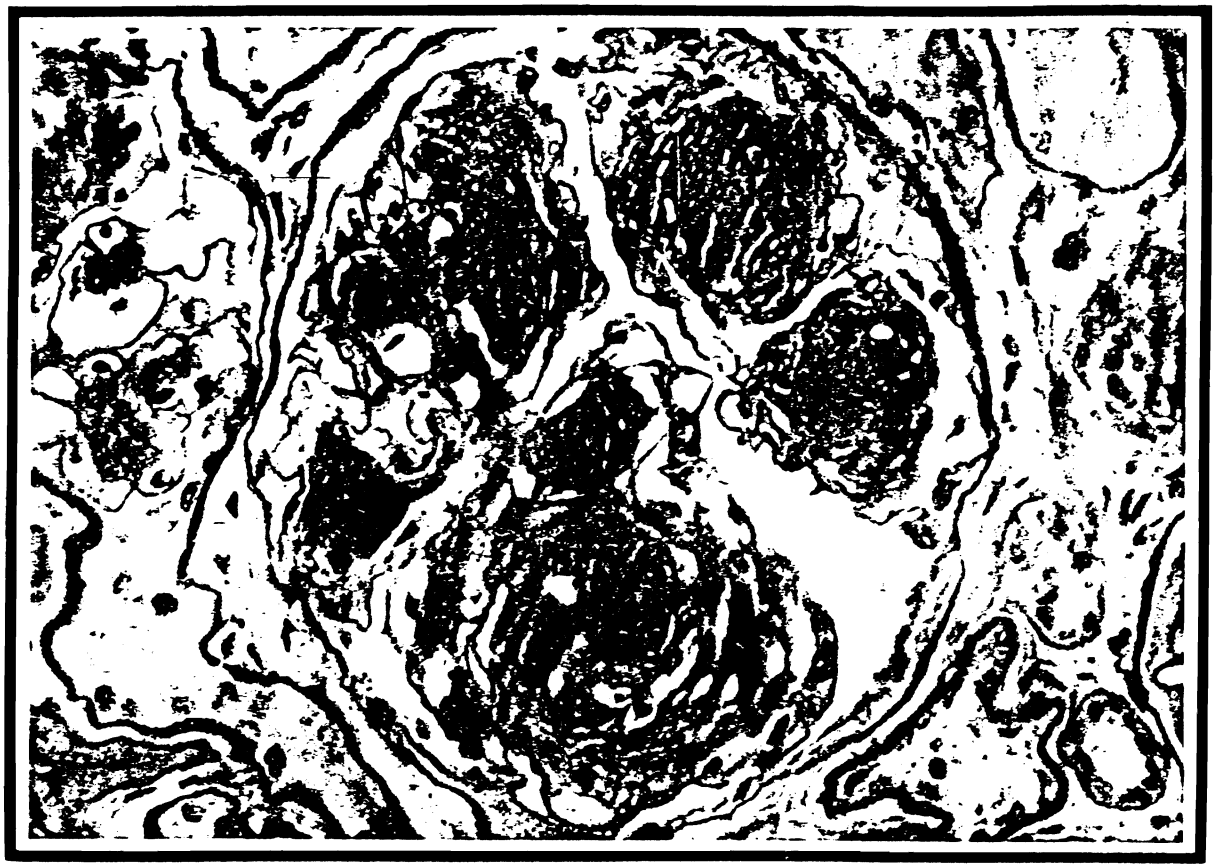
Diabetic Nephropathy



Cadaveric Renal Transplantation in Diabetics in the 1980's: with Special Reference to Cyclosporine

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When renal transplantation became a practical means of therapy almost two decades ago,[1] diabetes mellitus was considered a high risk factor, which precluded candidacy, except when related donors were available. Najarian et al.[2] popularized renal transplantation in diabetics, provided evidence that patient survival was superior to that with chronic dialysis, and emphasized the necessity for an inter-disciplinary health care team before and after transplantation.

In an exhaustive report covering a 10-year period, Najarian et al.[3] provided a follow-up for 109 diabetic patients who underwent primary cadaveric renal transplantation under treatment with azathioprine, prednisone, and antilymphocyte globulin (ALG). The one-year cadaveric graft survival of 60% was a high water mark, marred only by the patient mortality which was 30% in the first post-operative year. Discussions of Najarian's paper by several transplantation surgeons made it clear that others were not achieving even this level of success.[3]

The unsatisfactory results with cadaveric transplantation in diabetic, (or for that matter non-diabetic), patients has been a nagging indictment of the deficiencies of the techniques of immunosuppression, which have changed little since the mid-1960's. Treatment in most centers has been with the double drug combination of azathioprine-prednisone,[1-3] and in almost all of the rest, triple drug therapy with azathioprine, prednisone, and antilymphocyte globulin (ALG) has been used.[2-4] With either approach, high-dose chronic therapy with steroids has been an unusually adverse factor for diabetics, with a predictable increase in insulin needs, and with a high incidence of infections and vascular complications.

Minor variations from basic double and triple drug therapy have been reviewed.[5] These did not have a major impact. Other attempts to improve the outlook have been with tissue typing,[6,7] and with systematic preoperative blood transfusion of the recipient.[8]

With the introduction by Calne et al. [9,10] of the new drug, cyclosporine, as a single immunosuppressive agent, or with the use of cyclosporine plus a limited quantity of steroids as we have recommended,[11,12] there has been the prospect of better graft survival with less morbidity. To see if this objective has been realized, we report here the fate of diabetic patients during our early experience with cyclosporine-steroid therapy. For comparison, a small group of patients given azathioprine and steroids during the same time will be included.

METHODS

The cases were divided into three groups. There were three type I diabetics treated during pilot trials with cyclosporine and steroids in 1980 (Group 1); follow-ups are available of 2½ to 3 years (Table I). In 1981, seven type I diabetics were given cyclosporine and steroids (Group 2), most during participation in a randomized trial which included seven other patients (Group 3) treated with azathioprine and steroids (Table I).

All of the patients treated with azathioprine and prednisone (Group 3) were undergoing transplantation for the first time, whereas one of the 10 treated with cyclosporine (Groups 1 and 2) had rejected a primary kidney under conventional therapy, and was undergoing retransplantation (Table I). The features of the three groups are summarized in Table I. The patients were reasonably matched for age, lack of good typing at the A and B loci, and transfusion history, but with a slight advantage for the azathioprine-steroid group (Table I). Matching at the DR locus was random. The

Table I.
Type I Diabetics Receiving Cadaveric Kidneys 1980 – 1981 (Data, Mean ± SD)

Group	No. of Patients	No. Grafts	Age	Primary Transplantation	Matches A, B Loci	≥3 Preop Transfusions	Patient Followup (Months)
1 Cyclosporine-Steroids (Pilot)	3	3	44 ± 2	3/3	0.33 ± 0.57	0/3	33.3 ± 2.9
2 Cyclosporine-Steroids (Randomized)	7	8*	40.6 ± 10.8	6/7	1.57 ± 1.39	3/7	15.7 ± 2.9
3 Azathioprine-Steroids (Randomized)	7	8*	36.9 ± 6.2	7/7	2.00 ± 1.52	5/7	19.7 ± 2.9

*One of the kidneys in each group was transplanted in 1982 after loss of a graft transplanted in 1981.

DR matches were obtained after the transplantations had been completed, and were uniformly poor.

Azathioprine and prednisone were used together in the standard way,[1] beginning high dose steroid therapy at 200 mg on the day of operation, with subsequent gradual weaning. In Groups 1 and 2, cyclosporine was begun at 17 mg/Kg/day, and prednisone was begun at 200 mg, with daily decrements of 40 mg until a maintenance dose of 20 mg/day was reached in adults after 5 days. Further adjustments in cyclosporine or steroid doses were as previously described.[11-13]

RESULTS

Patient Survival

All 17 patients are alive with follow-ups of one to three years.

Graft Survival

Group One

All three of the cadaveric grafts in this pilot trial are still functioning after 2½ to 3 years. Two of the three patients have normal renal function. The third had nearly normal graft function for 2½ years, but developed an elevation of creatinine to 3.6 mg% when maintenance steroid therapy was reduced from 10 to 0/mg/day. The deterioration was reversed after return to low dose steroid therapy.

Group Two

Six of the seven recipients achieved chronic survival of their grafts (Table II). Through a blood typing error, the seventh patient who was of O blood type was given an A kidney, which underwent hyperacute rejection and renal vein thrombosis. Nine months later, this patient underwent cadaveric retransplantation, again with cyclosporine-steroid therapy, with a good result for the nine months of follow-up. Thus all seven patients are dialysis-free.

Five of the six original grafts function well enough to keep the serum creatinine concentration less than 2.5 mg%. The sixth patient has had chronic rejection with a creatinine of 6 mg% (Table III).

Group Three

Two of the seven kidneys were rejected after three and nine months. Four of the five other original transplants are maintaining serum creatinine values of less than 2.5 mg% (Table III).

One of the two patients whose primary allograft was rejected under azathioprine-steroid therapy underwent retransplantation 9 months later with cyclosporine-steroid therapy, and has good function three months later. Thus, six of the seven patients in the group are dialysis-free.

Table II.
Graft Survival, Blindness and Amputations

Group	Survival 1980–1981 Grafts	Survival of Subsequent Grafts	Patients Dialysis Free	Patients Legally Blind Preop	Post-Op Amputations
1	3/3	–	3/3	1/3	3/3
2	6/7	1*/1	7/7	2/7	1/7
3	5/7	1*/1	6/7	1/7	3/7
Total	14/17	2/2	16/17	4/17	7/17

*Subsequent grafts were placed in 1982 under cyclosporine-steroid therapy with present follow-ups of 9 (the patient in Group 2) and 4 (the patient in Group 3) months.

Steroid and Insulin Requirements

Comparison was made between Groups 2 and 3. In all patients of both groups the daily insulin requirements increased after transplantation (Table III), and in a number of recipients the upward adjustments were striking. The greatest increases were in the patients treated with conventional immunosuppression. With almost identical average periods of follow-up, the maintenance doses of prednisone are almost twice as high in the azathioprine-steroid group as in the cyclosporine-steroid group (Table III).

Diabetic Complications

All of the patients bearing kidneys have had a major improvement in well-being. Four of the 17 patients were legally blind before operation (Table II). None of the others have become blind since transplantation, but several have required ophthalmologic care, including laser treatment for detached retinae.

A striking statistic was the frequent necessity for amputation (Table II). During follow-ups of 2½ to 3 years, all 3 of the cyclosporine-steroid-treated patients in Group 1 have undergone unilateral below knee amputation, and one of the patients of Group 2 has had a finger amputation.

Three of the patients in the azathioprine-steroid series (Group 3) have had amputations (Table II), one each at the great toe, transmetatarsal, and below knee level.

DISCUSSION

The value of this experience is limited by the small number of patients. Nevertheless, the absence of mortality, the 90% one-year

Table III.
Graft Function, Steroids, and Insulin Requirements in Randomized Patients Still Bearing Grafts (Mean ± SD)

Group	No.	Creatinine Mg%	CR Range Mg%	Daily Prednisone Mg%	Daily Insulin Preop Units	Daily Insulin Now Units
2	7*	2.45 ± 1.68	1.0 to 6.1	12.5 ± 3.2	32.2 ± 21.6	51.6 ± 31.1
3	6**	1.6 ± 0.64	0.9 to 2.8	16.7 ± 2.6	44.7 ± 38.5	79.3 ± 30.8

*One of these patients had retransplantation 9 months ago, again under cyclosporine-steroids.
**One of these patients had retransplantation 4 months ago under cyclosporine-steroids and is receiving 20 mg/day prednisone.

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graft survival using cyclosporine-steroid therapy, the lower chronic maintenance doses of prednisone, and the lower eventual insulin requirements are worth noting in comparison to those in the azathioprine-steroid group. The results in the latter series were acceptable, however, in that six of the seven patients are dialysis-free.

No matter what the immunosuppression, there were reminders of the difficulty of treating patients with diabetes mellitus. Even with relatively low maintenance doses of steroids, the insulin requirements invariably rose, and not uncommonly doubled or tripled. Ophthalmalogic problems continued, with several patients requiring cataract removal or laser treatments. The fact that vascular disease had not been stabilized was reflected by amputation in 7 of 17 cases.

It seems unlikely that the patient or graft survival curves in diabetics will be able to match those of non-diabetic recipients as the years go by, unless there is perfect glucose control, an objective that cannot be achieved under ordinary clinical circumstances. Long term parity of results in diabetic and non-diabetic transplant recipients undoutedly will depend upon widespread application of insulin pump technology, or upon advances in pancreatic transplantation.

SUMMARY

The courses were reviewed of seventeen type I diabetic patients who were treated with cadaveric renal transplantation in 1980 and 1981, including 10 who were treated with cyclosporine-steroid immunosuppression, and seven who had azathioprine-steroid therapy. With follow-ups of 1 to 3 years, all 17 patients are alive, and 16 are dialysis-free. The results were better under cyclosporine-steroid therapy, but they were also acceptable under conventional immunosuppression. Whatever the treatment protocol, there was a high incidence of continuing diabetic complications, including ophthalmalogic disease and a striking need for limb or digit amputation.

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