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□ 원 저 □

Renal Effects of a Low Protein Diet and Antihypertensive Drugs on the Progression of Early Chronic Renal Failure in 5/6 Nephrectomized Rats

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Purpose : To study whether a low protein diet increase the efficacy of antihypertensive therapy on the progression of renal failure, we conducted an experimental study using 5/6 nephrectomized rats(n=63).

Methods : At 7 days after surgery, rats were randomly assigned to three groups according to receiving antihypertensive drug: no antihypertensive drug (U), enalapril (E), and nicardipine (N), respectively and fed a low protein diet (6% protein). Proteinuria, mesangial matrix expansion score and glomerular volume were assessed at 4, 12 and 16 weeks after renal ablation.

Results : Group U rats on a low protein diet developed progressive hypertension (140±8, 162±5, 171±5 and 184±11 mmHg at 4, 8, 12 and 16 weeks) which were controlled by E and N. Group U rats on a low protein diet developed proteinuria (74±15 mg/day at 16 weeks) which were decreased by E (42±12 mg/day) or N (48±8 mg/day) ($p < 0.05$). Mesangial matrix expansion score and glomerular volume were not different between groups U, E and N on a low protein diet regardless of the antihypertensive drugs administered.

Conclusion : A low protein diet did not affect blood pressure. Enalapril and nicardipine-treated rats on a low protein diet did not have different mesangial matrix expansion and glomerular volumes from rats on a low protein diet at 12 weeks and 16 weeks, in spite of the better controlling of systemic hypertension and lessening of proteinuria. Thus, combined treatment with a low protein diet and antihypertensive drugs didn't appear to show any additional effects to attenuate glomerular injury.

Key words : Chronic renal failure, A low protein diet, Antihypertensive drugs, Remnant kidney model

Introduction

Chronic renal diseases evolve to terminal renal failure by a process leading to progressive parenchymal damage, which appears to be relatively independently of the initial insult. The mechanism(s) leading to renal disease progression has been only partially clarified. Among the several theories on the pathophysiology of progressive nephropathies, the most convincing one suggests that the initial reduction in nephron number progressively damages the remaining ones, which suffer the consequences of adaptive increases in glomerular pressure and flow. Glomerular capillary hypertension is normally accompanied by enhanced transglomerular protein traffic and eventual glomerulosclerosis[1-3].

Subtotal renal ablation (5/6 nephrectomy) in adult rats has served as a useful and extensively studied animal model of this process. Subtotal renal ablation elicits a complex glomerular response, initially consisting of a rapid hypertrophic phase, followed by a variable period of relative quiescence, and finally by the development of segmental glomerular sclerosis[4]. 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[5]. In ablation models, numerous possible growth factors have been implicated in the development of glomerular hypertrophy. These factors could be derived from platelets, infiltrating mononuclear cells, or resident mesangial cells. Recent evidence points to an important role for angiotensin II as a growth factor independent of its hemodynamic effects[6]. The renin-

angiotensin system contributes substantially to the development of glomerular sclerosis after 5/6 nephrectomy.

Attenuating the progression of renal damage has thus become a priority for experimental and clinical research. The two most important factors among factors that improve the rate of renal deterioration are control of systemic hypertension or reduction of protein intake. In a previous study, we investigated the effects of antihypertensive treatment on the progression of renal damage in the renal ablation models. We found that control of hypertension with ACEI (angiotensin converting enzyme inhibitor), enalapril or nicardipine, second generation' dihydropyridine CCB (calcium channel blocker) afforded considerable protection from injury in the rat remnant kidney[7]. Few studies have reported the effect of protein restriction and control of hypertension on the progression of renal failure.

This study was carried out to determine whether a low protein diet would result in any improvement of renal protective effect of enalapril or nicardipine in excision remnant kidney model.

Materials and methods

A total of 63 male Sprague-Dawley rats weighing 200 to 250 g, which were obtained from Korean National Institute of Safety Research, were used in all experiments. Subtotal (5/6) nephrectomy was performed using methods as described in a previous study[7]. Rats were allowed free access to a standard rat chow (Jaeil Koksan Feed) containing 18.5% protein and water ad libitum.

At seven days after surgery, rats were matched for body weight and randomly assigned to three groups, according to receiving antihypertensive drugs; no antihypertensive drug group (U) (n=21), enalapril group (E) (n=21) or nicardipine group (N) (n=21), respectively. All rats were given on a diet with 6% protein contents, which was the same Calorie and the same amount of fat (3.8%), calcium (0.63%) and phosphorus (0.39%) with a standard rat chow from seven days after surgery. These were housed in individual cages. 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. Nicardipine (Perdipine, DongA Pharm. co.) were added to the rat chow, at a concentration of 0.2 mg/g throughout the duration of the study. Pilot study established that nicardipine was necessary to control systolic blood pressure at levels comparable to those achieved with enalapril. A preliminary pilot study showed identical food and water consumption by all rats, regardless of the drugs administered.

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

At the time of sacrifice at 4 weeks, 12 weeks and 16 weeks after ablation, the animals were anesthetized with ether, blood samples were drawn, and immediately afterwards the kidneys were removed, weighed, and each of them processed separately. Kidneys were fixed in 4 g/100 ml (10%) buffered formaldehyde solution and processed for light microscopy through paraffin embedding. Sections 3-μm thickness were stained with hematoxylin/eosin and periodic acid-Schiff reagent. Sections including superficial and juxtamedullary glomeruli were evaluated. Renal biopsies were analyzed by the same pathologist blind to the nature of the experimental groups.

In each tissue specimen, a minimum of 50 glomeruli were examined. Partly cut glomeruli were not included in counting. Mesangial matrix expansion scores were measured as the same method in a previous study[7].

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[8], 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 group means was 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 ere expressed as means±SD.

Results

After surgery, all rats on a low protein diet consumed similar amounts of feed regardless of the drugs administered (16 weeks; group U 37±2 g/d., group E 35±2 g/d., group N 39±0 g/d.). Water intake was also similar among the three groups (16 weeks; group U 59± 2 ml/d., group E 57±3 mL/d., group N 56±4 mL/d.). All rats on a low protein diet gained weight throughout the study and were similar body weights regardless of the antihypertensive drugs administered (16 weeks; group U 353±22 g, group E 371±22 g, group N 371±10 g). Growth of this study group was profoundly stunted compared to a previous study group (4 weeks; this study group 240±12 g, a previous study group 238±10 g; $p > 0.05$, 16 weeks; this study group 365±18 g, a previous study group 408±21 g; $p < 0.001$).

Table 1 shows the biweekly results of antihypertensive drugs on systolic blood pressure after nephrectomy. The blood pressure of rats on a low protein diet without medication further increased with time reaching the value of 184±11 mmHg by the end of the study despite of a low protein diet. In rats on a low protein diet of groups E and N, systolic blood pressure tended to decrease during the observation period.

Table 1. Systolic Blood Pressure (mmHg)

	group U	group E	group N
2wks.	138±7	138±8	142± 9
4wks.	140±8	138±5	134± 4
6wks.	159±5	149±6	141±12
8wks.	162±5	155±7*	145±13*
10wks.	171±5	149±6*	145±4*
12wks.	171±6	154±4*	149±3*
14wks.	180±4	145±6*	139±7*
16wks.	184±1	157±7*	145±6*

* $p < 0.05$ vs. group U

The 24 hour urinary protein at 16 weeks after ablation are reported in Table 2. 24 hour protein levels at the end of the experiment were significantly higher in group U on a low protein diet compared to groups E and N on a low protein diet ($p < 0.05$). There were no significant differences between groups E and N on a low protein diet.

Table 2. Proteinuria (mg/day) at 16 weeks. after Ablation

group U	74 ±15
group E	42 ±12*
group N	48 ± 8*

* $P < 0.05$ vs. group U

Creatinine clearance at 16 weeks after ablation in group U was 1.57±0.11 mL/min, while creatinine clearance in groups E and N was 1.37±0.14 mL/min and 1.11±0.16 mL/min.

Remnant kidney weight in group U rats on a low protein diet increased from 4 weeks to 12 weeks or 16 weeks (4 weeks; 1.33±0.04 g, 12 weeks; 1.45±0.05 g, 16 weeks; 1.44±0.16 g; respectively, $p< 0.05$ compared to 4 weeks). At 16 weeks after ablation remnant kidney weights of group E (1.41±0.17 g) and group N (1.46± 0.06 g) were not different from that of group U (1.44± 0.16 g).

Mesangial matrix expansion score in group U rats on a low protein diet increased from 4 weeks to 12 weeks or 16 weeks after nephrectomy (4 weeks; 1.65±0.07, 12 weeks; 1.91±0.02, 16 weeks; 1.90±0.02, respectively) (Table 3). There was no significant difference of

mesangial matrix expansion score at the 12 weeks and 16 weeks between groups U, E, and N on a low protein diet. No signs of focal segmental glomerular sclerosis, interstitial fibrosis, or inflammation were observed in remnant kidney of these animals on a low protein diet.

Table 3. Mesangial Matrix Expansion Score

	group U	group E	group N
4 wks.	1.67±0.07	1.63±0.07	1.71±0.03
12wks.**	1.91±0.02	1.91±0.07	1.94±0.02
16wks.**	1.90±0.03	1.94±0.03	1.93±0.01

* $P < 0.05$ vs. group U at same wks.

** $P < 0.05$ vs. 4 wks. at same group

The results of the morphometrical analysis are reported in Table 4. Mean glomerular volume averaged $0.72\pm0.10 \times 10^6$ μm^3 in group U rats on a low protein diet at 4 weeks and increased to 12 weeks ($1.07\pm0.18 \times 10^6$ μm^3) or 16 weeks ($1.17\pm0.19 \times 10^6$ μm^3)($p < 0.05$). Mean glomerular volume of groups E and N did not show significant increase at the 12 weeks and 16 weeks; thus, a low protein diet plus enalapril, and a low protein diet plus nicardipine treatment were associated with a lack of significant glomerular hypertrophy.

Table 4. Glomerular Volume (x 10^6 μm^3)

	group U	group E	group N
4wks.	0.72±0.10	0.75±0.16	0.77±0.12
12wks.**	1.07±0.18	1.06±0.13	1.04±0.16
16wks.**	1.17±0.19	1.19±0.17	1.30±0.19

* $P < 0.05$ vs. group U at same wks.

** $P < 0.05$ vs. 4 wks. at same group

Discussion

Extensive loss of renal mass in the rat leads to increased glomerular filtration rate (GFR) in the residual nephron. This 'compensatory' hyperfiltration is the result of increased hydraulic pressure and plasma flow rates within remnant glomerular capillaries. Eventually, these hemodynamic adjustments are followed by pathological processes in the residual glomeruli[9]. Increased mesangial matrix expansion, and epithelial cell foot process fusion, which were the early structural changes of glomerular injury that progress to glomerular scarring were accompanied by proteinuria attributable to both charge- and size-selective defects in glomerular permeability to macromolecules[10,11]. The increase in mesangial area quantitatively assessed by increased periodic acid Schiff staining. Adaptive glomerular hypertrophy develops concomitantly with the hemodynamic changes and it has been suggested that such hypertrophy rather than the glomerular hemodynamic changes is responsible for the development of glomerular sclerosis[12,13]. In the present study, glomerular volume was determined by the method of Wiebel and Gomez[8]. Bilous et al.[14] and Lane et al.[15] were described that this method was the most efficient estimate of mean glomerular volume.

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[1,9]. We have previously shown in 5/6 nephrectomized rats that antihypertensives prevents the early development of both glomerular morphologic changes and proteinuria. Marinides et al.[16] reported that the early lesions in the sequence of focal segmental glomerulosclerosis could be reversed by dietary protein restriction.

The purpose of the present study was to examine the effect of the dietary protein restriction and dietary protein restriction plus antihypertensives on the early development of glomerular structural lesion and proteinuria in renal ablation models. The 6% protein diet used were isocaloric and the same content of phosphorus and calcium with a standard rat chow containing 18.5% protein, in order to exclude any effect of these factors on any beneficial effect from a low protein diet[17-19].

In accord with expectations based on comparison of prior studies of renal ablation[7,9,16,20], the present results showed that dietary protein restriction retards early glomerular changes. Little change of kidney weight, mesangial expansion and glomerular volume from 12 weeks after ablation suggested a lack of kidney hypertrophy. Comparison of our previous study and the present study showed that the restriction of dietary protein limits the compensatory elevation in GFR as well

as the mesangial expansion, and proteinuria present soon after extreme renal ablation in rats on a standard protein chow. 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[10]. Lower GFR values in rats on a low protein diet were linked to reduced levels of proteinuria and glomerular changes, in comparison with our previous study. On the basis of this observation, compensatory hyperfiltration and hyperperfusion were incriminated as causative in the damage to residual glomeruli and the progressive decline in function of remnant kidneys of rats maintained on a standard diet.

Proteinuria also 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]. In recent years several studies have convincingly documented that excessive and sustained protein trafficking could have an intrinsic renal toxicity, which together with other independent risk factors such as hypertension can play a contributory role in the progression of renal damage[23-25].

Although elevations in systemic blood pressure and proteinuria may be injurious to the kidney[9], the beneficial effects of dietary protein restriction in renal ablation model were not achieved through an effect on arterial pressure and proteinuria. Rats on a low protein diet had the higher values of blood pressure and proteinuria with time after ablation. Nevertheless, these rats had consistently less glomerular injury as assessed by morphology. This finding serves to stress the notion that systemic blood pressure and proteinuria, at the state of protein restriction, is of less relevance in determining glomerular injury than are those pressure within the glomerular vasculature itself[9]. It has been shown that dietary protein intake in the rat is directly related to plasma renin activity, angiotensin I and aldosterone levels as well as vasodilatory prostaglandin levels and is associated with renal hypertrophy[26]. Considering all these data, it is conceivable that a low protein diet alone control glomerular capillary hypertension even in the presence of systemic hypertension and attenuate hypertrophic (and regenerative) processes in the glomeruli. It is possible then that in renal ablation model, a low protein diet acts by decreasing the activity of the renin-angiotensin system in the kidney, thereby decreasing the hypertrophic/regenerative response of the injured podocytes and possibly of the mesangial cells as well[16]. To the extent that there is indeed a link between degree of hypertrophy and sclerosis, the profound amelioration of early glomerular change seen in this experiment can also be explained.

Comparison of a low protein diet alone, a low protein diet plus enalapril and a low protein diet plus nicardipine demonstrated that rats on a low protein diet developed hypertension and proteinuria, which were lessened by enalapril or nicardipine. Rats of all three groups had consistently less glomerular injury from 12 weeks after ablation, suggesting that renal hypertrophy was prevented in all three groups. Thus, no additional efficacy of enalapril and nicardipine, at the state of protein restriction, against the development of renal lesions was revealed. The significant differences in blood pressure and proteinuria between a low protein diet group and a low protein diet plus enalapril or nicardipine groups do not seem important enough to explain these histologic changes. These results were unexpected and contrast with previous reports examining the renal effect of protein restriction and these drugs in a variety of conditions, whether or not they were associated with hypertension.

ACEI are the only antihypertensive that consistently lower urinary proteins, no matter the level of blood pressure reduction. ACEI normalized glomerular hypertension and reduced urinary proteins and renal injury better than conventional therapy, studies in the remnant kidney, confirmed the antiproteinuric and renoprotective properties of ACEI[2]. ACEI induce the improvement in the selective properties of the glomerular capillary wall, which reflected differences in macromolecular organization of the protein matrix in the glomerular basement membrane or in the slit-diaphragm of the podocytes. Therefore, ACEI are superior to other antihypertensive agents for small reductions in blood pressure, as in the case of normotensive or mildly

hypertensive patients[27]. However, the present study did not show any difference of blood pressure and proteinuria between a low protein diet plus enalapril and a low protein diet plus nicardipine. Nicardipine that had an antihypertensive effect comparable to that of ACEI also had a comparable effect on reducing proteinuria. This is consistent with the finding of the modification of Diet and Renal disease (MDRD) study[28]. The MDRD study suggested that different antihypertensives may equally reduce urinary protein excretion and slow renal disease progression, provided tight control of blood pressure (mean diastolic BP below 90 to 95 mmHg) is achieved and maintained. In more general terms the effect of different drugs on urinary proteins depends on the degree of blood pressure reduction achieved. The higher the effect of blood pressure reduction, the less dependent is the antiproteinuric response on the class of antihypertensive employed[27]. On the other hand, in severely hypertensive patients both ACEI, and non-nifedipine CCB as well as other antihypertensives have a distinct antiproteinuric effect[29]. Non-nifedipine CCB that had an antiproteinuric effect comparable to that of ACEI also had a comparable effect on the rate of GFR decline. Overall, independently of the mechanism(s), whenever urinary protein excretion is reduced and whenever the drug is used GFR is protected from declining with time[27].

The mechanisms through which a low protein diet plus enalapril or nicardipine cause improvement in the early change of chronic renal failure cannot answered by the present study. ACEI administered in the early stages were effective in attenuating the sclerosis without altering glomerular capillary hydraulic pressure in some models[30]. Taken together, the results of the studies appear consistent with the possibility that the renoprotective property of a low protein diet and antihypertensive drugs is in some sense driven by their capacity to control of systemic hypertension, and limit protein traffic and kidney hypertrophy.

The fact that no additional efficacy of antihypertensives such as enalapril and nicardipine, at the state of protein restriction, against the development of renal lesions was shown may indicate a too short observation in the presence of slow deterioration in remnant kidney model could hamper detection of differences among three groups.

In summary, dietary protein restriction did not affect the blood pressure. Enalapril and nicardipine-treated rats on a low protein diet did not have different mesangial matrix expansion and glomerular volumes from rats on a low protein diet at 12 weeks and 16 weeks, in spite of the better controlling of systemic hypertension and lessening of proteinuria. Thus, combined treatment with protein restriction and antihypertensive drugs didn't appear to show any additional effects to attenuate glomerular injuries.

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Enalapril used in this study was a gift from ChongWae Pharm. co.

Nicardipine used in this study was a gift from DongA Pharm. co.

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저단백 식이 및 항고혈압제의 투여가 만성신부전증의 진행에 미치는 영향에 관한 실험적 연구

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목 적 : 초기만성신부전증에서 저단백식이를 항고혈압제와 병행 투여하였을 때 저단백식이 단독 투여 때보다 만성신부전의 진행속도 및 혈압조절에 어떠한 영향을 주는지 알기 위하여 저자들은 실험동물 백서를 이용하여 excision remnant kidney model 로 만성 신부전을 유발시켰다.

방 법 : 5/6 신 절제술로 만성 신부전을 유발시킨 백서를 수술 제 7일부터 무작위로 저단백식이 (6% 단백식이) 단독투여군, 저단백식이 enalapril 투여군 (식수 1 L 당 50 mg), 저단백식이 nicardipine 투여군 (사료 g 당 0.2 mg) 로 나누어 신절제술후 4 주, 12 주, 16 주에 단백뇨의 변화, 신 조직의 mesangial matrix expansion score 및 morphometric analysis 로 분석한 사구체용적의 변화를 비교 분석하였다.

결 과 : 1) 저단백식이 단독투여군은 신절제술후 계속 혈압이 증가됨을 볼 수 있었으며, 저단백식이 항고혈압제투여군은 신절제술후 8 주부터 항고혈압제 투여 7 주 후부터 저단백식이 단독투여군에 비해 혈압이 조절되기 시작하였다.

2) 신절제술후 16 주 째의 24 시간 뇨단백은 세군 모두 크게 증가되지 않았으나 저단백식이 enalapril 투여군, 저단백식이 nicardipine 투여군은 저단백식이 단독투여군에 비해 24시간 뇨단백의 양이 통계적으로 의미있게 낮았다.

3) 신절제술후 16주째 크레아티닌 청소 율은 저단백식이 단독투여군은 1.57±0.11 mL/min, 저단백식이 enalapril 투여군 1.37±0.14 mL/min, 저단백식이 nicardipine 투여군 1.11±0.16 ml/min 이었다.

4) 저단백식이 단독투여군의 잔여 신장무게는 신절제술후 4 주 1.33±0.04 g, 12 주 1.45±0.05 g, 16주 1.44±0.16 g 으로 12 주 이후 잔여 신장무게의 증가를 관찰할 수 없었다. 신절제술후 16 주에 관찰한 저단백식이 단독투여군과 저단백식이 항고혈압제투여군간의 잔여신장무게는 통계적인 차이는 없었다.

5) 저단백식이 단독투여군의 mesangial matrix expansion score는 12주째 증가소견을 보였고 저단백식이 항고혈압제투여군은 항고혈압제 투여에도 불구하고 12주 이후 mesangial matrix expansion score 의 의미있는 증가소견이 없었고 세군 간의 차이도 없었다.

6) 저단백식이 단독투여군의 사구체용적은 12주째 증가소견을 보였고 저단백식이 항고혈압제 투여군은 항고혈압제 투여에도 불구하고 12주 이후 사구체용적의 의미있는 증가소견이 없었고 세군 간의 차이도 없었다.

결 론 : 초기만성신부전증에서 저단백식이는 혈압을 조절시키지 못하였고 저단백식이 항고혈압제투여군은 저단백식이 단독투여군보다 혈압조절 및 단백뇨의 감소 소견은 유의한 차이를 보였으나, mesangial matrix expansion score, 대상성 사구체비대는 통계적으로 유의한 차이를 보이지 않았다. 그러므로 만성신부전의 진행을 지연시키는데 있어서 저단백식이와 함께 항고혈압제를 추가하였을 때 항고혈압제에 의한 추가적인 지연 효과는 관찰되지 않았다.