

Original Article

Renal transplantation following renal failure due to urological disorders

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Abstract

Background. Renal allograft outcome, during an 8 year period (1985–1992), has been assessed in 56 renal transplants performed in 55 patients who had end-stage renal failure as a consequence of urological abnormalities. The abnormalities were: primary vesico-ureteric reflux (VUR) or renal dysplasia (26 patients); posterior urethral valves (PUV) (15); neuropathic bladders (6); vesico-ureteric tuberculosis (5); bladder exstrophy (3); and prune belly syndrome (1). Six patients had augmented bladders, and eight transplants were performed in seven patients with urinary diversions.

Results. Overall, 1 and 5 year actuarial graft survival was 89 and 66%, with mean creatinine of $154 \mu\text{mol/l} \pm 11$ (SE) and 145 ± 9 respectively. Patients with abnormal bladders or conduits ($n=28$) had worse graft function than those with normal bladders ($n=28$) although graft survival was not significantly different in the two groups at 1 and 5 years: 93 and 75% with normal bladders vs 86 and 57% with abnormal systems. Symptomatic urinary tract infections were common in the first 3 months after transplantation (63%); fever and systemic symptoms occurred in 39% with normal bladders and 59% with abnormal bladders. Urinary tract infection directly contributed to graft loss in six patients with abnormal bladders, but had no consequences in those with normal bladders.

Conclusions. Abnormal bladders must be assessed urodynamically before transplantation, and after transplantation adequacy of urinary drainage must be re-assessed frequently. Prophylactic antibiotics are now given for the first 6 months and urinary tract infections must be treated promptly. With these measures, good results, similar to those of patients without urological problems, can be obtained.

Key words: Abnormal bladder; enterocystoplasty; renal transplantation; urinary diversion

Introduction

A normal bladder acts as a low pressure, good volume urinary reservoir that is continent, sterile and empties freely and completely. Any other form of urinary reservoir aims to recreate such an environment. When such an environment is not achieved in either a natural or reconstructed bladder, complications such as sepsis and renal dysfunction may occur. As a result, there has been a reluctance to consider patients with abnormal lower urinary tracts for renal transplantation.

A variety of conduits and continent reservoirs have been developed to replace unusable bladders. Ileal conduit diversion has been used most widely for native kidneys although deterioration in renal function commonly occurs secondary to long-term complications including urosepsis, renal calculi and, most commonly, stenosis leading to obstruction [1–3]. However, with a high index of suspicion and an aggressive diagnostic and therapeutic approach, many of these problems can be detected and treated early, with resultant good long-term function of native kidneys [4]. Similar results may be obtained when renal transplants are performed in these patients [5–8]. Other forms of urinary diversion that are continent, and therefore more socially acceptable to patients, are now widely used in general urological practice and are beginning to be met in renal transplantation. These include augmented bladder draining via the urethra and augmented or intestinal bladders draining via continent stomas.

This retrospective study examines the 5 year outcome and complications of 56 renal allografts transplanted over an 8 year period with abnormal lower urinary tracts or a history of primary vesico-ureteric reflux (VUR).

Subjects and methods

During an 8 year period (1/1/85–31/12/92), 56 renal transplants were performed in 55 patients who had end-stage renal failure as a consequence of urological abnormalities. Thirty nine of the 56 transplants were from a cadaveric donor, and 17 from a live related donor. The mean age at

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transplantation was 36.0 ± 1.8 years (SE) (range 17–66 years) with a mean age for the live donor recipients of 25.3 ± 1.4 years (range 17–34).

The primary urological abnormalities (56) were: primary VUR or renal dysplasia in 26; posterior urethral valves (PUV) or congenital bladder outflow obstruction in 15; neuropathic bladders in six (one traumatic, one spinal cord infarction and four congenital); five patients with renal and vesico-ureteric tuberculosis; three with bladder exstrophy (one patient received two transplants); and one with prune belly syndrome. Five of these patients had augmented bladders (four patients with PUV and one with vesical tuberculosis). There was one ileo-caecal reservoir with a continent Mitrofanoff appendiceal stoma in a woman born with bladder exstrophy who, in the analysis, has been included as an augmented bladder. Eight transplants were performed in seven patients with ileal conduits.

Patients with their renal transplant draining into their native bladder could be divided into those with normal bladder function ($n=28$; 26 with primary VUR or renal dysplasia, and two with renal tuberculosis) and those with known bladder abnormality or conduit. The latter group were abnormal native bladder ($n=14$), augmented bladders ($n=6$) and there were eight ileal conduits as a consequence of vesico-ureteric tuberculosis (2), neuropathic bladder (4), and bladder exstrophy (1); the last patient received two transplants. Of the 17 kidneys from living donors, nine recipients had normal bladders, five abnormal bladders due to PUV, two neuropathic bladders (one conduit) and one prune belly. Before transplantation, urodynamic data by video-cystometrogram was obtained in 17 of the 20 patients with abnormal or augmented bladders and all patients had, at least, measurement of urine flow rate and post-micturition ultrasound. Three patients in the normal bladder group previously had had an ileal loop undiverted.

Immunosuppression in all patients was low-dose prednisolone and once daily cyclosporin; cyclosporin dose was initially 14 mg/kg body weight reducing to 3–6 mg/kg by 6 months to achieve a 12 h trough whole blood cyclosporin level of 100–150 ng/ml (radioimmunoassay with monoclonal antibody to parent compound). Since 1991, routinely we have added azathioprine to the immunosuppressive regime of all patients with abnormal lower urinary tracts in an attempt to minimize cyclosporin dosage. Patients and allografts were all ABO-blood group compatible. HLA matching varied from 0 to 6 antigen matches, avoiding mis-matched antigens encountered in any previous transplant.

Renal transplant surgery used standard techniques. All transplant ureters were kept open with a 6 French gauge double-J stent, which was removed cystoscopically after 3 months unless there was a clinical indication, such as repeated urinary tract infections (UTIs), for earlier removal.

Actual graft survival was calculated at 1 and 5 years. Differences at 5 years were compared by the χ^2 test. Failed grafts were defined as those in whom dialysis had been restarted or when patients died with a functioning graft. Mean plasma creatinine concentrations over the first 5 years were compared between different groups using unpaired Student's *t*-test. Data are expressed as mean \pm SE. A *P*-value < 0.05 was taken as indicating statistical significance.

Results

Outcome (Table 1)

Patient survival was excellent, with 100% survival at 1 year and 93% at 5 years. The four deaths (bladder

cancer, carcinomatosis, myocardial infarct and atypical pneumonia) all occurred in patients with normal bladder function and with good stable graft function (all had plasma creatinine < 150 $\mu\text{mol/l}$).

Overall, graft survival was good, with 1 and 5 year actuarial, uncensored graft survivals of 89 and 66%. Overall graft function was good, with mean creatinines of $154 \mu\text{mol/l} \pm 11$ ($n=51$) at 1 year and $145 \pm 9 \mu\text{mol/l}$ ($n=37$) at 5 years; the mean creatinine at 1 year of those 37 patients with functioning grafts at 5 years was $137 \pm 8 \mu\text{mol/l}$ (SE). In comparison, 170 other renal transplants were performed in the same period (37 live related), mean age 47 ± 1.0 (range 17–73 years), with 1 and 5 year graft survivals of 76 and 67% respectively.

Patients were divided into those with normal bladder function ($n=28$) and those with known bladder abnormality ($n=28$). Graft survival was similar in these two groups at 1 year (normal bladders 93% and abnormal systems 86%), but at 5 years outcome was better for normal bladders (75 and 57% respectively), although this difference was not statistically significant. Graft function, however, was significantly worse in the abnormal bladder group. Mean creatinines at 1 year were 130 ± 11 vs $179 \pm 17 \mu\text{mol/l}$ (normal vs abnormal; $P=0.02$), and 124 ± 7 vs $173 \pm 17 \mu\text{mol/l}$ (normal vs abnormal; $P=0.008$) at 5 years.

Normal bladders

Twenty eight patients were considered to have normal bladders and all had had at least a urine flow rate and post-micturition bladder ultrasound. Graft function was excellent (see Table 1). Actual graft survival at 5 years was 75% but, if the four patients who died with good function are excluded, then survival was 88%. The three graft losses were all from rejection.

Abnormal native bladder (not augmented)

Fourteen kidneys were transplanted into abnormal native bladders. Actual graft survival at 1 and 5 years was 86 and 50%. Mean plasma creatinine concentration at 1 year was $196 \pm 30 \mu\text{mol/l}$, which was higher than those with normal bladders ($P=0.009$). However, in those grafts surviving 5 years, mean creatinine did not change significantly from 1 to 5 years (see Table 1). Seven grafts were lost; two from transplant glomerulopathy with nephrotic syndrome (both receiving kidneys from the same donor), one renal artery stenosis, and in the other four the bladder was considered to play a role in the progressive graft loss, with renal biopsies showing features of progressive scarring and renal allograft nephropathy. ^{99}Tc -dimercaptosuccinic acid (DMSA) scans with tomography demonstrated multiple and progressive small scars in these patients [9].

Augmented native bladder

Six kidneys were transplanted into abnormal native bladders, which had been augmented by ileo-caecocystoplasty. Patients did well, with actual graft survival

Table 1. Graft outcome

		Creatinine at 1 year µmol/l			Creatinine at 5 years µmol/l		Actual survival at 5 years
Normal bladder	n=28	130±11	121±9 ^a	(n=26)	124±7	(n=21)	75%
Abnormal native bladder	n=14	196±30	150±14	(n=12)	161±28	(n=7)	50%
Augmented bladder	n=6	184±30	184±30	(n=5)	219±30	(n=5)	83%
Ileal Conduit	n=8	143±9	138±16	(n=7)	136±21	(n=4)	50%

Creatinine values are shown as mean ± SEM.

^aMean creatinine at 1 year of those patients with functioning grafts at 5 years.

at 1 and 5 years of 83%. Mean plasma creatinine concentration at 1 year was 184 ± 30 µmol/l, which was higher than those with normal bladders ($P=0.014$). One graft was lost at 11 months following severe early vascular rejection and one subsequently at 79 months from progressive scarring and UTIs.

One with a history of vesico-ureteric tuberculosis and an ileo-caecal bladder augmentation had a large residual post-micturition. After repeated counselling, he now practises double micturition regularly and, in the 10 years since transplantation, his plasma creatinine has improved from 210 to 160 µmol/l. Three of the four patients with PUV also had significant residual urine volumes: they have been less compliant with frequent and double voiding and, possibly as a result, have had a progressive deterioration in renal function; one recommenced dialysis 6 years after transplantation. None of them were able to perform intermittent self-catheterization.

One patient was transplanted into an ileo-caecal reservoir with an appendiceal continent Mitrofanoff stoma. Transplant function was good for the first year and then the plasma creatinine increased from 80 to 130 µmol/l during the next 8 months (her body weight was stable at 45 kg). Urodynamics showed that, above a volume of 300 ml, pressure within the reservoir increased to 50 cm H₂O. As catheterization of the pouch in the morning routinely produced 500–600 ml of urine, she now leaves an indwelling catheter on free drainage overnight and does not allow the day time volumes to exceed 300 ml. Since then, her plasma creatinine has been stable at 120 µmol/l for 6 years.

Urinary conduits

Patients with urinary diversions did well initially as a group, with good graft function and survival (Table 1). Actual graft survival at 1 and 5 years was 88 and 50% respectively. Mean plasma creatinine concentration at 1 year was 143 ± 9 µmol/l, which was similar to those with normal bladders. Surgical complications in the perioperative period were uncommon, although the transplant operation was often technically difficult. There was one early failure due to obstruction after an ureteric stent was inadvertently removed, and three later failures at 18, 37 and 49 months all associated with recurrent UTIs.

Urodynamic investigations

Eleven of 13 patients who were transplanted into a known abnormal bladder and all six with augmented bladders had urodynamics performed before the transplant. There was a tendency to worse graft outcome associated with higher maximum voiding pressure and residual volume, but no correlation with maximum bladder capacity, maximum filling pressure or maximum flow rate.

Urinary tract infection

UTIs, defined as a mid-stream urine with >10⁶ organisms/ml, were very common in the first 3 months after transplantation in all groups. UTIs were graded as (A) asymptomatic, (B) symptomatic with urinary symptoms (cystitis), (C) serious with systemic symptoms and fever (pyelonephritis).

In those with normal bladders, 10 (36%) had asymptomatic infection only (A), three (11%) cystitis (B), 11 (39%) systemic symptoms (C), and four had no documented UTI. There was no difference in the mean creatinines in the different groups either at 1 or 5 years, and no kidney was lost from infection.

In the groups with abnormal bladders, five (18%) had asymptomatic infection only, seven (25%) cystitis (B), 14 (50%) systemic symptoms (C), and two had no documented UTI. Creatinine values at 1 and 5 years were higher in those with symptomatic infections but the difference was not significant. Six kidneys were lost in which recurrent UTI had a significant effect. Four of the eight kidneys transplanted into ileal conduits were lost with multiple infections.

Since 1991, patients are all given prophylactic antibiotics routinely for the first 6 months. In this study only six patients were transplanted after this date and only one has had a serious (C) UTI.

Discussion

Renal transplantation in patients whose renal failure had a primary urological cause is safe and effective in our centre. In particular, patients with normal bladders had an excellent prognosis after transplantation. UTIs were relatively common in all patients, but only produced problems in patients with abnormal bladders.

Patients assessed as having abnormal bladders, of which PUV was the commonest cause, had worse graft function after transplantation when compared with those whose bladder function was assessed as being normal, although graft survival was not significantly different between the two groups. The cause of relatively poor graft function in patients with PUV or other causes of poor bladder function is unclear. Many have less than ideal bladder function, with high filling and/or voiding pressures and often inadequate bladder emptying. Renal biopsies in four patients with deteriorating function demonstrated multi-focal areas of scarring with extensive tubular atrophy and interstitial fibrosis, but little evidence of chronic cellular or vascular rejection. ^{99}Tc DMSA scanning with tomography has shown multiple small scars in these patients, consistent with a 'reflux nephropathy' process but not with chronic rejection [9]. Several studies report that transplantation in patients with PUV is less successful than in other patients and results in both poorer graft function and survival [10,11]. In contrast, a recent study by Ross and colleagues in 16 renal transplant patients with PUV suggests that graft function does not decline with long follow-up and that graft survival is comparable with other transplant recipients [12]. Graft function in their patients was good, with a mean plasma creatinine of $\sim 160\ \mu\text{mol/l}$ at 1 year with no decline over the following 7–8 years. A study in children with PUV demonstrated very similar results [13].

UTIs, although common, were not a major clinical problem in patients with normal bladders. However, infections were more common and more severe in those with abnormal systems, and directly contributed to graft loss in six patients. Our standard practice now is to give long-term antibiotics (a single dose at night) in all 'urological' patients for the first 6 months and to continue for longer if a UTI occurs. Our impression is that a urinary infection in the first few weeks after transplantation can trigger acute rejection, but that this rarely occurs later.

Transplants into ileal conduits usually result in good graft function and survival albeit with a high surgical complication rate [5,7,8,14]. Our patients with urinary diversions did well initially, although by 5 years half had been lost from recurrent UTI. This is in contrast to the review of our experience from 1977 to 1989 in which we reported nine transplants into ileal loops which resulted in good function and 67% graft survival at 5 years [7]. In that series, there were no patients with augmented bladders. It is against patients with ileal loops that transplantation into more sophisticated, usually continent, bladder augmentations and urinary diversions needs to be judged. Our six patients with augmented bladders did well, with excellent graft survival although renal function was relatively poor. All five kidneys that survived for >1 year have developed multiple small scars visible on tomographic DMSA scans, and renal biopsy in three of them showed no evidence of rejection. This suggests that graft dysfunction is related to poor bladder function in these

patients. One patient has now practised double micturition for several years with a subsequent improvement in graft function. If this is not sufficient to empty the bladder, then intermittent self-catheterization is started. The experience of others also indicates that transplantation into the augmented bladder works well provided renal and bladder function are monitored closely [14–16]. In two of our patients with deteriorating function attributed to bladder dysfunction, renal function was stabilized or improved after the bladder problem was treated.

Our single patient with a continent reservoir has done very well, although higher vesical pressures when the bladder was full led to some loss of graft function before this was recognized. There are several case reports of transplantation into continent urinary diversions [17,18]; these have done well in the short term although long-term data are still lacking. Experience with continent diversions draining native kidneys indicates that problems with obstruction and infection are common and require close supervision [19–21].

A recent study of urodynamics prior to transplantation indicates that poor bladder function as shown by small bladder volumes is a predictor of graft loss even in patients with previously normal bladder function [22]. We did not observe this, although poorer outcome was associated with higher voiding pressures and residual volumes.

Transplantation into the abnormal lower urinary tract requires careful evaluation and follow-up. Thorough preoperative assessment of bladder function is essential, including at least a post-micturition bladder ultrasound examination and urinary flow rate. Intermittent self-catheterization is safe and effective for a patient with a poor flow rate who fails to empty the bladder. This, however, is only possible with a normal urethra and a co-operative patient. When this is not practical, we would attempt to establish supra-pubic drainage via a continent stoma.

Adequacy of urinary drainage must be assessed frequently, even when renal function seems to be good. Our protocol is at 3 months, after removal of ureteric stent, to do (i) ^{51}Cr -EDTA glomerular filtration rate (GFR), (ii) ultrasound of kidney and bladder post-micturition, (iii) dynamic isotope scan (^{99}Tm -MAG3), and (iv) static isotope scan (^{99}Tm -DMSA) for baseline scarring. The GFR is repeated at 6 months and then annually. Ultrasound and ^{99}Tm -MAG3 are repeated at 1 year, and then when indicated. The 24 h urine collections for protein are done at 6 months and then annually. If there is renal dysfunction, imaging tests are repeated and, if there is no change from baseline, renal biopsy is performed to exclude an immunological cause of dysfunction. If there is a documented deterioration in renal function in the absence of rejection or cyclosporin toxicity, the DMSA scan is repeated and the bladder reassessed urodynamically.

UTIs must be detected and treated early, and recurrent infections may require long courses of antibiotics or even removal of the native tracts; but we do not routinely remove abnormal native kidneys before

transplantation. All our patients now receive prophylactic antibiotics for the first 6 months. If UTIs recur, then a cause must be sought with ultrasound of kidney and bladder. A plain abdominal X-ray is essential to look for stones in native or transplant kidneys, the bladder or urinary diversion. If there is a residual volume after double micturition, then the patient must be instructed to perform intermittent clean self-catheterization. With these measures, good results are obtained.

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