

# The Mismatch of Donor/Recipient Size Influences the Development of Proteinuria in Allograft Kidney Transplants

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=국문초록=

## 신공여자과 수혜자사이의 체격불균형이 이식신의 단백뇨 발생에 미치는 영향

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장기적인 신이식 소실은 주로 만성 이식신 기능장애로 인해 일어나며 이의 원인으로 면역학적인 요인 뿐만 아니라 비면역학적인 요인도 기여한다고 알려져 있다. 최근 비면역학적인 요인의 하나로 신이식시 불충분한 신원의 공급으로 인한 과여과 현상이 만성 이식신 기능 장애에 중요한 역할을 하며, 공여자의 신장무게/수혜자의 체중비(kidney weight/body weight ratio, 이하 KW/BW ratio)를 이러한 과여과 현상의 표지자로 이용할 수 있다고 제안되었다. 이에 저자 등은 신공여자과 수혜자 사이의 체격불균형이 만성 이식신 기능장애에 미치는 영향을 알아보려고, 1979년 4월부터 1994년 12월 사이에 연세의료원에서 신이식을 받은 환자 1256예 중 생체신이식을 받았고, 면역억제제로 cyclosporine A를 투여하였으며, 수술후 1년 이상 추적이 가능하였던 635예를 대상으로 KW/BW ratio가 단백뇨 및 신기능 부전에 미치는 영향을 연구하여 다음의 결과를 얻었다.

1) 신공여자 및 수혜자의 평균 연령은 각각  $35.2 \pm 11.2$ ,  $35.6 \pm 10.1$  세, 남녀비는 1.8 : 1, 2.1 : 1이었고, 혈연간 이식은 260예, HLA 6(A, B, DR) 항원 적합도는  $2.5 \pm 0.9$ , KW/BW ratio는  $2.72 \pm 0.45$ (1.75 ~ 4.39)g/kg, 추적 기간은  $48.2 \pm 24.2$ (13 ~ 124)개월이었다.

2) 대상 환자의 KW/BW ratio를 2.5g/kg을 기준으로 두군으로 나누었을 때, 2.5 g/kg이하인 군에서 여자 공여자로부터 남자 수혜자로의 이식의 빈도가 의미있게 많았으며(44.3% vs. 11.3%,  $p < 0.05$ ), 신공여자 대 수혜자의 체표면적비도 의미있게 낮았다( $0.94 \pm 0.06$  vs.  $1.12 \pm 0.10$ ,  $p < 0.05$ ).

3) 신이식후 임상 결과는 KW/BW ratio가 2.5 g/kg 이하인 군에서 2.5 g/kg 이상인 군에 비해 단백뇨의 발생이 의미있게 많았고(44.5% vs. 33.9% at 5 year,  $p < 0.05$ ), 5년 이식신 생존율도 의미있게 낮았으나(82.7% vs. 89.5%,  $p < 0.05$ ), 급성 거부반응 및 신부전증의 발생은 양군 사이에 차이가 없었다.

4) 다변량 분석 결과 신공여자의 연령(risk ratio 1.52, 95% confidence interval 0.55 ~ 0.79,  $p = 0.0000$ ), 이식후 1년내의 급성 거부반응 빈도(risk ratio 1.36, 95% confidence interval 0.62 ~ 0.87,  $p = 0.0003$ ), 그리고 KW/BW ratio(risk ratio 1.19, 95% confidence interval 1.01 ~ 1.40,  $p = 0.0367$ )가 이식신의 단백뇨 발생에 영향을 미치는 독립적인 인자이었다.

이상의 결과로 KW/BW ratio로 표현되는 신공여자과 수혜자 사이의 체격불균형이 이식신의 단백뇨 발생에 영향을 미치는 것으로 사료되며, 만성 이식신 기능 장애에 과여과 현상을 포함한 비면역학적인 요인이 미치는 영향에 대한 전향적 연구가 필요할 것으로 사료된다.

**Key Words:** Chronic allograft dysfunction, Size mismatch, Proteinuria, Kidney transplantation

Long-term renal graft losses are mainly due to chronic allograft dysfunction(CAD). In addition to immunologic factors, non-immunologic factors also contribute to CAD. It has recently been proposed<sup>1,2</sup> that hyperfiltration from inadequate nephron dosing at the time of kidney transplantation(KT) plays an important role in CAD and donor kidney weight(KW)/recipient body weight(BW) ratio can be a surrogate marker for that mismatch. To investigate the influence of the mismatch of donor/recipient size on the CAD, we evaluated the effect of KW/BW ratio for the development of proteinuria and renal insufficiency.

## PATIENTS AND METHODS

Between April 1979 and December 1994, 1256 renal transplantations were performed at our center and among them 635 cases were selected based on the following exclusion criteria; azathioprine-treated recipients, diabetic nephropathy, HBsAg(+) or anti-HCV(+) at the time of KT, pediatric recipients(<15 years old), non-compliance, follow-up duration of less than one year, and biopsy proven cyclosporine nephrotoxicity, transplant glomerulopathy, recurrent or de novo glomerulonephritis.

Medical records of donor and recipient were reviewed to calculate body surface area(BSA) and KW/BW ratio using the values of the donor and recipient's height(Ht) and body weight(BW) at the time of KT. BSA was calculated using the formula of DuBois<sup>3</sup>:  $BSA = BW^{0.425} \times Ht^{0.725} \times 0.007184$ . The weight of donated kidney was calculated using the formula of Kasiske and Umen<sup>4</sup>:  $KW = -36.6 + 195.1 \times BSA$ . Baseline serum creatinine was selected as the stable one at 3 months after KT, and the initiation of antirejection therapy was defined as acute rejection. CAD was regarded as the development of persistent proteinuria(>500 mg/day) or renal insufficiency (progressive increase in serum creatinine concentration by more than 50% from baseline) in the absence of other specific causes.

The mean age and sex(male:female) ratio of recipients were  $35.6 \pm 10.1$  years and 2.1 : 1, respectively. Those of donors were  $35.2 \pm 11.2$  years and 1.8 : 1 Two hundred

and sixty patients were living-related, and the number of HLA-A,-B, and -DR antigen matches was  $2.5 \pm 0.9$ (mean). The mean of KW/BW ratio was  $2.72 \pm 0.45$ (1.75 ~ 4.39) g/kg. Univariate and multivariate analysis using Kaplan-Meier and Cox regression analysis were performed.

## RESULTS

In patients with KW/BW ratio of  $\leq 2.5$  g/kg, the

**Table 1.** Characteristics of patients according to KW/BW ratio

	KW/BW ratio	
	$\leq 2.5$ g/kg (N=219)	$> 2.5$ g/kg (N=416)
Recipient Age(years)	$37.1 \pm 10.2^*$	$34.8 \pm 10.1$
Sex(% of male)	85.4*	58.7
Donor Age(years)	$36.8 \pm 1.6^*$	$34.3 \pm 11.0$
Sex(% of male)	45.7*	73.8
No. of HLA 6 Ag match $< 3 : \geq 3$	113 : 106	228 : 188
% of grafts from female to male	44.3*	11.3
D/R BSA <sup>1</sup> ratio	$0.94 \pm 0.06^*$	$1.12 \pm 0.10$
Follow-up duration(months)	$47.7 \pm 24.5$	$48.5 \pm 24.1$

\* $p < 0.05$ , vs. KW/BW ratio  $> 2.5$ , Values are Mean  $\pm$  S.D.

<sup>1</sup>D/R BSA: donor/recipient body surface area

**Table 2.** Comparison of the renal outcome according to KW/BW ratio

	KW/BW ratio	
	$\leq 2.5$ g/kg (N=219)	$> 2.5$ g/kg (N=416)
Acute rejection(%)	31.5	32.5
Postop. proteinuria(%)	63/219(28.8)*	86/416(17.1)
Postop. renal insufficiency(%)	50/219(22.8)	93/416(22.4)
% of proteinuria at 5 year	44.5*	33.9
% of renal insufficiency at 5 year	34.0	38.6
Graft survival at 5 year(%)	82.7*	89.5

\* $p < 0.05$ , vs. KW/BW ratio  $> 2.5$ , Values are Mean  $\pm$  S.D.

**Table 3.** Cox regression analysis of variables affecting the development of proteinuria after KT

Vairables	Risk atio	95% C.I.	P value
Donor age>50	1.52	0.55~0.79	0.0000
Acute rejection*	1.36	0.62~0.87	0.0003
KW/BW ratio≤2.5	1.19	1.01~1.40	0.0367

\*acute rejection within 1 year post-KT

frequency of graft from female to male was significantly higher, and the donor-to-recipient BSA ratio was also lower, compared to the patients with KW/BW ratio of > 2.5 g/kg(Table 1). The proportions of patients exhibiting proteinuria at 5 year and graft survival at 5 year were significantly lower in KW/BW ratio of ≤ 2.5 g/kg than in KW/BW ratio of > 2.5(Table 2).

On multivariate analysis of variables affecting the development of proteinuria, old-aged donor, acute rejection within 1 year post-KT, and KW/BW ratio of ≤ 2.5 g/kg were independent risk factors(Table 3). However the KW/BW ratio was not the risk factor for renal insufficiency. The independent risk factors affecting renal insufficiency were old-aged donor, acute rejection within 1 year post-KT, and recipient age younger than 50 years of age.

## DISCUSSION

The results of our study showed that KW/BW ratio was one of the risk factors for the development of proteinuria following renal allograft. As to the mechanism involved proteinuria, the hyperfiltration caused by size mismatch between donor and recipient is speculated. Our finding is compatible with the notion that KW/BW ratio can be a marker of nephron dosing as proposed by Brenner et al<sup>1</sup>. On the other hand, KW/BW ratio did not significantly influence the renal insufficiency, but it should be confirmed by further long-term follow-up. The range of KW/BW ratio was relatively narrow, because cadaveric transplantation had rarely been performed. In conclusion, the size mismatch between donor and recipient as expressed by the ratio of KW/BW seems to influence the development of proteinuria, but further studies are needed to ascertain the potential impact of non-immunologic factors including hyperfiltration on allograft dysfunction.

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