

# Early Experience with Dual Kidney Transplantation in Adults using Expanded Donor Criteria

GIUSEPPE REMUZZI,\* JOSEP GRINYÒ,<sup>†</sup> PIERO RUGGENENTI,\* MARCO BEATINI,<sup>‡</sup> EDWARD H. COLE,<sup>§</sup> EDGAR L. MILFORD,<sup>||</sup> BARRY M. BRENNER,<sup>||</sup> and

THE DOUBLE KIDNEY TRANSPLANT GROUP (DKG)<sup>^</sup>

*\*Ospedali Riuniti di Bergamo, Clinical Research Center “Aldo e Cele Daccò” and “Mario Negri” Institute for Pharmacological Research, Bergamo, Italy; <sup>†</sup>Istitut Catala de la Salut, Ciutat Sanitaria i Universitaria de Bellvitge, L’Hospitalet de Llobregat, Barcelona, Spain; <sup>‡</sup>Ospedale San Marino, Genova, Italy; <sup>§</sup>The Toronto Hospital, St. Michael’s Hospital, Toronto, Ontario, Canada; and <sup>||</sup>Brigham and Women’s Hospital, Boston, Massachusetts.*

**Abstract.** Dual transplant of marginal kidneys otherwise not considered for single transplant may give access to an expanded pool of cadaveric organs without exposing recipients to the drawbacks of a limited nephron mass supply. This prospective, case-control study compares adverse events and graft outcome in 24 recipients of two marginal kidneys from donors who were >60 yr old or who had diabetes, hypertension, or non-nephrotic proteinuria (cases), with that of 48 age- and gender-matched control subjects who received single ideal grafts at the same center and were given the same immunosuppressive therapy. Marginal kidneys with no macroscopic abnormalities were selected for the double transplant on the basis of a predefined score of histologic damage. Six-month patient and kidney survival was 100% with both of the procedures. Incidence (20.8% versus 20.8%) and median (range) duration of posttransplant anuria (5 [2 to 12] versus 7 [2 to 13] days) were comparable in cases and control subjects, respectively. Time to normal serum creatinine and mean serum

creatinine values at each time visit were comparable as well, but with significantly lower levels in cases compared with control subjects from month 2 to last follow-up ( $1.56 \pm 0.65$  versus  $1.74 \pm 0.73$  mg/dl,  $P = 0.04$ ). Diastolic BP values averaged during the entire posttransplant period were significantly lower in cases than in control subjects ( $83.2 \pm 11.5$  versus  $85.1 \pm 12.5$  mmHg, respectively,  $P = 0.008$ ). Donor/recipient body weight ratio was the only covariate significantly associated at univariate ( $P = 0.002$ ) and multivariate ( $P = 0.001$ ) analysis with last available serum creatinine concentrations. Incidence of acute allograft rejections (20.8% versus 18.8%) and of major surgical complications was comparable in the two groups. No renal artery or vein thrombosis was reported in either group. Dual transplants of marginal kidneys are as safe and tolerated as single transplants, and possibly offer an improved filtration power without exposing the recipient to enhanced risk of delayed renal function recovery, acute allograft rejection, or major surgical complications.

In an effort to overcome the disparity between supply of cadaveric donors and demand, various strategies have emerged to expand the existing donor selection criteria. Kidneys have been used from donors of 50 yr or more, or with a prolonged history of hypertension and diabetes, or other evidence of renal disease (1,2). Although this is technically feasible, there is major concern about the use of such organs based on experimental (3,4) and clinical (5,6) evidence that kidneys with preexisting injury or reduced function may have poor outcomes. Actually, in humans, transplantation of a single kidney

with a suboptimal number of nephrons to start with serves to create the clinical counterpart of experimental reduction of renal mass (7). Indeed, in most cases, cold ischemia time, one or more acute rejections, and toxicity of medications—particularly cyclosporin A and tacrolimus—further reduce the already limited number of nephrons that a single suboptimal kidney provides (7). This remnant kidney—now containing 20 to 30% of viable parenchyma or less compared to that in two optimal kidneys—initiates a self-perpetuating program of progressive deterioration, as commonly seen in animals undergoing renal mass ablation (8). That nephron mass is a determinant of chronic allograft failure has been formally tested in animal experiments showing that increasing the number of viable nephron mass by simultaneous transplantation of two kidneys into the same recipient effectively prevented the progressive deterioration in renal function that occurs in control subjects given a single kidney (9,10). Although routine use of two ideal kidneys in humans is unlikely in the short term due to an insufficient number of organs available for all those in need, use of two marginal kidneys in a single recipient might be an option. Most transplant centers currently discard kidneys from

Received March 9, 1999. Accepted June 1, 1999.

See Appendix for participating investigators and affiliated organizations.

Dr. J. Harold Helderman served as Guest Editor and supervised the review and final disposition of this manuscript.

Correspondence to Dr. Giuseppe Remuzzi, Clinical Research Center “Aldo e Cele Daccò” Villa Camozzi, “Mario Negri” Institute for Pharmacological Research, Via Gavazzoni 11, 24125 Bergamo, Italy. Phone: +39 035 319 888; Fax: +39 035 319 331; E-mail: gremuzzi@cyberg.it

1046-6673/1012-2591

Journal of the American Society of Nephrology

Copyright © 1999 by the American Society of Nephrology

donors older than 60 yr, diabetic patients, or those with evidence of other renal diseases (11). Actually, recipients of single kidneys from older donors were at increased risk of posttransplant anuria and relatively poor graft function up to 6 mo follow-up (12). However, if two marginal organs were given to the same recipient, this may result in as many or more functioning nephrons as in a single ideal organ. Thus, use of compromised kidneys, rather than burdening the already limited pool of cadaveric organs, might actually enhance availability. Indeed, analyses of dual marginal *versus* single ideal transplant outcomes found a comparable 1-yr graft survival and renal function recovery by both of the procedures (13,14). However, these encouraging results could have been influenced to some extent by the nonrandomized, monocenter, retrospective design of the studies and by the use—in as many as one-third of cases—of organs with evidence of acute, rather than chronic, injury that conceivably contributed to improve the outcome of the dual procedure (13).

Thus, the present study was designed to formally compare in a prospective, controlled, multicenter design the short-term outcome of transplantation of two marginal *versus* single ideal kidneys to extend our experience with this approach and thereby enhance the organ donor pool.

## Materials and Methods

In October 1996, the Double Kidney Transplant Group (DKG) was established with the goal of identifying potential donors of suboptimal kidneys and performing double kidney transplants in eligible recipients. Guidelines for donor and recipient selection, the surgical procedures, and the study design were defined in a study protocol finalized by the DKG and approved by the Institutional Review Committees at each participating center and by the Ethics Committee of the Clinical Research Center “Aldo & Cele Daccò,” Villa Camozzi, Ranica, which was also appointed to monitor ethical and statistical issues and, in particular, to evaluate the safety and efficacy profile of the procedures. Each recipient gave written informed consent to enter the study.

### Study Objectives and Design

This was a prospective, case-control study designed to compare the incidence of major events (including posttransplant anuria, acute rejections, surgical complications, graft failures, and deaths) and the outcome of renal function over 6-mo of follow-up in each recipient of two suboptimal kidneys (cases) with that of two age- and gender-matched recipients each receiving a single optimal kidney (control subjects). Secondly, the study aimed to identify baseline clinical and histologic predictors of outcome in recipients of two suboptimal kidneys.

### Selection Criteria

**Donors.** Donors potentially eligible for the double transplant were identified among subjects with established diagnosis of cerebral death, but not selected for the single transplant because of one or more of the following:

- Age >60 yr
- History of diabetes or hypertension
- Clinical proteinuria (urinary protein excretion rate up to 3 g/24 h)

Donors with heavy proteinuria (urinary protein excretion rate >3 g/24 h) were not considered, being predicted to provide kidneys at

increased risk of premature failure (15). Donors potentially eligible for the single transplant were identified at each center according to standardized local criteria.

**Kidneys.** Kidneys were considered eligible for the double transplant only if at macroscopic evaluation major vascular abnormalities that could substantially increase the risk of surgical complications were excluded. Kidneys with macroscopic evidence of focal scarring (*i.e.*, chronic pyelonephritis) were not considered as well, due to the nonhomogeneous distribution of the histologic changes that would have affected the representativeness of the bioptic material. A biopsy taken from both kidneys served to precisely quantify the severity of tissue damage according to a score *a priori* defined by a panel of renal pathologists (see Table 1). To limit imprecision in score estimation related to too limited material, only biopsy specimens with at least 25 glomeruli per kidney were considered representative, and only paired kidneys with a biopsy score of 4 to 6 (see Table 1) were selected for the double transplant. Kidneys with a biopsy score of 3 or less were considered adequate for a single transplant, and those with a score of 7 or more were discarded.

Kidneys potentially eligible for the single transplant were identified at each center according to standardized local criteria.

**Recipients.** Patients eligible for the double transplant were selected among the subjects already on a waiting list who satisfied the following criteria:

- No previous kidney transplant or pelvic surgery
- Panel-reactive antibody titer <50%

All patients satisfying the above criteria were given full explanation of all of the potential risks and benefits of the procedure. Those providing written informed consent were included in an additional waiting list for the double kidney transplant. Those who refused to give consent remained on the waiting list for a single kidney transplant. All patients that eventually received the double transplant were considered as cases. For each case, two control subjects were identified among patients who received a single transplant at the same center. Control subjects were gender-matched recipients of a single transplant who were less than 10 yr older or younger than the corresponding cases, received the graft at the same center within 3 mo of the index cases, and were given the same immunosuppressive therapy.

### Outcome Measures

The primary outcome measure of the study was the incidence of major events, including posttransplant anuria (*i.e.*, time to discontinuation of chronic dialysis), acute rejections and surgical complications (*i.e.*, vascular thrombosis, bleeding requiring reintervention, fistulas, sepsis from the wound or the urinary tract), graft failures, and deaths. Additional efficacy parameters were time to serum creatinine concentration <1.4 mg/dl and course of serum creatinine concentration and BP during follow-up.

### Surgical Procedures and Treatment

Within each center, the double transplants were done through a double inguinal incision by the same surgical groups who performed the single kidney transplants. The procedures for the vascular and ureterovesical anastomoses were the same for cases and control subjects.

All cases and control subjects were given the same immunosuppressive therapy including oral cyclosporine targeted at blood trough levels of 350 to 450 ng/ml in the first 10 posttransplant days and 250 to 350 ng/ml thereafter (monoclonal RIA on whole blood), prednisone

**Table 1.** Pretransplant biopsy protocol: semiquantitative method of evaluation of slides<sup>a</sup>**Glomerular global sclerosis**

Based on three sections (the first, middle, and last sections, if available); the number of globally sclerosed glomeruli expressed as a percentage.

- 0 none globally sclerosed
- 1+ <20% global glomerulosclerosis
- 2+ 20 to 50% global glomerulosclerosis
- 3+ >50% global glomerulosclerosis

**Tubular atrophy**

- 0 absent
- 1+ <20% of tubuli affected
- 2+ 20 to 50% of tubuli affected
- 3+ >50% of tubuli affected

**Interstitial fibrosis**

- 0 absent
- 1+ <20% of renal tissue replaced by fibrous connective tissue
- 2+ 20 to 50% of renal tissue replaced by fibrous connective tissue
- 3+ >50% of renal tissue replaced by fibrous connective tissue

**Arterial and arteriolar narrowing**

For the vascular lesions, if the changes are focal, the most severe lesion present gives the final grade.

- 0 absent
- 1+ increased wall thickness but to a degree that is less than the diameter of the lumen
- 2+ wall thickness that is equal or slightly greater to the diameter of the lumen
- 3+ wall thickness that far exceeds the diameter of the lumen with extreme luminal narrowing or occlusion

**Final grade**

The final grade can range from 0 to a total of 12.

- |         |          |                            |
|---------|----------|----------------------------|
| 0 to 3  | mild     | OK for single transplant   |
| 4 to 6  | moderate | OK for double transplant   |
| 7 to 12 | severe   | should not be transplanted |

<sup>a</sup> Only biopsies with at least 25 glomeruli are considered for slide evaluation. Kidneys with evidence of acute tubular necrosis are not considered for the double transplant. Biopsies are graded as mild if they have 0 to 3 points in total provided they are less than 3 in any one category. Biopsies are graded as moderate if they have 4 to 6 points in total provided they do not have 3 points in more than one category.

200 mg/d progressively tapered to 20 mg/d, and mofetil mycophenolate 2 g/d.

**Donor and Recipient Evaluation**

Donor and recipient history, age, gender, body weight, serum creatinine, and HLA-A, -B, and -DR histocompatibility were recorded at the time of single or double transplants, as well as kidney cold and warm ischemia times. Then, all recipients had daily routine evaluations including BP and body weight measurements, serum creatinine and electrolytes, blood cell count, and blood cyclosporine trough levels up to discharge and/or at 1 mo follow-up. Within each center, cases and control subjects followed the same prophylaxis protocols for cytomegalovirus and *Pneumocystis* pneumonia infections. Anti-hypertensive therapy was targeted at diastolic BP <90 mmHg in all patients. Acute rejection episodes were diagnosed and treated according to the same local standardized procedures for cases and control subjects.

**Diagnosis of Acute Graft Rejection**

The diagnosis of acute rejection was made on the basis of clinical criteria (16), including the simultaneous occurrence of (1) an increase in serum creatinine concentration >0.3 mg/dl for more than 2 d over the basal value associated with a stable trough blood cyclosporine

level; (2) a renal ultrasonogram and Eco-color Doppler that excludes any other cause of allograft dysfunction (including urinary tract obstruction or renal artery stenosis); (3) a response to antirejection therapy (at least 3 d of intravenous methylprednisolone pulses, 0.5 g each, or OKT3 monoclonal antibody or rabbit antithymocyte globulin infusions in steroid-resistant cases) with improvement of renal function.

**Statistical Analyses**

This was a pilot, explorative study primarily aimed to evaluate the safety profile of the double kidney procedure. Thus, the sample size was not estimated on the basis of an expected effect on predefined outcome parameters, but rather on the number of cases predicted to receive a double kidney transplant over a predefined recruitment period of 1 yr. Assuming a mean recruitment rate of four cases per center per year, it was estimated that a sample size of 20 cases could be reasonably achieved by the five centers of the DKG. According to the 1 case–2 control design, 40 matched control subjects had to be identified at the same centers over the same time period.

All data were reported in dedicated case record forms and centralized at the Clinical Research Center where all the statistical analyses were done by SAS software (version 6.11). Dichotomous and polytomous baseline characteristics were compared with Fisher exact

test; continuous baseline characteristics were compared with Wilcoxon rank-sum tests. For the analysis of the length of time to event end points (discontinuation of chronic dialysis, normal serum creatinine), product-limit life table distributions were compared with the log-rank statistic. Univariate and multivariate regression analysis was used to determine interactions between final serum creatinine concentration and the following covariates: donor and recipient age, donor and recipient gender, donor/recipient body weight and body mass index (BMI) ratios, donor/recipient mismatches, recipient diabetes or hypertension, posttransplant anuria, and double *versus* single transplant. Univariate and multivariate logistic regression analysis was used to determine interactions between urinary tract fistulas and recipient age, pretransplant anuria and duration of dialysis, and double *versus* single kidney transplant. Relation between donor/recipient body weight or BMI ratios and final serum creatinine concentration was evaluated with regression analysis.

## Results

Twenty-four cases and 48 control subjects received a double and a single kidney transplant, respectively, from November 1996 to September 1998. Double kidney donors and recipients were significantly older compared with single kidney donors (age:  $68.7 \pm 6.8$  *versus*  $46.7 \pm 15.2$  yr, respectively,  $P = 0.0001$ ) and recipients (age:  $59.4 \pm 9.9$  *versus*  $50.2 \pm 12.1$  yr,  $P = 0.002$ ). Of the 24 donors, 22 were more than 60 yr old. Of these, 13 were hypertensive and four were hypertensive and diabetic. The two donors less than 60 yr old were diabetic. No donor had clinical proteinuria. Donor creatinine clearance estimated by the Cockcroft-Gault formula was available in 23 cases and 41 control donors and, as expected, was significantly lower in case donors ( $54.5 \pm 16.0$  *versus*  $78.1 \pm 48.0$  ml/min per  $1.73 \text{ m}^2$ ,  $P = 0.03$ ). HLA-A, -B, and -DR donor/recipient mismatches ( $3.9 \pm 1.2$  *versus*  $3.8 \pm 1.2$ ) and recipient baseline characteristics were comparable in the two groups (Table 2). Mean cold ( $20.3 \pm 0.3$  *versus*  $20.4 \pm 0.6$  h) and warm ( $0.37 \pm 0.02$  *versus*  $0.38 \pm 0.02$  h) ischemia times were comparable in cases and control subjects as well.

Median (range) follow-up was 6 (3 to 6) and 6 (4 to 6) mo in cases and control subjects, respectively. At last follow-up, patient and organ survival was 100% with both of the procedures. The incidence of posttransplant anuria was identical in cases and control subjects. Overall, five cases (20.8%) *versus* 10 control subjects (20.8%) required posttransplant chronic dialysis for a median (range) of 5 (2 to 12) and 7 (2 to 13) d,

Table 2. Main baseline characteristics of double (cases) and single (control subjects) kidney recipients

Characteristic	Cases	Controls	P Value
Age (yr)	$59.4 \pm 9.9$	$50.2 \pm 12.1$	0.002
Male	79.2%	81.2%	1.00
Caucasian	79.2%	79.2%	1.00
Weight (kg)	$71.4 \pm 19.1$	$73.1 \pm 16.2$	0.71
Body mass index	$25.3 \pm 5.4$	$25.3 \pm 4.7$	0.84
Hypertension	77.3%	71.7%	0.77
Diabetes mellitus	4.4%	6.4%	1.00

respectively. Time to chronic dialysis discontinuation was remarkably comparable in the two groups (Figure 1). Time to normal serum creatinine was comparable in the two study groups as well (Figure 2). Overall, mean serum creatinine values at each time visit and, on average, during the whole follow-up period were almost identical ( $4.2 \pm 3.4$  *versus*  $4.3 \pm 3.3$  mg/dl,  $P = 0.16$ ), but with significantly lower levels in cases compared with control subjects ( $1.56 \pm 0.65$  *versus*  $1.74 \pm 0.73$  mg/dl,  $P = 0.04$ ) from month 2 to last follow-up (Figure 3). At 6 mo, serum creatinine was numerically lower in cases than in control subjects ( $1.48 \pm 0.54$  *versus*  $1.77 \pm 0.93$  mg/dl), but the difference failed to achieve statistical significance ( $P = 0.24$ ). At each visit, estimated creatinine clearance was comparable in cases and control subjects and, in parallel with the decline in serum creatinine, progressively increased throughout the follow-up period in both groups (data not shown). At last follow-up, cases had a mean creatinine clearance virtually identical to that of corresponding donors ( $51.1 \pm 22.2$  *versus*  $54.5 \pm 16.0$  ml/min,  $P = 0.55$ ). On the contrary, at last follow-up control subjects had significantly lower creatinine clearances than corresponding donors. However, since control subjects received only one kidney from corresponding donors, we repeated the analyses comparing recipient creatinine clearances with *halved* donor creatinine clearances and found significantly higher values in recipients than in donors ( $53.6 \pm 16.2$  *versus*  $41.0 \pm 22.8$  ml/min,  $P = 0.006$ ). In other words, the filtration power of donor kidneys increased by about 30% after they were singly engrafted in the recipient. Overall, 13 kidneys were found to have a histology score  $<3$  and were transplanted as single kidneys at the institutions involved in the double kidney transplant study. Of note, final serum creatinine of recipients of these kidneys was  $1.5 \pm 0.4$  mg/dl and did not differ from that of other control subjects ( $1.9 \pm 0.7$  mg/dl,  $P = 0.09$ ). Six kidneys were discarded because they had a histology score  $>7$ .

In the majority of the posttransplant visits, systolic and diastolic BP values were comparable in the two groups, with significantly lower values in cases compared with control subjects only at days 0 and 1 (systolic) and at days 0 and 9

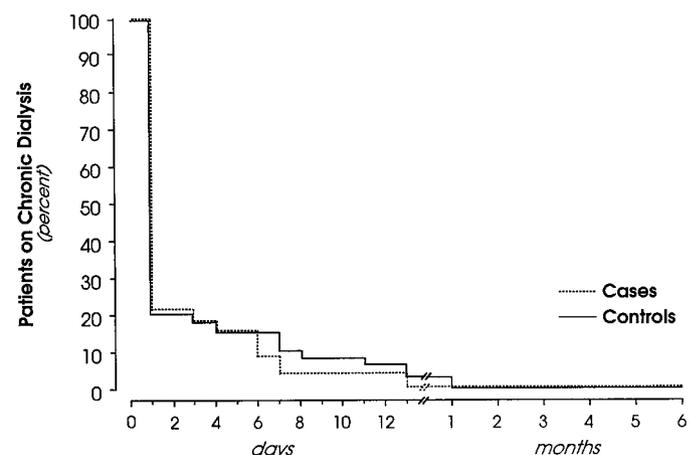


Figure 1. Percentage of cases and control subjects on chronic dialysis at different times.

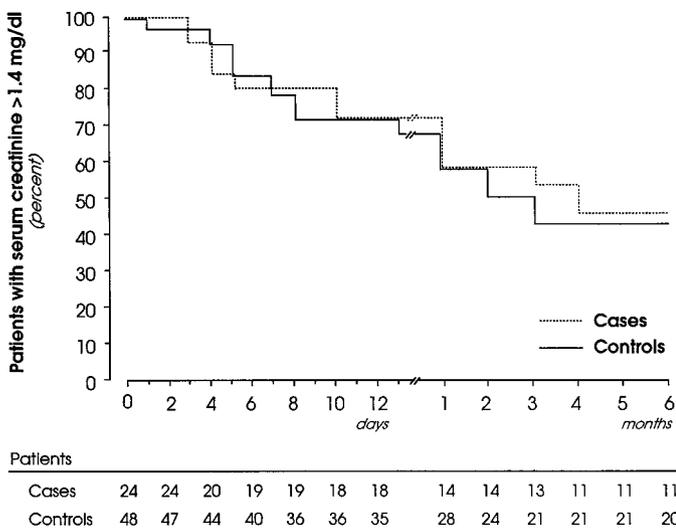


Figure 2. Percentage of cases and control subjects with serum creatinine >1.4 mg/dl at different times.

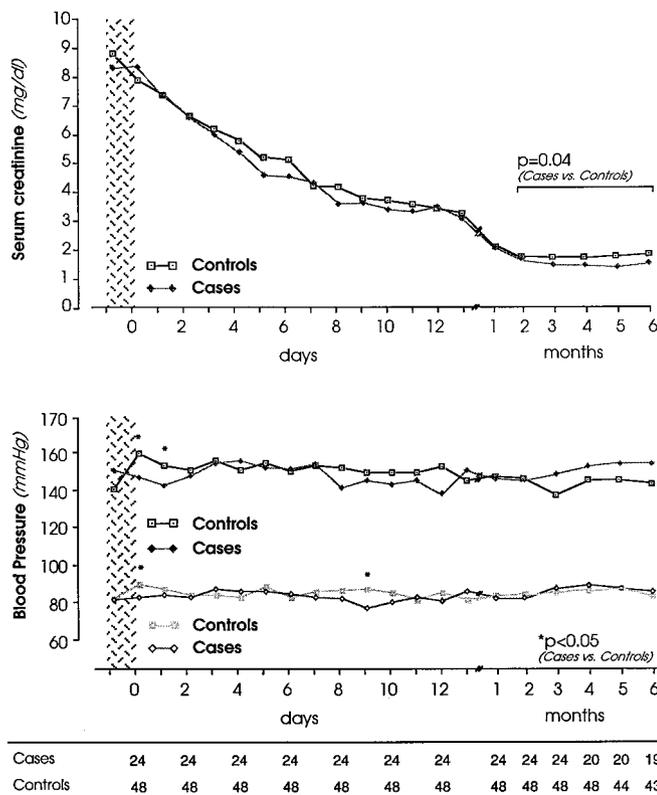


Figure 3. Time course of serum creatinine concentration and systolic/diastolic BP in cases and control subjects. Absolute numbers of cases and control subjects on follow-up at different times are given.

(diastolic) after transplant (Figure 3). Overall, average follow-up systolic BP values were comparable in the two groups ( $147.5 \pm 22.5$  versus  $148.9 \pm 21.6$  mmHg in cases and control subjects, respectively,  $P = 0.32$ ). On the contrary, average follow-up diastolic BP values were significantly lower in cases than in control subjects ( $83.2 \pm 11.5$  versus  $85.1 \pm 12.5$  mmHg,  $P = 0.008$ ).

In the entire study group, among the considered donor and recipient baseline characteristics, donor/recipient body weight was the only variable significantly associated at univariate ( $P = 0.0001$ ) and multivariate ( $P = 0.001$ ) analysis with last available serum creatinine concentrations (Table 3). Of note, the model found a similar trend even for donor/recipient BMI ratio at univariate ( $P = 0.01$ ) and at multivariate ( $P = 0.07$ ) analysis. Furthermore, both donor/recipient body weight ( $r = -0.549$ ,  $P = 0.0001$ , Figure 4) and BMI ( $r = -0.416$ ,  $P = 0.009$ ) ratios negatively correlated with serum creatinine values at last available visit. At univariate and multivariate analyses, the type of transplant and recipient anuria were not associated with last available serum creatinine values (Table 3). Donor creatinine clearance had no predictive value as well (Table 3), and did not correlate with final serum creatinine ( $r = -0.12$ ,  $P = 0.38$ ). When recipient creatinine clearance was considered as outcome variable, again donor/recipient body weight and BMI ratios were the only variables with a significant predictive value at univariate and at multivariate analyses (data not shown).

The incidence of acute allograft rejection was comparable in the two groups. Five cases (20.8%) versus 9 control subjects (18.8%) had one episode of acute rejection responsive to intravenous steroids ( $P = 1.00$ ). Rejection episodes occurred at posttransplant days 9, 13, 60 (two episodes), and 90 in cases, and at posttransplant days 4 (two episodes), 5, 7, 8, 9, 10, 13, and 150 in control subjects ( $P = 0.94$ ).

The overall incidence of major surgical complications was comparable in the two groups, but with a trend to an increased risk ( $P = 0.06$ ) of urinary tract fistulas requiring surgical correction among cases compared with control subjects (Table 4). At univariate analysis, recipient age was the only covariate

Table 3. Results of univariate and multivariate regression analysis of final serum creatinine concentration for different donor and recipient parameters

Parameter	Univariate P Value	Multivariate P Value
Donor age	0.44	0.265
Recipient age	0.81	0.264
Donor gender	0.35	0.616
Recipient gender	0.01	0.368
Donor creatinine clearance	0.85	0.163
Donor/recipient body weight	0.0001	0.001
Recipient diabetes mellitus	0.05	0.166
Recipient hypertension	0.99	0.143
Recipient anuria	0.18	0.459
Donor/recipient mismatches	0.97	0.781
Double versus single transplant	0.91	0.928

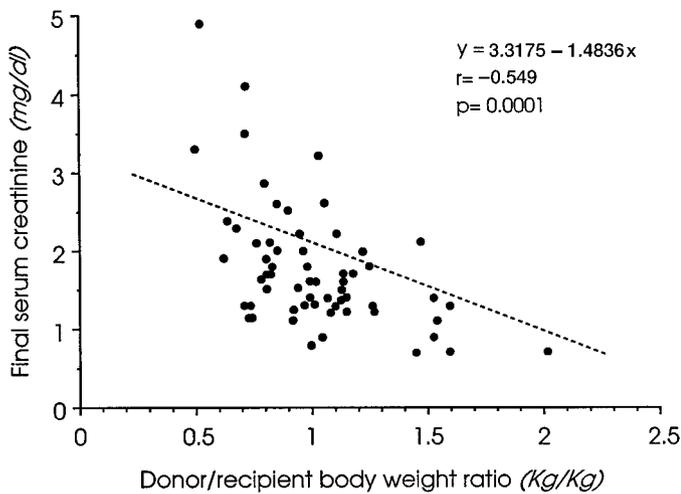


Figure 4. Correlation between donor/recipient body weight ratio and final serum creatinine concentration in the whole study group.

Table 4. Severe adverse events reported in double (cases) and single (control subjects) kidney recipients up to 6-mo follow-up

Adverse Event	Cases	Control Subjects
Urinary tract fistula	4	1
Sepsis from urinary tract	2	2
Deep vein thrombosis	1	1
Hematoma	1	0
Cytomegalovirus infection	2	3
Gastrointestinal bleeding	1	0
Bowel occlusion	0	1
Angina/angioplasty	0	1
Lung cancer	0	1

associated with the risk of urinary tract fistula ( $P = 0.04$ ). At multivariate analysis, however, none of the considered covariates (including double *versus* single transplant) was significantly associated with this risk. No renal artery or vein thrombosis was reported in either group.

## Discussion

This is the first study formally designed to compare in a prospective, controlled, and multicenter manner the short-term outcome of double transplants of marginal kidneys with that of single transplants of optimal kidneys. Overall, we found that double and single kidney transplants were associated with remarkably good short-term patient and organ survival, which reached 100% with both of the procedures. Furthermore, the overall incidence of surgical or infectious complications was comparable. These findings corroborate preliminary evidence from uncontrolled (13,14,17) or small (18,19) series, and from

the United Network of Organ Sharing Registry data (H. S. Mackenzie, G. M. Chertow, B. M. Brenner, E. L. Milford. Dual kidney transplantation in the United States, 1987–1995: A review of the United Network of Organ Sharing (UNOS) database, submitted for publication) showing a relatively good safety profile of the procedure, and would indicate that fear of more surgical complications or more infections should not prevent the systematic use of marginal kidneys in double procedure protocols.

The incidence and duration of posttransplant anuria requiring continued renal replacement therapy were virtually identical in cases and control subjects. The rate of renal function recovery was comparable as well, as documented by the similar course of serum creatinine concentrations and the comparable incidence of patients achieving normal renal function at each posttransplant evaluation. It is of note, however, that cases compared with control subjects had lower serum creatinine values over the last 5 mo follow-up and lower diastolic BP levels averaged during the entire study period. These findings could not be attributed to bias in donor/recipient selection, because all relevant clinical and laboratory parameters that could affect renal function recovery were accurately matched in the two groups. There also were no differences in general medical support or in immunosuppressive protocols between cases and control subjects. Cold and warm ischemia times were comparable in the two groups and likewise could not explain the better functional recovery in cases compared with control subjects. On the contrary, a worse short-term outcome would have been predicted on the basis of the older age of donors and recipients of double marginal kidneys compared with donors and recipients of single kidneys (20). Indeed, the finding that cases showed a trend to a better recovery would suggest that the increased number of nephrons provided by the double procedure might have contributed to enhanced filtration power of the graft despite the older age of the donors. Actually, findings that higher donor/recipient body weight and BMI ratios were both significantly associated with a better renal function recovery suggested that in our series better outcomes actually reflected conditions of more nephrons. This would indicate that the greater the renal mass to start with, the higher the number of viable nephrons that can survive a given ischemic, toxic, or early immune insult and therefore continue to provide enough filtration power to sustain graft function. This enhanced functional reserve might have contributed to the lower diastolic BP we found in double compared with single kidney recipients during the entire follow-up period. This might be of major clinical relevance, since it is well established that high BP is one of the strongest predictors and determinants of accelerated renal function deterioration and eventual failure of the graft (21). Evidence that kidneys after a single transplant, but not after a dual transplant, increased their filtration power by about 30% may have some relevance as well for long-term graft outcome. Of interest, single transplants from donors more than 60 yr old to age- and gender-matched recipients performed as well as kidneys from younger donors, since the excess of graft failure in the old-donor-age group was due entirely to recipient deaths (22).

Of note, the incidence of acute rejections was virtually identical in the two groups. This finding, therefore, suggests that the enhanced antigenic load provided by more nephron mass supplied with the double transplant does not enhance the immune response of the host. Actually, experimental data suggest that at least in some circumstances the opposite is true (23).

We conclude that transplanting two marginal kidneys otherwise destined to be discarded is as safe and tolerated as a single transplant, and possibly offers an improved filtration power without exposing the recipient to enhanced risk of delayed renal function recovery, acute allograft rejection, or kidney loss because of major surgical complications.

In the present report, we showed the main results of a short-term study. Follow-up data, which will become available in the next few years, will reveal whether transplanting two marginal kidneys is an effective way to expand the limited donor pool, thereby offering new hope for transplantation to a substantial percentage of patients on dialysis. Further investigations will also show whether double kidney transplantation, by providing more nephron mass, will serve to delay or prevent chronic allograft dysfunction in the long-term.

## Acknowledgments

This work was supported in part by Fondazione Casse di Risparmio delle Province Lombarde and by a special grant of the Istituto Superiore di Sanità, Rome, Italy.

## Appendix

### Investigators and Institutions

N. Serrallach, S. Gil-Vernet, D. Seron, J. M. Grino (Istituto Català de la Salut - Ciutat Sanitaria i Universitària de Bellvitge - L'Hospitalet de Llobregat, Barcelona); G. Locatelli, G. Rota, P. Ruggenenti, G. Remuzzi (Azienda Ospedaliera, Ospedali Riuniti, Bergamo); E. L. Milford, R. Kirkman, B. M. Brenner, (Brigham and Women's Hospital, Boston, MA); M. Beatini, U. Valente, V. Arcuri (Ospedale San Martino, Genova); M. Scalamogna, G. Sirchia (North Italian Transplant, Ospedale Maggiore Policlinico, Milano); J. Duke, E. H. Cole, L. C. Paul (The Toronto Hospital - St. Michael's Hospital, Toronto, Ontario, Canada).

### Database and Analysis

B. Ene-Jordache, A. Remuzzi, L. Tammuzzo, M. Lesti (Clinical Research Center for Rare Diseases "Aldo & Cele Daccò," Mario Negri Institute for Pharmacological Research, Bergamo).

### Score Definition and Analysis

A. Katz (St. Michael's Hospital, Toronto, Ontario, Canada) and T. Bertani (Azienda Ospedaliera, Ospedali Riuniti, Bergamo).

## References

- Cofan F, Oppenheimer F, Campistol JM: Advanced age donors in the evolution of renal transplantation. *Transplant Proc* 27: 2248–2249, 1995
- Alexander JW, Zola JC: Expanding the donor pool: Use of marginal donors for solid organ transplantation. *Clin Transplant* 10: 1–19, 1996
- Brenner BM, Meyer TW, Hostetter TH: Dietary protein intake and the progressive nature of kidney disease: The role of hemodynamically mediated glomerular injury in the pathogenesis of progressive glomerular sclerosis in aging, renal ablation, and intrinsic renal disease. *N Engl J Med* 307: 652–659, 1982
- Remuzzi G, Bertani T: Pathophysiology of progressive nephropathies. *N Engl J Med* 339: 1448–1456, 1998
- Feduska NJ: Donor factors in cadaveric renal transplantation. *Clin Transplant* 351–357, 1993
- Kuo PC, Johnson LB, Schweitzer EJ, Alfrey EJ, Waskewitz J, Bartlett ST: Utilization of the older donor for renal transplantation. *Am J Surg* 172: 551–555, 1996
- Brenner BM, Cohen RA, Milford EL: In renal transplantation, one size may not fit all. *J Am Soc Nephrol* 3: 162–169, 1992
- Rennke HG: Pathology of glomerular hyperfiltration. In: *The Progressive Nature of Renal Disease: Contemporary Issues in Nephrology*, Vol. 14, edited by Mitch WE, Brenner BM, Stein JH, New York, Churchill-Livingstone, 1986, pp 111–113
- MacKenzie HS, Azuma H, Rennke HG, Tilney NL, Brenner BM: Renal mass as a determinant of late allograft outcome: Insights from experimental studies in rats. *Kidney Int* 52: S38–S42, 1995
- Taal MW, Tilney NL, Brenner BM, MacKenzie HS: Renal mass: An important determinant of late allograft outcome. *Transplant Rev* 12: 74–84, 1998
- UNOS: Annual Report, and the UNOS Scientific Registry of Transplant Recipients. Richmond, VA, United Network of Organ Sharing, 1996
- Alfrey EJ, Lee CM, Scandling JD, Pavlakis M, Markezich AJ, Dafoe DC: When should expanded criteria donor kidneys be used for single versus dual kidney transplants? *Transplantation* 64: 1142–1146, 1997
- Lee CM, Scandling JD, Pavlakis M, Markezich AJ, Daloe DC, Alfrey EJ: A review of the kidneys that nobody wanted: Determinants of optimal outcome. *Transplantation* 65: 213–219, 1998
- Dafoe DC, Alfrey EJ: The expanded donor kidney: The Stanford experience with dual renal grafts. *Grafts* 1: 11–12, 1998
- Ruggenenti P, Perna A, Mosconi L, Pisoni R, Remuzzi G, on behalf of the "Gruppo Italiano di Studi Epidemiologici in Nefrologia (GISEN): Urinary protein excretion rate is the best independent predictor of ESRF in non-diabetic proteinuric chronic nephropathies. *Kidney Int* 53: 1209–1216, 1998
- Perna A, Gotti E, de Bernardis E, Perico N, Remuzzi G: A logistic regression model provides novel guidelines to maximize the anti-acute rejection properties of cyclosporine with a minimum of toxicity. *J Am Soc Nephrol* 7: 786–791, 1996
- Johnson LB, Kuo PC, Schweitzer EJ: Double renal allografts. *Transplant Rev* 12: 59–63, 1998
- Andrés J, Morales JM, Praga M, Ortuno T, Hernandez E, Rodicio JL, Diaz-Gonzalez R, Polo G, Aguirre F, Leiva O: Simultaneous double kidney from very old donors: Short-term outcome [Abstract]. *J Am Soc Nephrol* 8: 673A, 1997
- Remuzzi G, Ruggenenti P, Locatelli G, Camozzi L, Rota G, Resta B, on behalf of the Double Kidney Transplant Group: Double transplant of marginal kidneys is safe and allows a faster function recovery than single transplant of optimal kidneys [Abstract]. *J Am Soc Nephrol* 9: 694A, 1998
- Lucas BA, Vaughn WK, Spees EK, Sanfilippo F: Identification of donor factors predisposing to high discard rates of cadaver kidneys and increased graft loss within one year posttransplan-

- tation – SEOPF 1977–1982. South-Eastern Organ Procurement Foundation. *Transplantation* 43: 253–258, 1987
21. Opelz G, Wujciak T, Ritz E, for the Collaborative Transplant Study: Association of chronic kidney graft failure with recipient blood pressure. *Kidney Int* 53: 217–222, 1998
22. Sola R, Guirado L, Lopez Navidad A, Caballero F, Agraz I, Diaz M, Paredes D, Rodriguez S, Vizcarra D: Renal transplantation with limit donors: To what should the good results obtained be attributed? *Transplantation* 66: 1159–1163, 1998
23. Bishop GA, McCaughan GW, Sun J, Ross Sheil AG: Microchimerism and transplant tolerance. *Immunol Today* 18: 455–456, 1997

**This article can be accessed in its entirety on the Internet at  
<http://www.lww.com/JASN> along with related UpToDate topics.**