Impact of Graft Mass on the Clinical Outcome of Kidney Transplants

Magali Giral,* Jean Michel Nguyen,† Georges Karam,‡ Michelle Kessler,§ Bruno Hurault de Ligny,‖ Mattias Buchler,¶ François Bayle,# Carole Meyer,** Yohann Foucher,† Marie Laure Martin,† Pascal Daguin,* and Jean Paul Soulillou*

**Institut de Transplantation Et de Recherche en Transplantation and INSERM U437 (Immunointervention dans les Allo et Xénotransplantation), Nantes; †Service de Biostatistique, Pôle d'Information Médicale d'Evaluation et de Santé Publique, Saint Jacques Hospital, Nantes University Hospital, Nantes; ‡Service d'urologie, Place Alexis Ricordeau, Nantes; §Service de néphrologie, CHU, Nancy; ‖Service de néphrologie, Caen; ¶Service de néphrologie, Tours; #Service de néphrologie, Grenoble; and **Service de néphrologie, Strasbourg, France*

The effect of nephronic mass reduction of kidney transplants has not been analyzed specifically in a large cohort. Transplant injuries in cadaver kidney graft may have led to an underestimation of the magnitude of this factor. The aim of this study was to analyze the consequences of kidney mass reduction on transplantation outcome. The weights of 1142 kidney grafts were collected prospectively immediately before grafting. Donors and recipients <15 yr of age, simultaneous kidney/pancreas grafts, and technical failures before day 7 were excluded from the analysis. The analysis was performed on Cockroft-calculated creatinine clearance and proteinuria in 964 patients for whom all of the necessary information was available. This study reports that the smallest kidneys transplanted into the largest recipients (donor kidney weight/recipient body weight [DKW/RBW] <2 g/kg, $n = 88$) increased their clearance by 2.38 ml/min every month for 6 mo ($P < 0.0001$) and by 0.27 ml/min thereafter ($P < 0.0001$). Conversely, creatinine clearance did not change for the largest kidneys transplanted into the smallest recipients (DKW/RBW ratios ≥4 g/kg). Next, using a Cox model analysis, it was shown that the risk of having a proteinuria >0.5 g/kg was significantly increased for the low DKW/RBW ratios <2 g/kg with 50% of patients having a proteinuria, compared with DKW/RBW ratios ≥4 g/kg ($P < 0.001$). In cadaver transplant recipients, graft mass has a rapid impact on graft filtration rate and proteinuria. Avoiding major kidney/recipient inadequacy should have a significant influence on long-term transplant function.

J Am Soc Nephrol 16: 261–268, 2005. doi: 10.1681/ASN.2004030209

Kidney transplantation is the method of choice for the treatment of ESRD (1). Long-term kidney graft function depends on multiple influences, among which the host *versus* graft immune response represents a major component. Nevertheless, with the increasing life span of transplants, nonimmune factors that affect graft function, including high blood pressure (2) and metabolic disorders (high blood sugar, hyperlipidemia, and chronic nephrotoxicity of immunosuppressive drugs), also have been well identified (3,4). The major influence of nonimmune factors is indicated by the fact that the rate of graft loss is poorly influenced by the strength of the immunosuppressive regimen only after 1 year (2,5).

Another factor that may affect the long-term function and survival of a kidney transplant is the functional mass of the graft at the time of transplantation. Pioneered by Brenner (6), it is known that experimental acute reduction in kidney mass results in compensatory mechanisms that affect both the size of the remaining tissue and its function (7–10). However, hyperfiltration that occurs in the remaining nephrons has also been suggested as causing albuminuria and glomerulonephrosclerosis (11,12). More pertinent to the transplantation situation is the seemingly moderate mass reduction that prevails after donor uninephrectomy and also results in an adaptive response of the remaining kidney and hyperfiltration (13–15). Several studies have shown that the remaining kidney may present proteinuria after several decades (16–18). In addition, because kidneys that are used for transplantation have sustained insults stemming from donor trauma, in particular as a result of brain death (19) and the harvesting procedure, and because transplantation leads to new conditions of function in a new recipient environment (*e.g.*, mismatch between graft and recipient masses), the actual nephronic reduction of a transplant that is harvested from a cadaver donor is most likely underestimated (18,20).

In this article, we report on the first study of the effects of the allocation of a kidney graft mass (*i.e.*, kidney weight) on the long-term outcome of cadaveric kidney transplantation in a large cohort (1142 recipients). We show that the graft/recipient mass ratio has a significant impact on filtration rate and proteinuria. This last effect is noticeable even after a short interval,

Received March 18, 2004. Accepted September 17, 2004.

Published online ahead of print. Publication date available at www.jasn.org.

Address correspondence to: Dr. Jean Paul Soulillou, Institut de Transplantation et de Recherche en Transplantation and Inserm U437 (Immunointervention dans les Allo et Xénotransplantation), 30 bd Jean Monnet, 44093, Nantes, France. Phone: 33-2-40-08-74-10; Fax: 33-2-40-08-74-11; E-mail: jps@nantes.inserm.fr

Copyright © 2005 by the American Society of Nephrology

ISSN: 1046-6673/1601-0261

particularly when the adaptive response of the graft to the recipient mass is expected to be considerable. The effect of this parameter, alone or in combination with other immune or nonimmune factors that are known to influence graft success rate, is discussed.

Materials and Methods

Patients

Between April 1995 and June 2001, the weight of 1142 kidney grafts was collected prospectively and consecutively immediately before grafting. Our institution in Nantes and six other French transplantation centers (Nancy, Caen, Grenoble, Paris Bicêtre, Tours, and Strasbourg) participated in the study. Donors ($n = 40$) and recipients ($n = 15$) who were younger than 15 yr were excluded from the study, according to the growth-related changes in kidney and recipient size after transplantation. In addition, because some participating centers used bladder drainage for simultaneous kidney and pancreas grafts, we did not include these patients ($n = 103$) because their proteinuria measurements were uninterpretable. Patients in whom technical failure occurred, as defined as a definitive return to dialysis during the first 7 d after surgery, were also excluded ($n = 8$). Finally, data from one center (Paris Bicêtre) that initially participated in the weighing protocol but failed to provide patient follow-up were also excluded from the study ($n = 12$). Analysis thus was performed in the 964 remaining patients (including 7 living related donors) for whom all information was available. The mean follow-up period was 32 mo with a maximum of 94 mo. All patients received anticalcineurin inhibitors for maintenance therapy.

Kidney Weight

All participating centers were provided with the same electronic weighing scales (Maul; Gilbert Fourniture, France) with an accuracy of 1 g. The scales were located in the operating room. According to common procedure recommendations, kidney grafts were prepared first then weighed by the surgeon.

Parameters Studied

Clinical and biologic data concerning donors and recipients were obtained prospectively at the time of inclusion and centralized in the anonymous and coded study data bank located at Nantes University Hospital, in accordance with the local ethical committee requirements. Donor data include age, gender, creatinemia (μmol/L), and kidney weight (donor kidney weight [DKW] in g). Recipient data at the time of inclusion concerned age, gender, weight (recipient body weight [RBW] in kg), the ratio between DKW and RBW (DKW/RBW; in g/kg), the number of grafts, HLA-A-B-DR incompatibilities, anti–T panel reactive antibodies (%), and cold ischemia time (min). Moreover, at the time of each follow-up (3, 6, and 12 mo, and then every 12 mo until 48 mo), the following data were collected from recipients: Weight, creatinemia (μmol/L), creatinine clearance calculated according to the Cockroft formula {[(140 − age) × weight (kg)]/creatinemia μmol/L) × 1.04 for female or 1.23 for male recipient} (ml/min) and daily proteinuria (g/24 h). Also recorded were the occurrence of delayed graft function (as defined by the time interval, in days, to reach a Cockroft-calculated creatinine clearance >10 ml/min) (5), the occurrence of acute rejection episodes, and the time of death or definitive graft failure with return to chronic dialysis.

Statistical Analyses

The first objective of the study was to assess the effect of kidney and recipient mass at the allocation, defined by the DKW/RBW ratio, on graft function (Cockroft-calculated creatinine clearance [cCrCl]). To take into account interindividual variability, we first used a linear mixed-effect model (21). In this model, the effect of the DKW/RBW ratio was adjusted on all historical cofactors. As a preliminary study showed that the relationship between the cCrCl and the time interval from transplantation was linear with a break point at 6 mo, we then modeled the relation between the time and the clearance according to the two different slope before and after 6 mo. On the basis of biologic observations (change of mean of cCrCl at each data collected point), it was possible to identify three groups of patients according to three classes of ratio: DKW/RBW ratio (g/kg) <2, between 2 and 4, and ≥4. To allow for different cCrCl evolution in the three classes, we considered in the linear mixed-effect model an interaction between the time interval from transplantation and the DKW/RBW ratio.

The second aim was to assess the consequences of changes in graft filtration rate on the occurrence of kidney injury defined as a proteinuria. We built a Cox proportional-hazards model to determine which covariates and particularly DKW/RBW ratios were risk factors for the first occurrence of a proteinuria above a threshold of 0.5 g/24 h. Patients who died or underwent graft failure were censored. Finally, to study the impact and the rank of the DKW/RBW ratio on graft survival, we built a second Cox model whereby graft loss was defined as death or a definitive return in dialysis. For all tests, any variable that reached a $P < 0.20$ in the univariate analysis was introduced to the multivariate analysis. The Wald test was used to prove the effect of the variables. All data that were collected prospectively at the time of inclusion and during the follow-up were tested in each statistical model previously described. Finally, because a multicentric study implies that some clinical practice procedures and patient characteristics can vary between each center, each Cox proportional-hazards model was stratified on centers. The Software used was S-Plus 6.0 Professional.

Results

Demographic Characteristics

Among the 964 patients included in the study, 88.7% were recipients of a first graft. Sixty-two percent were male recipients, and 68% received a kidney from a male donor. The mean HLA incompatibility was 3 ± 1.3, with only 12% of patients having 5 or fewer incompatibilities. Pregraft anti–T cell immunization was observed in 23% of patients. The mean delayed graft function was 5.4 d after surgery. Finally, 20% of patients developed an acute rejection episode during their follow-up period. The population characteristics are given in Table 1.

Kidney Weight Distribution According to Donor Gender and Age

The mean kidney weight ± SD of the whole population was of 202 ± 56 g (range 76 to 460). As expected, male kidneys were heavier than female kidneys with a mean weight of 216 ± 56 g (range 76 to 460) and 173 ± 42 g (range 94 to 335), respectively ($P < 0.0001$). In effect, 76% of female kidneys weighed <200 g as compared with only 44% for male kidneys. DKW distribution according to donor gender is illustrated in Figure 1A. Moreover, kidney weight increased significantly with donor age from 15 to 45 yr, independent of gender. However, after 45 yr of age, kidney weight remained stable, as shown in Figure 1B. Similarly, the mean recipient weight, which was used for the calculation of the DKW/RBW ratio, also increased with age (Figure 1C).

Table 1.[a] Demographic characteristics

Recipient age (yr)	45.2 ± 13 (range 15–75)
Recipient gender (male)	62%
Recipient weight (kg)	65.4 ± 13 (range 26–165)
First graft	88.74%
HLA-A-B-DR incompatibility	3 ± 1.3 (range 0–6)
HLA incompatibility ≤1	12% (n = 116)
HLA incompatibility ≥5	12% (n = 116)
Anti–T PRA >0%	23% (n = 224)
Anti–T PRA >80%	3.5% (n = 34)
Cold ischemia time (h)	24.4 ± 9.6 (range 1–50)
Delayed graft function (d)	5.37 ± 6 (range 1–50)
Acute graft rejection ≥1	20% (n = 197)
Donor age (yr)	40.3 ± 14 (range 15–74)
Donor gender (male)	68% (n = 653)
Last donor creatinemia (μmol/L)	100 ± 60 (range 5–890)
Kidney weight (g)	202 ± 56 (range 76–460)

[a]PRA, panel reactive antibodies.

Effect of DKW/RBW Ratio on Graft Function

Because body and kidney masses varied significantly between women and men as well as with age (Table 2), we took the option to analyze the effect of gender and the DKW/RBW ratio separately. On the one hand, despite a similar DKW/RBW ratio for male kidneys transplanted to male recipients (3.2 ± 1.2 g/kg; range 0.9 to 8.0) and for female kidneys transplanted to female recipients (3.1 ± 1 g/kg; range 1.2 to 6.9; NS), the 1-yr cCrCl was 20% higher for the first combination (cCrCl 63 ml/min) than for the second combination (52 ml/min; $P < 0.0001$). On the other hand, although the DKW/RBW ratio was highly different when male kidneys were given to female recipients (3.7 ± 1.3 g/kg; range 1.5 to 8.4) compared with female kidneys given to male recipients (2.6 ± 0.9 g/kg; range 1 to 5.6; $P < 0.0001$), the 1-yr graft function was similar for both with a cCrCl of 58.7 ± 23 ml/min (range 16 to 149) and 58 ± 19 ml/min (range 11 to 140), respectively, indicating that small female kidneys donated to large male recipients (*i.e.*, a small DKW/RBW ratio) increased their filtration rate to fit their new body mass (Table 2). In contrast, large male kidneys that were donated to small female recipients (*i.e.*, a high DKW/RBW ratio) were not associated with an increased function. Next, the effects of DKW/RBW ratios were studied, irrespective of donor and recipient gender. The mean 1-yr cCrCl was 54 ± 18 ml/min (range 15 to 108) for high DKW/RBW ratios ≥4 g/kg (n = 205; largest kidneys/smallest recipients) and increased by 10% for ratios between 2 and 4 g/kg (60 ± 20 ml/min; range 7 to 134; $P < 0.02$) and by 20% for small ratios <2 g/kg (n = 88; smallest kidneys/largest recipients; 69 ± 24 ml/min; range 25 to 149; $P < 0.001$). Moreover, a significantly higher mean cCrCl was observed at each follow-up interval (3, 6, 12, 24, and 36 mo), which continuously increased after 3 mo for the small ratios <2 g/kg and ratios between 2 and 4 but not for ratios ≥4 g/kg (Figure 2). The highest cCrCl observed for small ratios cannot be explained by an increase in weight of the patients of this group during the follow-up. In effect, only patients in a high DKW/RBW ratio group (≥4 g/kg) had a significant increase of weight after the graft ($P < 0.001$). In summary, whatever the recipient and donor gender, small kidneys that were donated to large recipients could adapt to the recipient body mass by increasing their function.

Patients with a Low DKW/RBW Ratio Dramatically Increase Their Filtration Rate

This analysis was performed on a specific population that excluded patients with graft failure or those who died (n = 780). To test the hypothesis of graft filtration rate adaptation in conditions of small DKW/RBW ratios, we constructed a linear mixed-effect model. We showed that creatinine clearance evolved differently in the time before and after 6 mo according to the DKW/RBW ratios. As shown in Table 3, for DKW/RBW ratios <2 g/kg (smallest kidneys in largest recipients), creatinine clearance increased significantly by 2.38 ml/min every month until 6 mo ($P < 0.0001$) and by 0.27 ml/min thereafter ($P < 0.0001$). For DKW/RBW ratios between 2 and 4, cCrCl increased significantly by 1.14 ml/min every month for the first 6 mo ($P < 0.0001$) and by 0.11 ml/min per mo thereafter ($P < 0.0001$). However, for DKW/RBW ratios ≥4 g/kg, creatinine clearance did not change with time. Other covariates that were found to influence cCrCl in time after transplantation were donor and recipient age, which had a similar impact on graft function ($P < 0.0001$), cold ischemia time ($P = 0.0093$), and delayed graft function ($P < 0.0001$). Finally, at 12 mo, female recipients had a cCrCl 11 ml/min less than male recipients who received a male kidney ($P < 0.0001$) when they received a female kidney and 5.86 ml/min when they received a male kidney ($P < 0.0001$). To summarize, cCrCl was affected by donor and recipient gender and age, cold ischemia time, delayed graft function, and DKW/RBW ratio in time.

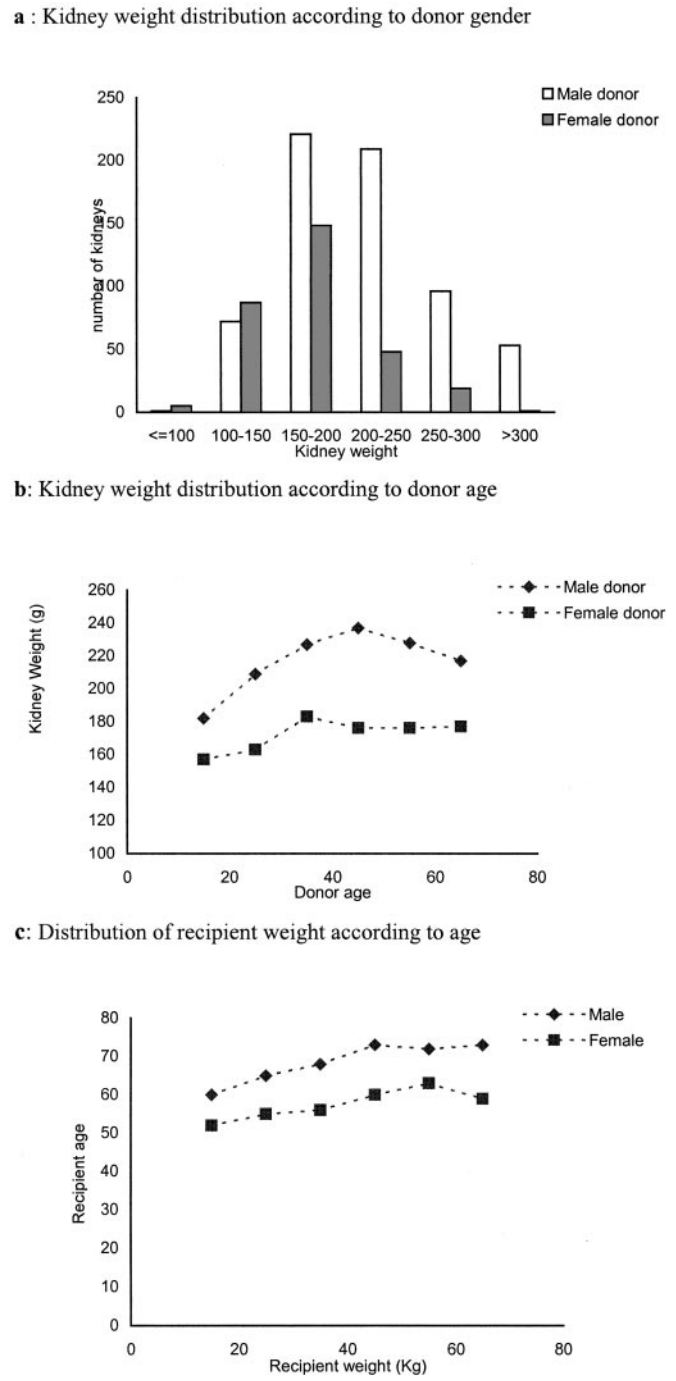

Figure 1. (A) Kidney weight distribution according to donor gender; 76% of female kidneys weighed <200 g. (B) Kidney weight distribution according to donor age. In both men and women, kidney weight increased with donor age until 45 yr of age and decreased thereafter. (C) Distribution of recipient weight according to age. Recipient body weight increased until 45 yr of age and remained stable thereafter.

*Low DKW/RBW Ratios Are Associated with Proteinuria (*n *= 909)*

We next investigated whether the highest filtration rate observed with low DKW/RBW ratios resulted in deleterious consequences in terms of graft function and particularly the occurrence of proteinuria, the first quantifiable usual parameters that correlate with kidney graft injuries after hyperfiltration. We observed that recipient gender interfered significantly with donor age ($P = 0.005$); the results then were calibrated for donor age at, for instance, 45 yr (Table 4). One third of patients presented a proteinuria >0.5 g/24 h during the follow-up. Patients with the lowest DKW/RBW ratio (<2 g/kg) presented the highest (50%) and earliest occurrence (10.43 mo) of proteinuria compared with 33% and 13.44 mo for DKW/RBW ratios between 2 and 4 g/kg and 23% and 14.33 mo for DKW/RBW ratios ≥4 g/kg. The probability of the proteinuria >0.5 g/24 h occurring for the first time during the follow-up correlated with the DKW/RBW ratio. In effect, the risk of proteinuria occurrence increased 1.4-fold for the low ratios <2 g/kg, compared with DKW/RBW ratios between 2 and 4 g/kg ($P = 0.03$) and 2-fold compared with DKW/RBW ratios ≥4 g/kg ($P < 0.001$). Delayed graft function and the recipient's being male were also found to be risk factors for the occurrence of proteinuria.

*Graft Survival Analysis (*n *= 905)*

Despite the effects of small DKW/RBW ratios on the filtration rate and proteinuria, no effect of DKW/RBW ratios *per se* on graft survival was observed according to Cox multivariate analysis at the end of the study survey (Figure 3). However, the risk of graft loss increased significantly with increasing donor age (in years; relative risk 1.02; 95% confidence interval 1.00 to 1.03; $P = 0.019$) and for six HLA incompatibilities (relative risk 3.10; 95% confidence interval 1.39 to 6.81 $P < 0.0053$). When the covariates that also were found to be significantly associated with proteinuria were tested for a possible synergistic effect with low DKW/RBW ratios (<2 g/kg; recipient gender and delayed graft function, see Table 4), no significant impact on graft survival was noted. Finally, no additional effect of other parameters classically associated with poor long-term graft survival (cold ischemia time, panel reactive antibodies, acute rejection episodes, and donor and recipient age) was observed.

Discussion

Graft/recipient mass ratio represents a potentially important parameter in terms of kidney graft outcome. However, this "simple" parameter has never been studied in a large cohort of kidney transplant recipients. In addition, in this study, we investigated the direct effect of kidney graft mass on transplant function in recipients of unrelated grafts. Given the multicentric nature of the study, to limit the risk of multiplication of data errors related to a more accurate formula (*e.g.*, Nankivell), we chose to use the most simple validated formula (Cockroft and Gault) to assess graft function (22).

Several studies have explored the effect of graft mass on transplantation outcome via indirect estimation using parameters such as the donor body mass or body surface area (23–25). However, body surface area has been shown to correlate positively with glomerular volume but not with the number of glomeruli (26). In contrast, kidney mass is related to the number of glomeruli and to the adaptive capacity of a grafted organ to its new physiologic conditions after transplantation. Moreover, actual donor body weight is difficult to estimate in the

Table 2.[a] Effect of the DKW/RBW ratio on graft function according to the kidney/recipient gender combination

Mean	Male Kidney/Male Recipient (n = 423)	Male Kidney/Female Recipient (n = 230)	Female Kidney/Male Recipient (n = 175)	Female Kidney/Female Recipient (n = 135)
Kidney weight (g)	218 ± 60 (76–128)	211 ± 50 (120–360)	175 ± 42 (94–335)	171 ± 42.8 (95–300)
Recipient weight (kg)	70 ± 12.6 (41–124)	59 ± 12.6 (26–107)	69 ± 12.4 (41–112)	57 ± 12 (30–100)
DKW/RBW ratio (g/kg)	3.22 ± 1.2 (0.9–8)	3.70 ± 1.3 (1.5–8.4)	2.64 ± 0.9 (1–5.6)	3.10 ± 1 (1.2–7)
Recipient age	45.6 ± 12 (18–73)	44.7 ± 12 (15–75)	44.5 ± 13.5 (15–69)	46 ± 13 (15–70)
Serum creatinine at 12 mo (μmol/L)	143 ± 49 (54–400)	119.5 ± 50 (54–400)	156 ± 56 (78–465)	124 ± 52 (60–453)
cCrCl at 12 mo (ml/min)	63.6 ± 20 (7.6–133)	58.7 ± 23 (16–149)	58 ± 19 (11–140)	52 ± 19 (10–124)
cCrCl at 48 mo (ml/min)	60 ± 25 (9–131)	57 ± 25 (13–148)	58 ± 21.5 (25–151)	53 ± 22 (22–139)

[a]DKW/RBW, donor kidney weight, recipient body weight; cCrCl, Cockroft-calculated creatinine clearance.

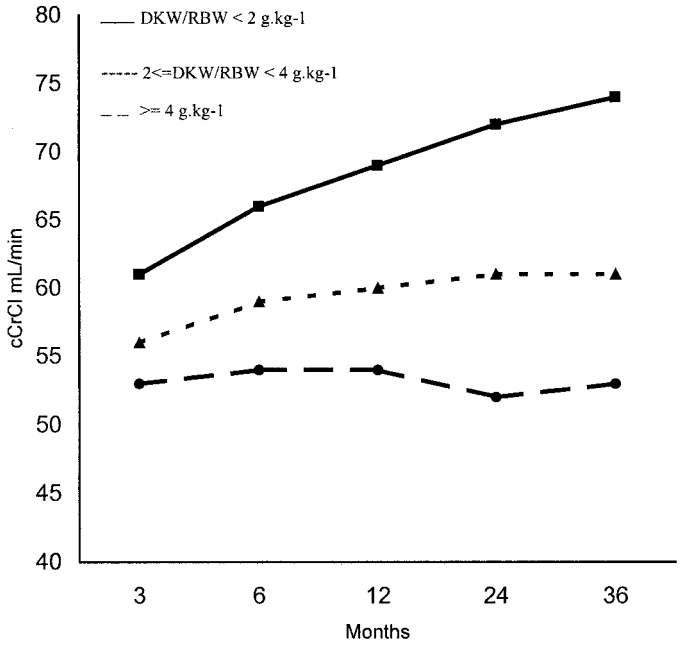

Figure 2. Kidney graft function in time according to the donor kidney weight/recipient body weight (DKW/RBW) ratio. The distribution of the mean Cockroft-calculated creatinine clearance at 3, 6, 12, 24, and 36 mo in each class of DKW/RBW ratios is shown. Small ratios <2 g/kg result in an increase in cCrCl at each data time point. When transplantations were performed with a high DKW/RBW ratio (≥4 g/kg), graft function remained stable in time.

case of cadaver donor transplantation, although a more precise measurement can be obtained in the case of living related donors. However, even in this latter situation, donor height and weight do not account for more than one third of kidney weight variability (27). Recent data that have revisited the relationship among kidney mass, glomerular volume, and glomerulus number (28,29) reinforce the need to analyze directly the DKW in this type of study.

Only two studies have explored the impact of DKW/RBW ratios but on a limited cohort of transplants (132 and 259, respectively) (30,31). In addition, these studies were restricted to living related donors, a situation in which functional graft loss is minimal as a result of the selection of healthy donors and in which several factors that are known to aggravate nephron loss in cadaver grafts are absent (see reference (18) for review). Two other studies were based on the analysis of kidney size (32) or volume (33) in cadaver donors and showed discordant effect on graft survival. Insufficient precision of nephron mass estimation, together with limited cohort sizes and statistical power, may explain some divergent results concerning the impact of kidney mass on transplant survival rate and late outcome (see reference (34) for review).

Donor gender has a significant impact on graft survival; in particular, old kidneys that are from female donors and transplanted into male recipients have been shown to have the poorest outcome (35). Terasaki *et al.* (36) and Brenner and Milford (37) suggested that the gender effect may be explained by a mismatch between the functional demand of the recipient and an inadequate nephronic mass. However, although we found no difference in graft survival according to donor and recipient gender match (data not shown), we observed a gender effect on graft function that cannot be explained exclusively by the DKW/RBW ratio (Table 3).

Our study, based on a cohort of 964 kidney recipients, enabled the analysis of a significant number of transplantations performed in strongly mismatched donor/recipient combinations with a low DKW/RBW ratio (<2 g/kg) representing the population at risk (approximately 10%). We show that the kidney grafts with the smallest DKW/RBW ratios (<2 g/kg) strongly improved their filtration rate not only in the early phase after transplantation (*i.e.*, approximately 15 ml/mo for the first 6 mo) but continuously and significantly for the entire 4-yr survey period (Figure 2). Importantly, a large proportion (50%) of the kidney grafts that were transplanted in this situation developed proteinuria, a difference that was highly significant compared with the other combinations studied. The cohort then was reanalyzed retrospectively for antihypertensive medication in all centers, except one in Strasbourg (n = 69) for technical reasons. However, no difference in the percentage of patients on at least one antihypertensive drug was observed. The global 84% of patients who were taking antihypertensive medication was equally distributed in the three groups of ratio. Moreover, because a difference in the use of an angiotensin-

Table 3.[a] Mixed linear model analysis of CrCl changes according to DKW/RBW ratios and parameters classically influencing graft function

	b	95% CI	*T* Test	*P* Value
Recipient age (yr)	−0.36	0.28 to 0.44	−9.00	0.0001
Donor age (yr)	−0.36	0.28 to 0.44	−9.00	0.0001
Gender[b]				
female kidney in female recipient	−11.03	−14.22 to −7.84	−6.77	0.0001
female kidney in male recipient	−6.06	−9.00 to −3.12	−4.04	0.0001
male kidney in female recipient	−5.86	−8.47 to −3.25	−4.41	0.0001
Cold ischemia time (h)	−0.15	−0.27 to −0.03	−2.50	0.0093
Delayed graft function (d)	−0.38	−0.56 to −0.20	−4.22	0.0001
Time interval from transplantation <6 mo				
DKW/RBW <2 g/kg	2.38	1.52 to 3.20	5.70	0.0001
DKW/RBW 2–4 g/kg	1.14	0.84 to 1.45	7.32	0.0001
DKW/RBW ≥4 g/kg	0.26	−0.29 to 0.82	0.92	0.3560
Time interval from transplantation ≥6 mo				
DKW/RBW <2 g/kg	0.27	0.19 to 0.35	6.42	0.0001
DKW/RBW 2–4 g/kg	0.11	0.07 to 0.14	6.63	0.0001
DKW/RBW ≥4 g/kg	−0.02	−0.08 to 0.04	−0.70	0.4861

[a]CI, confidence interval;
[b]Reference class: Male donor kidney in male recipient.

Table 4.[a] Cox model analysis of proteinuria occurrence

	b	s(b)	RR	95% CI (RR)	*P* Value
DKW/RBW (g/kg)[b]					
2.0 ≤ DKW/RBW < 4.0	−0.362	0.170	0.70	0.50 to 0.97	0.0340
DKW/RBW ≥4.0	−0.708	0.215	0.49	0.32 to 0.75	0.0010
Recipient gender[c]	0.309	0.126	1.36	1.06 to 1.74	0.0140
Delayed graft function (d)	0.022	0.007	1.02	1.0 to 1.04	0.0430

[a]RR, relative risk.
[b]Reference class: DKW/RBW <2.0 g/kg.
[c]Reference class: Female recipient.

converting enzyme (ACE) and/or angiotensin II receptor antagonists (ARA) could have influenced the assessment of proteinuria, the cohort was also reanalyzed for ACE and ARA medication. No significant difference was observed in the distribution among the three groups of DKW/RBW ratios despite the highest percentage of patients on ACE or ARA medication in the lowest ratio group (40% compared with 38% and 32% in group 2 to 4 g/kg and ≥4 g/kg, respectively). This clearly rules out the possibility that, in the low ratio group, proteinuria was associated with a lower rate of ARA and ACE medication. Rather, this finding fits with an expected increase in such a prescription in proteinuric patients. Whereas an increase in glomerular filtration can be considered as a physiologic adaptation of the graft to its new conditions (38), the proteinuria onset that occurred during the first 4 yr of follow-up in the patients who received a graft with a low DKW/RBW ratio (<2) sharply contrasted with the delay of proteinuria onset reported in nephrectomized healthy individuals that usually exceeded 10 yr (see reference (13) for review). This early occurrence of proteinuria validates the hypothesis that the cadaveric donor source of these transplants represents a situation that is of a different nature to that prevailing after nephrectomy in a healthy individual in terms of estimated reduction in nephron mass (harvesting trauma, cold ischemia time, and brain death; see reference (18) for review). That low DKW/RBW ratios were not found to result in an increase in proteinuria in a study that was limited to transplantation that was performed with living related kidney donors (31), whereas more severe kidney mass reduction (>50%) after nephrectomy as a result of kidney carcinoma resulted in proteinuria mimicking the situation of low DKW/RBW ratios, fits with this concept.

However, we did not find evidence that this adaptive response—even in the lowest DKW/RBW ratio group with proteinuria—affected graft survival at the end of the 4-yr survey period of our study. Moreover, we were unable to find a synergistic effect between low DKW/RBW ratios and the usual detrimental factors detected in our study or classically linked to late graft dysfunction such as donor or recipient age, cold

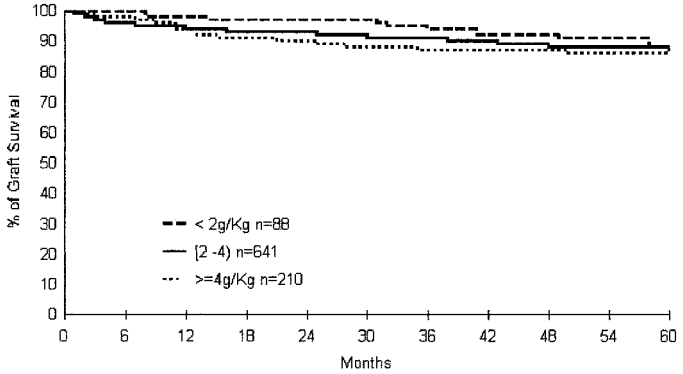

Figure 3. Kaplan-Meier graft survival according to the DKW/RBW ratio. The DKW/RBW ratios have no impact on graft survival at the end of the study survey. One and 4-yr graft survival was 98 and 89% for patients with small DKW/RBW ratios <2 g/kg, 94 and 88% for patients with ratios between 2 and 4 g/kg, and 94 and 85% for patients with ratios ≥4 g/kg, respectively.

ischemia time, acute graft rejection, or delayed graft function. Nevertheless, in animals, hyperfiltration with proteinuria has been clearly identified as a major risk factor for renal failure (39,40). The eventuality that grafting with a low DKW/RBW ratio will not ultimately result in increased graft loss is also contradicted by the finding that in human nephronic mass, reduction exceeding 50% of the initial renal mass is associated with renal failure after 10 yr (11), a time lapse that is pertinent to the current expected graft function in cadaver transplantation. Taken together, our data suggest that kidney mass, a parameter that is simple to measure, should be taken into account during kidney attribution. Furthermore, our results suggest that grafting in the context of DKW/RBW ratios <2 g/kg, a condition that was closely linked with early occurrence of proteinuria, should be avoided.

References

1. Hariharan S, Johnson CP, Bresnahan BA, Taranto SE, McIntosh MJ, Stablein D: Improved graft survival after renal transplantation in the United States, 1988 to 1996. *N Engl J Med* 342: 605–612, 2000
2. Opelz G, Dohler B: Cyclosporine and long-term kidney graft survival. *Transplantation* 72: 1267–1273, 2001
3. Suthanthiran M, Strom TB: Renal transplantation. *N Engl J Med* 331: 365–376, 1994
4. Paul LC, Muralidharan J, Benediktsson H: Immunological and hemodynamic mechanisms in chronic renal allograft rejection. *Transpl Immunol* 4: 39–42, 1996
5. Dantal J, Hourmant M, Cantarovich D, Giral M, Blancho G, Dreno B, Soulillou JP: Effect of long-term immunosuppression in kidney-graft recipients on cancer incidence: Randomised comparison of two cyclosporin regimens. *Lancet* 351: 623–628, 1998
6. Brenner BM: Nephron adaptation to renal injury or ablation. *Am J Physiol (Lond)* 249: F324–F337, 1985
7. Malt RA: Humoral factors in regulation of compensatory renal hypertrophy. *Kidney Int* 23: 611–615, 1983
8. Conti FG, Striker LJ, Lesniak MA, MacKay K, Roth J, Striker GE: Studies on binding and mitogenic effect of insulin and insulin-like growth factor I in glomerular mesangial cells. *Endocrinology* 122: 2788–2795, 1988
9. Rennke HG, Klein PS: Pathogenesis and significance of nonprimary focal and segmental glomerulosclerosis. *Am J Kidney Dis* 13: 443–456, 1989
10. Wesson LG: Compensatory growth and other growth responses of the kidney. *Nephron* 51: 149–184, 1989
11. Novick AC, Gephardt G, Guz B, Steinmuller D, Tubbs RR: Long-term follow-up after partial removal of a solitary kidney. *N Engl J Med* 325: 1058–1062, 1991
12. Hostetter TH, Olson JL, Rennke HG, Venkatachalam MA, Brenner BM: Hyperfiltration in remnant nephrons: A potentially adverse response to renal ablation. *J Am Soc Nephrol* 12: 1315–1325, 2001
13. Fotino S: The solitary kidney: A model of chronic hyperfiltration in humans. *Am J Kidney Dis* 13: 88–98, 1989
14. Velosa JA, Offord KP, Schroeder DR: Effect of age, sex, and glomerular filtration rate on renal function outcome of living kidney donors. *Transplantation* 60: 1618–1621, 1995
15. Ramcharan T, Matas AJ: Long-term (20–37 years) follow-up of living kidney donors. *Am J Transplant* 2: 959–964, 2002
16. Hakim RM, Goldszer RC, Brenner BM: Hypertension and proteinuria: Long-term sequelae of uninephrectomy in humans. *Kidney Int* 25: 930–936, 1984
17. Kasiske BL, Ma JZ, Louis TA, Swan SK: Long-term effects of reduced renal mass in humans. *Kidney Int* 48: 814–819, 1995
18. Taal M, Tilney N, Mackenzie H: Renal mass: An important determinant of late allograft outcome. *Transplant Rev* 12: 74–84, 1998
19. Schnuelle P, Berger S, de Boer J, Persijn G, van der Woude FJ: Effects of catecholamine application to brain-dead donors on graft survival in solid organ transplantation. *Transplantation* 72: 455–463, 2001
20. Brenner BM, Cohen RA, Milford EL: In renal transplantation, one size may not fit all. *J Am Soc Nephrol* 3: 162–169, 1992
21. Laird NM, Ware JH: Random-effects models for longitudinal data. *Biometrics*. 38: 963–974, 1982
22. Nankivell BJ, Gruenewald SM, Allen RD, Chapman JR: Predicting glomerular filtration rate after kidney transplantation. *Transplantation* 59: 1683–1689, 1995
23. Gaston RS, Hudson SL, Julian BA, Laskow DA, Deierhoi MH, Sanders CE, Phillips MG, Diethelm AG, Curtis JJ: Impact of donor/recipient size matching on outcomes in renal transplantation. *Transplantation* 61: 383–388, 1996
24. Cho Y, Terasaki P, Cecka J: Should excessive height and weight differences between the kidney donor and recipient be avoided. *Transplant Proc* 29: 104–105, 1997
25. Lee L, Auersvald L, Claus E: Body size mismatch between donor and recipient and the developments of chronic in renal transplantation. *Transplant Proc* 29: 111, 1992
26. Nyengaard JR, Bendtsen TF: Glomerular number and size in relation to age, kidney weight, and body surface in normal man. *Anat Rec* 232: 194–201, 1992
27. Kasiske BL, Umen AJ: The influence of age, sex, race, and body habitus on kidney weight in humans. *Arch Pathol Lab Med* 110: 55–60, 1986

28. Jones SE, Nyengaard JR, Flyvbjerg A, Bilous RW, Marshall SM: Birth weight has no influence on glomerular number and volume. *Pediatr Nephrol* 16: 340–345, 2001
29. Neugarten J, Kasiske B, Silbiger SR, Nyengaard JR: Effects of sex on renal structure. *Nephron* 90: 139–144, 2002
30. Nishimura Y, Tomikawa S, Beck Y: Kidney graft weight as an important risk factor for long term graft survival. *Transplant Proc* 30: 107–110, 1998
31. Kim Y, Kim M, Han D: Evidence that the ratio of donor kidney weight to recipient body weight, donor age, and episodes of acute rejection correlate independently with live graft function. *Transplantation* 74: 280–283, 2002
32. Nicholson ML, Windmill DC, Horsburgh T, Harris KP: Influence of allograft size to recipient body-weight ratio on the long-term outcome of renal transplantation. *Br J Surg* 87: 314–319, 2000
33. Miles AM, Sumrani N, John S, Markell MS, Distant DA, Maursky V, Hong JH, Friedman EA, Sommer B: The effect of kidney size on cadaveric renal allograft outcome. *Transplantation* 61: 894–897, 1996
34. Kasiske BL, Snyder JJ, Gilbertson D: Inadequate donor size in cadaver kidney transplantation. *J Am Soc Nephrol* 13: 2152–2159, 2002
35. Neugarten J, Srinivas T, Tellis V, Silbiger S, Greenstein S: The effect of donor gender on renal allograft survival. *J Am Soc Nephrol* 7: 318–324, 1996
36. Terasaki PI, Cecka JM, Takemoto S, Yuge J, Mickey MR, Park MS, Iwaki Y, Cicciarelli J, Cho Y: Clinical transplants 1988. Overview. *Clin Transpl* 409–434, 1988
37. Brenner BM, Milford EL: Nephron underdosing: A programmed cause of chronic renal allograft failure. *Am J Kidney Dis* 21: 66–72, 1993
38. Terasaki PI, Koyama H, Cecka JM, Gjertson DW: The hyperfiltration hypothesis in human renal transplantation. *Transplantation* 57: 1450–1454, 1994
39. Praga M, Morales E: Renal damage associated with proteinuria. *Kidney Int Suppl* 82: 42–46, 2002
40. Reichel H, Zeier M, Ritz E: Proteinuria after renal transplantation: Pathogenesis and management. *Nephrol Dial Transplant* 19: 301–305, 2004