Transplantation

Clinical Implications for Graft Function of a New Equation Model for the Ratio of Living Donor Kidney Volume to Recipient Body Surface Area

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Purpose: We propose an equation that predicts graft function after kidney transplantation by using donated kidney volume and recipient body surface area (BSA).
Materials and Methods: Included were 261 cases of living kidney transplantation between 2007 and 2009. Preoperative computed tomography scans were performed and the donated kidney volume was measured by use of a three-dimensional reconstruction program (Ripidia). The estimated glomerular filtration rate (eGFR) was calculated by using the modification of diet in renal disease formula. Donated kidney volume, preoperative renal function, and demographic factors of both donors and recipients were evaluated as predictors.
Results: The mean ages of the donors and recipients were 40.8 and 41.6 years, respectively. The mean donated kidney volume and donated kidney volume/recipient BSA ratio were 153.4 mL and 96.9 mL/m^2, respectively. Mean preoperative and postoperative 12-month eGFR of recipients were 7.1 and 59.7 mL/min, respectively, and the mean preoperative eGFR of donors was 92.2 mL/min. Donated kidney volume/recipient BSA ratio, donor age, and recipient gender were the significant predictors of eGFR level (p < 0.001) and eGFR < 45 mL/min at postoperative 12 months (p=0.005, p < 0.001, and p=0.006). From the multiple linear regression equation and predicted probability from logistic regression, we could calculate the equation for the ratio of living donor kidney volume to recipient BSA on graft function.
Conclusions: Graft kidney volume/recipient BSA ratio, donor age, and recipient gender were predictors of graft function 12 months after kidney transplantation. Although we are concerned only with the preoperative, this equation model could help physicians to counsel patients concerning their postoperative prognosis and to avoid insufficient volume donations.

Keywords: Delayed graft function; Kidney; Living donors; Organ size; Transplantation

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INTRODUCTION

Although the kidney transplantation field has grown significantly, several barriers to success remain. The primary barrier is the imbalance between supply and demand of organs. With increasing numbers of patients with end-stage renal disease, there is a growing need for kidney transplantation, yet the numbers of donors are limited. Thus, to overcome the imbalance, it is necessary to maximize kidney graft survival. From this perspective, we ini-

tiated investigation of factors to improve graft function and survival after kidney transplantation [1].

Factors related to graft function after kidney transplantation are generally classified into donor-dependent factors and recipient-dependent factors: age, sex, pretransplant or posttransplant course, ischemia and reperfusion injury, rejection, and immune suppression are included [2]. Among these, graft renal volume is a useful factor for prediction before surgery and is related to graft outcome after kidney transplantation [3-5].

Insufficient nephron volume does not satisfy the metabolic demand of recipients and eventually causes kidney hyperfiltration in recipients. This may lead to progression of kidney diseases and ultimately to chronic allograft failure [2].

In previous studies, to prove the association between nephron volume and graft outcome, the kidney volume was measured by using ultrasound to measure either the donor body surface area (BSA) or donated kidney. Recently, not only living donor kidney anatomy but also the kidney volume before transplantation can be measured via three-dimensional computed tomography (3D-CT) [3]. By doing this, multiple prognostic analyses have been done of recipient graft function after the surgery via donor kidney volume [6-10]. However, to the best of our knowledge, no study has developed an equation based on the objective analysis of graft function by donated kidney volume and recipient BSA.

In this study, we analyzed graft function after kidney transplantation on the basis of donated kidney volume and recipient BSA as measured by the 3D-CT scan. An equation was derived via statistical analysis to predict the graft function of recipients before the surgery.

MATERIALS AND METHODS

Living kidney transplantations were performed for 302 subjects from 2007 through 2009 by a single center. Of them, 41 cases with findings including posttransplant ischemic injuries of the graft, episodes of rejection, drug toxicities, systemic or local infection, or any surgical complications, such as adverse vascular or urologic events that resulted in functional decease of the kidney graft, were excluded. Thus, 261 cases of living kidney transplantations were included in the study. The study protocol was reviewed and approved by the Institutional Review Board.

1. Preoperative CT scan
All CT examinations were performed by use of a standardized examination protocol with a multislice 64 detector row helical CT scanner (Lightspeed, GE Medical Systems, Milwaukee, WI, USA). The slice width of the CT scan was 40 mm. Scanning was initiated with a scout image covering the abdomen. A precontrast image was with 2.5-mm slices; the table rotation time was 0.5 seconds with 120 kV and 100 mAs. The arterial phase was obtained 12 seconds and the venous phase 60 seconds after the initiation of the contrast

FIG. 1. A parenchymal boundary in the sliced image used in calculating total kidney volume.

bolus. The arterial phase included a volume covering the diaphragm to the pelvis. After the image was acquired, the arterial phase and venous phase images were reconstructed by axial 3-mm and 1-mm images and coronal 3-mm images. A 3D reconstruction image was acquired with 0.625-mm slices.

2. Measurement of renal volume
CT images of the renal parenchyma with a 5-mm slice thickness were used. Functioning renal parenchyma was defined as normally enhanced areas on CT images. Kidney volume was measured with the tissue segmentation tool program Rapidia (Infinitt, Seoul, Korea). When we drew a parenchymal boundary in every sliced image, the program automatically calculated intraboundary area and calculated total kidney volume by summing the areas (Fig. 1).

3. Analysis of recipient graft function
To evaluate graft function, estimated GFR (eGFR) was calculated by using the modification of diet in renal disease (MDRD) formula in recipient group, preoperatively and postoperatively (postoperative 12 months). The preoperative eGFRs of the donors were also calculated. Donated kidney volume, preoperative renal function, and demographic factors of both donors and recipients were evaluated as predictors.

4. Statistical analysis
Multivariate analysis using the chi-square test and Student t-test was performed to identify predictors of outcomes. Multiple linear regression and multivariate logistic regression analysis were also applied on the equation for estimated graft function. All statistical analyses were performed by using SPSS ver. 17.0 (SPSS Inc., Chicago, IL, USA). $p < 0.05$ was considered statistically significant.

RESULTS

The mean age of the donors and recipients was 40.8 and

41.6 years, respectively. The body mass index (BMI) and BSA of the donors and recipients were 23.5±2.8 kg/m^2 and 1.70±0.16 m^2, and 21.7±3.1 kg/m^2 and 1.63±0.17 m^2, respectively. Preoperative creatinine (Cr; mg/dL) and postoperative 1 year Cr of donors and recipients were 0.86±0.13 and 1.21±0.21, and 9.45±3.8 and 1.39±0.70, respectively. The preoperative MDRD (mL/min/1.73 m^2) and postoperative 1 year MDRD of donors and recipients were 92.2±14.0 and 62.5±9.84, and 7.16±3.88 and 59.7±17.3, respectively (Table 1).

In the univariate analysis, donated kidney volume/recipient BSA ratio, donor age, donor gender, and pre-

operative donor eGFR were statistically significant for eGFR and eGFR < 45 mL/min at 12 months. For the multivariate analysis, we chose the variables that were not multicollinear. Preoperative eGFR was a significantly related factor in the univariate analysis, but there was multicollinearity when we entered that term into a model with donor age and donated kidney volume/recipient BSA ratio. For donor-recipient match, which is the object of this study, we must include the variable that contains the recipient characteristics during the multivariate analysis. We included the donated kidney volume/recipient BSA ratio variable and excluded the preoperative GFR variable. Donated kidney volume/recipient BSA ratio, donor age, and donor gender were significant predictors of the eGFR level and eGFR < 45 mL/min/1.73 m^2 at postoperative 12 months (Table 2). This combination was more predictable than 1) the combination of donor age and donor gender (r^2=0.136, p < 0.001) and 2) the combination of donor age, preoperative MDRD of donor, and donated kidney volume (kidney size), which were previously known as preoperative predictors of graft renal function (r^2=0.220, p < 0.001).

With the regression coefficient and odds ratios from the regression analysis, we predicted 12-month graft function. From the multiple linear regression equation and predicted probability equation from the logistic regression, we could devise the new equation for estimated graft function (Table 3). In a total of 261 cases, eGFR > 45 occurred in 215 cases and eGFR < 45 occurred in 46 cases. The area under the curve (AUC) of the receiver operator characteristic curve for the predicted probability equation was 0.772 (p < 0.001, standard error [SE]=0.04) (Fig. 2). This equation was a more powerful predictor than 1) the equation from donor age and donor gender and 2) the equation from donor age, preoperative MDRD of donor, and donated kidney vol-

TABLE 1. Overall characteristics of donors and recipients

Characteristic	Mean±SD
Donor	
Age (y)	40.8±10.8
Sex (male/female)	131:130
Body mass index (kg/m^2)	23.5±2.8
Body surface area (m^2)	1.70±0.16
Preoperative creatinine (mg/dL)	0.86±0.13
Postoperative 1 y creatinine (mg/dL)	1.21±0.21
Preoperative MDRD (mL/min/1.73 m^2)	92.2±14.0
Postoperative 1 y MDRD (mL/min/1.73 m^2)	62.50±9.84
Recipient	
Age (y)	41.6±12.1
Sex (male/female)	114:147
Body mass index (kg/m^2)	21.7±3.1
Body surface area (m^2)	1.63±0.17
Preoperative creatinine (mg/dL)	9.45±3.80
Postoperative 1 y creatinine (mg/dL)	1.39±0.70
Preoperative MDRD (mL/min/1.73 m^2)	7.16±3.88
Postoperative 1 y MDRD (mL/min/1.73 m^2)	59.7±17.3

SD, standard deviation; MDRD, modification of diet in renal disease.

TABLE 2. Univariate and multivariate analysis of 12-month graft function

Graft function	Significant factor	Univariate p-value	Multivariate Mean effect or odds ratio	Multivariate 95% CI	Multivariate p-value
eGFR at 12 mo	Donated kidney volume/recipient BSA ratio	< 0.001	0.306	0.194–0.419	< 0.001
	Donor age	< 0.001	−0.538	−0.725 to −0.352	< 0.001
	Donor gender	0.011			
	Preoperative donor eGFR	< 0.001			
	Recipient age	0.900			
	Recipient gender	0.658	−6.164	−10.524 to −1.803	< 0.001
	Preoperative recipient eGFR	0.401			
eGFR < 45 mL/min at 12 mo	Donated kidney volume/recipient BSA ratio	0.018	−0.033	0.945–0.990	0.005
	Donor age	< 0.001	0.092	1.050–1.143	< 0.001
	Donor gender	0.001			
	Preoperative donor eGFR	0.007			
	Recipient age	0.941			
	Recipient gender	0.202	1.194	1.414–7.707	0.006
	Preoperative recipient eGFR	0.935			

CI, confidence interval; eGFR, estimated glomerular filtration rate; BSA, body surface area.

TABLE 3. Predictive equation for 12-month graft function

	Equation
eGFR (mL/min)	$=60.536+0.306$ [V/BSA (mL/m^2)]-0.538 [donor age]-6.164 (if female recipient, -12.328) ($r^2=0.228$, $p<0.001$)
Prediction probability of eGFR<45 mL/min	$=1 <1+\exp \{-4.197-0.033$ [V/BSA (mL/m^2)]$+0.092$ (donor age)$+1.194$ (if female recipient, $+2.388$)$\}>$

eGFR, estimated glomerular filtration rate; V/BSA, kidney volume/body surface area.
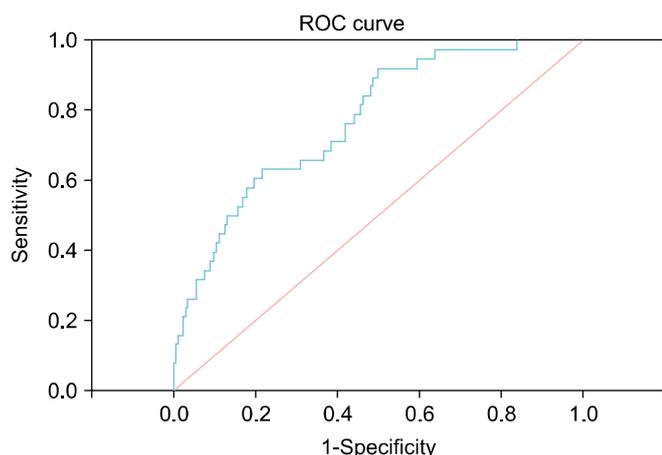

FIG. 2. Receiver operator characteristic (ROC) curve for predictive equation for 12-month graft function.

ume (for each: AUC=0.746, $p<0.001$, SE=0.04; AUC= 0.735, $p<0.001$, SE=0.38).

DISCUSSION

Kidney transplantation is the treatment of choice in end-stage renal diseases because it provides better patient survival and quality of life compared with dialysis. Living kidney donor transplantation gives the most favorable outcomes in general compared with deceased donor kidney transplantation and is performed with very careful examinations before the surgery [11-16]. However, needs in kidney transplantations heavily outnumber the number of organs, meaning that not all patients can be treated. Although many efforts have been made to resolve such issues, the most important point is to maximize efficiency by selecting the most appropriate donor and recipient in advance of the surgery. To achieve this, it is critical to predict kidney graft function before surgery so that appropriate donors and recipients can be found.

Surrogate markers predicting kidney graft function after transplantation have been researched. These markers include kidney weight/recipient body weight, donor body weight or BSA/recipient body weight or BSA, graft kidney volume/recipient body weight, graft kidney volume/recipient BSA, graft weight or volume or donor BMI, and recipient BMI. Stoves et al. [17] reported that the risk of proteinuria was higher with a low donor-to-recipient body weight

(<2 g/kg) ratio than with a high ratio (>4 g/kg) after transplantation [18-20]. Further, Douverny et al. [10] showed a low kidney graft survival rate in renal transplant recipients with high BMI compared with recipients with low BMI. It was reported that BMI is strongly associated with graft outcome, meaning that either extremely high or low BMI would result in unfavorable graft outcomes. In that study, it was shown that recipient BMI was related to eGFR 12 months after kidney transplantation [10]. A study investigated the effects of donor kidney size on recipient outcomes. Poggio et al. [11] addressed the strong association between recipient GFR, measured by 125I-iothalamate, and kidney volume, which was measured via conventional techniques 2 years after the surgery (i.e., transplantation of kidney). In addition, lower kidney volume may cause acute rejection as well. Hugen et al. [1] reported a correlation between kidney volume and recipient outcomes by using the CT volumetric technique.

In contrast with the above findings of an association between living-donor kidney volume and graft functions, there was a lack of association between deceased-donor kidney volumes and kidney function/recipient survival. This might be because additional factors (e.g., cold ischemia) affect outcomes in deceased-donor kidney [6]. Furthermore, Nyengaard and Bendtsen [18] found that graft function was not related to donated kidney volume as measured by preoperative 3D-CT in Taiwanese patients, but that only effective renal plasma flow and donor age seemed to be associated with early graft function.

When it comes to graft function, various studies have focused only on volume and its association with graft function. Insufficient nephron volume does not satisfy the metabolic demand of recipients and eventually causes kidney hyperfiltration in recipients. This may result in progression of kidney diseases and is significant because it may end in chronic allograft failure [2]. To avoid such hyperfiltration, it is very important to confirm the proper nephron volume early. Although weight has been considered an important surrogate marker because nephron numbers cannot be estimated *in vivo* [13-17], it is difficult to be accurate because it counts the weights of other attached tissues (e.g., sinus fat, renal pelvis, hilar fat, some perirenal fat) along with actual renal parenchyma. On the basis of the results of a study that addressed the significant association between kidney volume, analyzed by using 3D-CT, and graft kidney weight, measured in a operation room, it was suggested that measuring functional volume

might be more effective [3].

Poggio et al. [11] studied the predictors of graft function after kidney transplantation with donor kidney volume/recipient body weight ratio. Lee et al. [3] studied the relationship between donor kidney volume or the ratio of donor kidney volume to recipient BSA and graft function of recipients. They also included variables of recipient body weight, BSA, and donor age. They found that the donor kidney volume and the ratio of donor kidney volume to recipient BSA had significant meaning for graft function at 1 month and 6 months after transplantation (b=2.090, p=0.039 at 1 month, and b=0.223, p=0.018 at 6 months vs. b=0.235, p=0.039 at 1 month, and b=0.269, p=0.014 at 6 months, respectively). So, they proposed the ratio of donor kidney volume to recipient BSA as an important predictor after transplantation.

There are several methods for measuring kidney volume, such as plain radiography, intravenous pyelography, ultrasonography, and CT. Of them, the 3D-CT method has been investigated most extensively. 3D-CT possesses several merits for measuring kidney volume. First, it is less invasive than conventional angiography. Second, it can predict the outline of the kidney more accurately. 3D-CT makes it easy to differentiate the main vessel, ureter, renal parenchymal, and so on. Thus, 3D-CT has benefits because it accurately analyzes kidney parenchymal volume, representing the actual nephron via volumetric software. By doing that, relative GFR can be estimated on the basis of the relative ratio of left-right kidney volumes [18]. In fact, it was shown that the volume (of kidney) and estimated GFR were strongly associated each other [21].

The objective of the present study was to find functionally appropriate donor and recipient patients before the actual surgery; the authors aimed to improve the prediction by drawing a novel equation that had not previously been tested. The authors were able to predict graft functions 12 months after surgery by using information (e.g., such as donor age, recipient sex, and donated kidney volume/recipient BSA ratio) retrieved before the surgery from the patients who received the living kidney. The equation derived from this study should be informative and helpful for screening for a donor kidney that may not maintain the eGFR of the graft kidney in recipients higher than 45, in advance of the actual surgery. This is believed to be beneficial for patients being counseled regarding findings in renal function after the surgery.

On the other hand, the present study also had several limitations. First, it was a retrospective study and a relatively small number of patients were included. Second, the study could not investigate the association between kidney volume and histological findings of the graft kidney because histological examinations were not performed. Last, other factors that may affect renal functions (e.g., factors derived in the middle of or after the surgery) were excluded in the analysis to focus on our original study objective, which was predicting factors prior to surgery.

CONCLUSIONS

Graft kidney volume/recipient BSA ratio, donor age, and recipient gender are predictors of graft function 12 months after kidney transplantation. Although we were concerned only with the preoperative variables, this equation could help physicians to counsel patients on the postoperative prognosis before transplantation and to avoid an insufficient volume donation.

CONFLICTS OF INTEREST
The authors have nothing to disclose.

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