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□ 원 저 □

Effects of Dietary Protein on the Progression of Early Chronic Renal Failure in Subtotally Nephrectomizid Rats

Kyo Sun Kim, Kee Hyuk Kim, Sang Yun Kim, Yong Joo Kang, and Won Jae Maeng

Dept. of Pediatrics and Pathology, KonKuk University, College of Medicine, and Dept. of Feed and Nutritional Science, College of Animal Husbandry, Seoul, Korea.

= Abstract =

Purpose : The protective effects of dietary protein on the progression of renal failure were studied in subtotally nephrectomized rats.

Methods : Treatment groups were as follows; 5/6 nephrectomy and a normal protein (18.5%) diet (NP); 5/6 nephrectomy and a low protein (6%) diet (LP); 5/6 nephrectomy, a normal protein diet and converting enzyme inhibitor, enalapril (NPE); 5/6 nephrectomy, a low protein diet and enalapril (LPE). Both diets were isocaloric and had the same phosphorus content. Proteinuria, remnant kidney weight, mesangial matrix expansion score and glomerular volume were assessed at 4, 12 and 16 weeks after renal ablation.

Results : LP and NP developed progressive hypertension. Eight weeks after surgery, LPE and NPE controlled hypertension. LP, LPE, and NPE had significantly less proteinuria than NP at 16 weeks ($P<0.05$). Kidney weight in LP were markedly less enlarged than NP ($P<0.05$). There was no difference in kidney weight between LPE and NPE. At 12 and 16 weeks the mesangial matrix expansion score was significantly less in LP, LPE, and NPE compared to NP ($P<0.05$). At 12 and 16 weeks mean glomerular volume was significantly less in LP compared to NP ($P<0.05$). At 12 and 16 weeks mean glomerular volume in LPE was significantly less compared to NPE.

Conclusion : Dietary protein restriction afforded considerable protection from renal injury in the rat remnant kidney model. During the enalapril treatment, there was no additional protective effect of dietary protein restriction against the development of renal lesions.

Key words : Chronic renal failure, Dietary protein restriction, Converting enzyme inhibitor, Remnant kidney model

INTRODUCTION

Chronic renal disease is commonly associated with the progressive loss of nephron. When nephron loss is severe the remaining nephron respond by compensatory functional and structural hypertrophy[1,2].

Pharmacologic intervention by restriction of dietary protein intake ameliorates the proteinuria and the structural abnormalities usually observed in a number of experimental models[3-6]. A similar response was achieved by the use of converting enzyme inhibitor (CEI) in rats after subtotal nephrectomy. That is, treatment with CEI resulted in a diminution of proteinuria and fewer glomerular lesions[7,8].

In the previous study, we investigated whether dietary protein restriction would enhance the renal protective effect of

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책임저자: 김교순, 건국의대 소아과학교실
Tel: 02-450-9675 Fax: 02-458-1134

antihypertensive treatment in the excision remnant kidney model. We found that the combined treatment of a low protein diet and antihypertensive drugs didn't appear to show any additional effect to attenuate glomerular injury[9].

The present study was designed to evaluate the effects of two diets with a low and a normal protein content on the progression of early chronic renal failure in the remnant kidney model. Subtotal nephrectomy induces persistent hypertension, heavy proteinuria and compensatory hypertrophy in rats[10,11]. An increase in mesangial matrix and/or cellularity, epithelial cell fusion, and glomerular hypertrophy, seen in the remnant kidney model, which were the early structural changes of glomerular injury, that eventuated in glomerular scarring[12]. The sclerotic lesion results from the progressive accumulation of several extracellular matrix proteins and mesangial cell proliferation and matrix expansion following various stimuli to mesangial cells[13].

This study was carried out to determine the protective effect of dietary protein restriction, by comparing the data of nephrectomized rats on both a low and a normal protein diet. We also compared the data of enalapril-treated nephrectomized rats on both a low and a normal protein diet.

MATERIALS AND METHODS

Experiments were performed on male Sprague-Dawley rats weighing 200 to 250 grams that were randomly divided into 4 treatment groups of 21 animals each. The first study evaluated the effects of dietary protein on 5/6 nephrectomized rats. The treatment groups were as follows: 5/6 nephrectomy and a normal protein diet (NP); 5/6 nephrectomy and a low protein diet (LP). The second study analyzed the effects of dietary protein on enalapril-treated 5/6 nephrectomized rats. The treatment groups were as follows: 5/6 nephrectomy, a normal protein diet and enalapril (NPE); 5/6 nephrectomy, a low protein diet and enalapril (LPE).

Rats were allowed free access to water and rat chow diets. Diets varied in the amount of protein casein (18.5% versus 6%), but were equal in caloric content (383 Kcal/g) and phosphorus (0.40%). Diets also contained the same proportion of fat, fiber, electrolytes, trace minerals, and vitamins. Diets were complete in all nutritional requirements. The essential amino acid contents were equal in both diets. Enalapril (Renitec, ChongWae Pharm. co.) was dissolved in drinking water, at a dose of 50 mg/liter throughout the duration of the study. The solution was replaced every 24 hours, and its daily consumption was calculated. A preliminary pilot study showed identical food and water consumption by all animals. All animals were housed in individual metabolic cages in a temperature (23°C), humidity (60% to 65% R.H.), and light (12 hours light: 12 hours dark) controlled environment.

All rats were weighed every 2 weeks. Food and water consumption was monitored daily during the study. Baseline studies included systolic blood pressure measurements, 24 hour urine collection for protein and creatinine, and serum creatinine determination. Systolic blood pressure measurements were measured every 2 weeks in awake, quiet, restrained rats using the tail cuff method. At least three separate determinations were made to obtain a mean systolic blood pressure measurement for each rat. At 4, 12 and 16 weeks after surgery, urine was collected for the 24 hour protein and creatinine excretion rate, using the methods as described in the previous study. Urine protein and creatinine values were determined by spectrophotometer 4010 (Germany) and Hitachi 7150 autochemistry analyzer (Japan), respectively. Serum creatinine was measured by automatic techniques using a Hitachi 7150 auto chemistry analyzer (Japan).

At the time of sacrifice at 4, 12 and 16 weeks after renal ablation, the animals were anesthetized with ether. Blood samples were drawn, and immediately afterwards; kidneys were removed, weighed, and each of them processed separately. Kidneys were fixed in 4 g/100 ml (10%) buffered formaldehyde solution, embedded in paraffin, sectioned in 3-μm thickness, and stained with hematoxylin/eosin and periodic acid-Schiff reagent. Sections including superficial and juxtamedullary glomeruli were evaluated. Each kidney was evaluated by the same pathologist who had no prior knowledge as to which group the rats belonged.

In each tissue specimen, a minimum of 50 glomeruli

were examined. Partially cut glomeruli were not included in counting. Mesangial matrix expansion scores were measured as described in the previous study[11].

At least 50 glomeruli per animal were counted to determine the glomerular volume. Histologic sections were examined at a mean magnification of 150X, which was determined with a stage micrometer. A grid with points 0.5 cm apart was used for point counting. The measurement of glomerular volume was performed as described by the method of Wiebel and Gomez[14], which involves determining a mean glomerular profile area and calculating mean volume from the following formula: glomerular volume = area$^{1.5}$ x 1.38/1.01 where 1.38 is β, the shape coefficient for a sphere, and 1.01 is the size distribution coefficient assuming a 10% coefficient of variation.

The statistical significance of differences between groups means were assessed using analysis of variance with the Bonferroni method for comparing multiple groups. Nonparametric data were analyzed using the Kruskal-Wallis method. Differences were considered significant if the P value was less than 0.05. All results were expressed as means $\pm$SD.

RESULTS

After surgery, all animals increased their weights throughout the study. During the study, food consumption was not different between the LP and NP rats (LP: 37$\pm$2 g/d. vs. NP: 39$\pm$0.5 g/d., P=NS). The initial body weights were not different between the LP and NP rats (LP: 240$\pm$12 g vs. NP: 238$\pm$10 g, P=NS). However, the final body weights tend to be significantly less in the LP rats compared to the NP rats (LP; 353$\pm$22 g vs. NP: 424$\pm$36 g, P<0.001). The LPE and NPE rats had similar body weight regardless of two diets with a low and a normal protein content (16 weeks; LPE; 371$\pm$22 g vs. NPE; 399$\pm$21 g, P=NS).

Table 1 shows the effect of a low protein diet on systolic blood pressure. The blood pressure of the LP and NP rats increased progressively by the end of the study. No significant differences in blood pressure were observed between the LP and NP rats. In contrast, systolic blood pressure in both NPE and LPE rats tended to decrease during the observation period.

Restriction of protein intake was found to limit urinary protein loss significantly; 74$\pm$15 mg/24 hours in the LP rats at 16 weeks compared with 101$\pm$15 mg/24 hours in the NP rats (P<0.05) (Table 2). Comparison of the LPE and NPE rats demonstrated a marked reduction in urinary protein loss associated with a low protein diet (LPE; 42$\pm$12 mg/24 hours vs. NPE; 67$\pm$15 mg/24 hours, P<0.05).

At 16 weeks after ablation, creatinine clearance in the LP and NP rats was 1.57$\pm$0.11 ml/min and 1.40$\pm$0.13 ml/min, while that of the LPE and NPE rats was 1.37$\pm$0.14 ml/min and 1.10$\pm$0.17 ml/min.

Remnant kidneys from the LP rats were enlarged far less than those observed in the NP rats (LP: 4 weeks; 1.33$\pm$0.04g, 12 weeks; 1.45$\pm$0.05g, 16 weeks; 1.44 $\pm$ 0.16g vs. NP: 4 weeks; 1.58$\pm$0.19g, 12 weeks; 1.79$\pm$ 0.15g, 16 weeks; 1.99$\pm$0.12g, P<0.05) (Table 3). At the end of the study, the LP rats had significantly less kidney weight compared with the NP rats. Although the LPE rats (1.41$\pm$0.17g) had a numerically less mean kidney weight than NPE rats (1.58$\pm$0.14 g), it did not achieve statistical significance.

Table 1. Systolic blood pressure (mmHg) changes in subtotally nephrectomized rats treated with/without enalapril according to dietary protein content

	Untreated		Enalapril-treated	
	Normal protein	Low protein	Normal protein	Low protein
2wks.	141$\pm$10	138$\pm$7	135$\pm$7	138$\pm$8
4wks.	147$\pm$6	140$\pm$8	135$\pm$4	138$\pm$5
6wks.	160$\pm$6	159$\pm$5	148$\pm$5	149$\pm$6
8wks.	175$\pm$11	162$\pm$5	151$\pm$1*	155$\pm$7*
10wks.	173$\pm$4	171$\pm$5	158$\pm$6*	149$\pm$6*
12wks.	180$\pm$6	171$\pm$6	159$\pm$7*	154$\pm$4*
14wks.	192$\pm$5	180$\pm$4	151$\pm$4*	145$\pm$6*
16wks.	200$\pm$6	184$\pm$1	159$\pm$5*	157$\pm$7*

* P <0.05 vs. untreated rats on the same diet

**P < 0.05 vs. the same group of rats on a normal protein diet

Mesangial expansion scores at 12 and 16 weeks were significantly less in the LP rats compared to those in the NP rats (LP: 12 weeks; 1.91±0.02, 16 weeks; 1.90±0.02 vs. NP: 12weeks; 2.29±0.09, 16 weeks; 2.55±0.16, $P<0.05$) (Table 4). The LPE and NPE rats were not significantly different in mesangial expansion scores at all times.

Morphometric analysis of sections obtained from these kidneys revealed that the LP rats had a significantly smaller mean glomerular volume than the NP rats at 16 weeks (LP; 1.17±0.19 x 10^6 μm^3 vs. NP; 1.98±0.16 x 10^6 μm^3, $P<0.05$) (Table 5). Comparison of the LPE and NPE rats showed a marked reduction in mean glomerular volume associated with a low protein diet (LPE; 1.19±0.17 x 10^6 μm^3 vs. NPE; 1.81±0.22 x 10^6 μm^3, $P<0.05$). Mean glomerular volume of the LP and LPE rats did not increase significantly at the 12 and 16 weeks; thus, a low protein diet was associated with a lack of significant glomerular hypertrophy.

Table 2. Proteinuria (mg/day) at 16 weeks after renal ablation according to dietary protein content

	Untreated	Enalapril-treated
Normal protein	101±15	67±15*
Low protein	74±15**	42±12*,**

* $P < 0.05$ vs. untreated rats on the same diet
** $P < 0.05$ vs. the same group of rats on a normal protein diet

Table 3. Remnant kidney weight (g) at 16 weeks after renal ablation according to dietary protein content

	Untreated	Enalapril-treated
Normal protein	1.99±0.12	1.58±0.14*
Low protein	1.44±0.16**	1.41±0.17

* $P < 0.05$ vs. untreated rats on the same diet
** $P < 0.05$ vs. the same group of rats on a normal protein diet

DISCUSSION

Several experimental maneuvers that suppress the early hemodynamic changes in the remnant glomeruli of subtotally nephrectomized rats also reduce the extent of later glomerular structural changes[4,15]. The purpose of the present study was to examine the effect of the dietary protein on the early development of glomerular structural lesion and proteinuria in the remnant kidney models. The remnant kidney model was induced by 5/6 nephrectomized rats and characterized by heavy persistent proteinuria and compensatory hypertrophy at 16 weeks after nephrectomy, which were incriminated as a causative in the damage to residual glomeruli and the progressive decline in function of remnant kidneys of rats fed on a normal protein diet.

The two diets used were isocaloric, and the same in contents of phosphorus and calcium, in order to exclude any possible effect of these factors on any beneficial effect from a low protein diet[16-18].

Table 4. Mesangial matrix expansion score changes according to dietary protein content

	Untreated		Enalapril-treated	
	Normal protein	Low protein	Normal protein	Low protein
4wks.	1.67±0.07	1.65±0.07	1.63±0.07	1.63±0.07
12wks.**	2.29±0.09	1.91±0.02*	1.96±0.04*	1.91±0.07*
16wks.**	2.55±0.16	1.90±0.03*	1.99±0.16*	1.94±0.03*

* $P < 0.05$ vs. untreated rats on a normal protein diet for 4, 12 and 16 wks.
** $P < 0.05$ vs. the same group of rats on the same protein diet at 4 weeks

Table 5. Glomerular volume (x 10^6 μm^3) changes according to dietary protein content

	Untreated		Enalapril-treated	
	Normal protein	Low protein	Normal protein	Low protein
4wks.	1.09±0.11	0.72±0.10*	0.97±0.16	0.75±0.16
12wks.**	1.50±0.11	0.07±0.18*	1.35±0.08	1.06±0.13*
16wks.**	1.98±0.16	1.17±0.19*	1.81±0.22	1.19±0.17*

* $P < 0.05$ vs. the same group of rats on a normal protein diet for 4, 12 and 16 wks.

** $P < 0.05$ vs. the same group of rats on the same protein diet at 4 weeks

By sacrificing animals at 12 and 16 weeks, the observation was made that a low protein diet inhibited compensatory renal growth and prevented renal failure, which present soon after extreme renal ablation in rats on a normal protein diet. In the nephrectomized rats fed a normal protein diet, damage of the kidneys persisted and progressed. The light microscopic study and morphometric analysis of kidneys indicated that a low protein diet appeared to be effective in reducing mesangial expansion and glomerular volume. In accordance with expectations based on comparison of prior studies of renal ablation[4,11,15,19], the present results showed that dietary protein restriction retarded early glomerular changes. The increase in mesangial area, quantitatively assessed by increased periodic acid Schiff (PAS) staining, is proposed to be an early sign of glomerular injury that progresses to glomerular scarring[12,20]. Consistently, less kidney weight was associated with little change of glomerular structural injury from 12 weeks after ablation, suggesting that renal hypertrophy was prevented by a low protein diet. The finding of significantly smaller glomerular volumes at 16 weeks in a low protein diet animals compared to those in a normal protein diet animals also would suggest the prevention of glomerular hypertrophy. We used these parameters to evaluate the progression in remnant kidney model, since clinical measures of renal function (creatinine clearance) do not reveal any abnormalities at this early stage of the disease in this model. Data from morphometric analysis (showing smaller glomerular volume in kidney sections from rats on a low protein diet compared to a normal protein diet) confirmed the validity of these parameters in this models.

The changes in histology and proteinuria in remnant kidney model are concomitant. The present study showed that a low protein diet rats had a great decrement in their proteinuria present in subtotally nephrectomized rats on a normal protein chow. Proteinuria reflects disturbed glomerular capillary function which appears to be characterized not only by increased leakiness of the glomerular capillary filter but also by increased traffic of serum protein such as macromolecules into and through the mesangium resulting in mesangial injury and glomerulosclerosis[21,22]. The beneficial effects of dietary protein restriction in renal ablation model were partially achieved through an effect on proteinuria. A low protein diet in rats with renal mass ablation; by restoring the size-selective properties of the glomerular barrier, prevented proteinuria and renal injury[12].

Systemic blood pressure in nephrectomized rats were not affected by the protein content of the diet. The blood pressure of the nephrectomized rats fed a low protein diet increased progressively. Dietary protein restriction was found to have no effect on systemic blood pressure. This is similar to what has been described by Hostetter et al.[15] in the remnant kidney model. Nevertheless, these rats had consistently less glomerular injury as assessed by morphology and morphometric analysis. This finding stresses the notion that systemic blood pressure, at the state of dietary protein restriction, is not relevant to determining glomerular injury than are those pressure within the glomerular vasculature itself[15,23].

Considering the data, it is conceivable that a low protein diet attenuate hypertrophic (and regenerative) processes in the glomeruli; even in the presence of systemic hypertension. It is possible that in renal ablation model, a low protein diet acts by decreasing the hypertrophic/regenerative responses of the injured podocytes and possibly of the mesangial cells as well[4].

CEI are the antihypertensive that reduce urinary protein and renal injury better than conventional therapy, studies in the remnant kidney, confirmed the antiproteinuric and renoprotective properties of CEI[1,7]. CEI improves the selective properties of the glomerular capillary wall, which reflect differences in macromolecular organization of the protein matrix in the glomerular basement membrane or in the slit-diaphragm of the podocytes. CEI administered in the early stages were effective in attenuating thesclerosis without altering glomerular capillary hydraulic pressure in some experimental models[24].

In the present study, we analyzed the effects of dietary protein on enalapril-treated 5/6 nephrectomized rats. The present study did not demonstrate any difference of lowering systemic blood pressure, and lessening kidney weight and mesangial expansion score between enalapril-treated rats fed a low protein diet and a normal protein diet. Although the enalapril-treated rats on a low protein diet had a numerically less proteinuria and mean glomerular volume than the enalapril-treated rats fed a normal protein diet, it did not achieve statistical significance. Thus, little additional benefit of dietary protein restriction, at the state of enalapril treatment, against the development of renal lesions was revealed.

Comparison of a low protein diet treatment and enalapril treatment demonstrated that a low protein diet rats and enalapril-treated rats on either a low or a normal protein diet had consistently less glomerular injury.

The mechanisms through which a low protein diet cause improvement in the early change of chronic renal failure cannot be answered by the present study. The results of the studies appear consistent with the possibility that the renoprotective property of a low protein diet is in some sense driven by the capacity to limit protein traffic and kidney hypertrophy.

In summary, dietary protein restriction effectively retarded proteinuria and glomerular injury in nephrectomized rats, even in the presence of systemic hypertension, while there was little additional effect of dietary protein restriction, at the state of enalapril treatment, against the development of renal lesions. Thus, both dietary protein restriction and CEI were beneficial in attenuating glomerular injury, but combination therapy of dietary protein restriction and CEI had little additional benefit.

However, combined treatment of dietary protein restriction and antihypertensives may be helpful in patients with chronic renal disease. Dietary protein restriction did not affect systemic blood pressure but did CEI control hypertension.

The outcome of this study raises the possibility that the use of a low protein diet in clinical renal disease with renal failure may allow the reversal of the self-perpetuating process towards end-stage renal failure and the healing of the early renal failure lesions.

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저단백식이의 투여가 만성신부전증의 진행에 미치는 영향에 관한 실험적 연구

건국대학교 의과대학 소아과학교실, 해부병리학교실 및 건국대학교 축산대학 사료영양학과
김교순, 김기혁, 김상윤, 강용주, 맹원재

〈 한 글 요 약 〉

목 적 : 초기만성신부전증에서 저단백식이의 투여가 만성신부전의 진행속도 및 혈압조절에 어떠한 영향을 미치는지를 알기 위함이다.

방 법 : 5/6 신절제술로 만성 신부전을 유발시킨 백서를 수술 제 7일부터 무작위로 enalapril을 투여하지 않은 군과 enalapril 투여군 (식수 1 L 당 50 mg) 으로 나누고 각군을 정상단백식이군 (18.5% 단백식이), 저단백식이군 (6% 단백식이) 으로 나누어 비교하여 보았다. 신절제술후 4 주, 12 주, 16 주에 단백뇨의 변화, 잔여 신장무게, 신 조직의 mesangial matrix expansion score 및 morphometric analysis 로 분석한 사구체용적의 변화를 비교 분석하여 다음과 같은 결과를 얻었다.

결 과 : 1) 정상단백식이군 및 저단백식이군은 신절제술후 혈압이 올라가기 시작하여 지속적인 고혈압소견을 보였다 (정상단백식이군; 4주 147±6 mmHg, 8주 175±11mmHg, 12주 180±6 mmHg, 16주 200±6 mmHg: 저단백식이군; 4주 140±8 mmHg, 8주 162±5 mmHg, 12주 171±6 mmHg, 16주 184±11 mmHg). Enalapril 투여군은 식이의 단백량과 관계없이 신절제술후 8 주부터 혈압이 조절되기 시작하였다.

2) 16 주째 저단백식이군의 24시간 뇨단백은 74±15 mg 으로 정상단백식이군 (101±15 mg)보다 의의있게 적었다 (P<0.05). Enalapril 투여군도 저단백식이의 경우 42±12mg 으로 정상단백식이(67±15 mg) 보다 의의있게 적었다 (P<0.05).

3) 신절제술후 16주째 크레아티닌 청소율은 정상단백식이군 1.40±0.13 ml/min, 저단백식이군은 1.57±0.11 ml/min, enalapril 정상단백식이군은 1.10±0.17 ml/min, enalapril 저단백식이군은 1.37±0.14 ml/min 이었다 (P=NS).

4) 저단백식이군의 잔여 신장무게의 증가는 정상단백식이군의 신장 무게의 증가에 비해 의의있게 낮았다 (저단백식이군; 4주 1.33±0.04 g, 12 주 1.45±0.05 g, 16주 1.44±0.16 g: 정상단백이군; 4주 1.58±0.19 g, 12 주 1.79±0.15 g, 16주 1.99±0.12 g, P<0.05). 16주에 관찰한 enalapril 투여군의 신장무게를 보면 저단백식이, 정상단백식이에 따른 차이는 없었다.

5) 12주, 16주째 저단백식이군의 mesangial matrix expansion score은 정상단백식이군보다 의의있게 감소되었다 (저단백식이군; 12주 1.91±0.02, 16주 1.90±0.02: 정상단백식이군 ; 12주 2.29±0.09, 16주 2.55±0.16, P<0.05). Enalapril 투여군의 mesangial matrix expansion score 는 식이의 단백량에 따른 차이는 없었다.

6) 16 주째 저단백식이군의 사구체용적은 정상단백식이군보다 의의있게 감소되었다 (16주, 저단백식이군; 1.17±0.19 x 10^6 μm^3: 정상단백식이군; 1.98±0.16 x 10^6 μm^3, P<0.05). Enalapril 투여군의 사구체용적은 저단백식이의 경우 정상식이 때 보다 의의있는 감소를 보였다 (16주, 저단백식이군; 1.19±0.17 x 10^6 μm^3: 정상단백식이군; 1.81 ± 0.22x10^6 μm^3, P<0.05).

결 론 : 항고혈압제를 쓰지 않은 군에서의 저단백식이의 효과는 매우 현저하였고 항고혈압제를 쓴 군에서는 저단백식이와 정상단백식이의 차이가 없었다. 따라서 저단백식이와 항고혈압제는 각각 신조직 손상의 진행을 확실히 지연시키나 두가지를 같이 병용하면 각각 지연시키는 것에 비하여는 additional effect 가 미미하였다. 그러나 혈압조절은 저단백식이로는 만족할만하지 못하고 항고혈압제에 의한 혈압조절이 도움이 되므로 만성신부전 환자에서 저단백식이와 항고혈압제의 병용요법이 필요한 것으로 사료된다.