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Effects of Dietary Salt Restriction on the Development of Renal Failure in the Excision Remnant Kidney Model

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= Abstract =

Purpose: To evaluate whether or not sodium restriction had its own beneficial effect and increased the efficiency of the anti-hypertensive drugs on the progression of renal failure.

Methods: We studied using the excision remnant kidney model. Treatment groups were as follows: 5/6 nephrectomy and a 0.49% (normal-high) sodium diet (NN); 5/6 nephrectomy and a 0.25% (normal-low) sodium diet (LN); 5/6 nephrectomy, a 0.49% sodium diet and enalapril (NNE); 5/6 nephrectomy, a 0.49% sodium diet and nicardipine (NNN); 5/6 nephrectomy, a 0.25% sodium diet and enalapril (LNE); 5/6 nephrectomy, a 0.25% sodium diet and nicardipine (LNN). Both diets were isocaloric and had the same content of protein, phosphorus and calcium. Proteinuria, remnant kidney weight, mesangial expansion scores, and glomerular volume were assessed.

Results: Blood pressure tended to be lower in LN compared to NN ($P<0.05$). NN developed progressive hypertension. LNE, LNN, NNE, and NNN reduced blood pressure. LNE, LNN, NNE, NNN, and LN had significantly less proteinuria than NN at 16 weeks ($P<0.05$). At 24 weeks, LN developed proteinuria (82 mg/day), which were lessened in LNE (54 mg/day) and not lessened in LNN (76 mg/day). Mesangial expansion scores were significantly less in LN rats compared to those in NN rats. Glomerular volumes at 24 weeks in LN rats were significantly less compared to those at 16 weeks in NN rats. Mesangial expansion scores and glomerular volumes at 4, weeks, 12 weeks, and 24 weeks were not different among LN, LNE, and LNN groups.

Conclusion: Dietary salt restriction lessens renal damage, at least in part, by inhibiting compensatory renal growth and reducing blood pressure. Enalapril was particularly successful in reducing proteinuria and glomerular injury when combined with dietary salt restriction.

Key words: Chronic Renal failure, Moderate sodium restriction, Antihypertensive drugs, Remnant kidney model

Introduction

Dietary protein restriction reduces renal injury in virtually all models of experimental renal disease. Studies using the remnant kidney model of rats and humans demonstrated that a low protein diet early or late in the course of chronic renal failure greatly lessens the severity of various functional and structural indicators of renal damage[1-6].

Systemic hypertension seems to be one of the major factors in the initiation and progression of chronic renal failure of experimental animals and humans[7]. The reduction of systemic blood pressure in rats with renal ablation reduces proteinuria, preserves renal function, and attenuates the severity of glomerular sclerosis[8]. The

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progression of chronic renal failure in diabetic nephropathic patients and non-diabetic patients is favorably affected by antihypertensive therapy[9, 10].

In a previous study, we evaluated the effect of two diets with a low and a normal protein content on the progression of early chronic renal failure in the remnant kidney model[12]. We found that dietary protein restriction afforded considerable protection from renal failure in the rat remnant kidney model but there was little additional effect of dietary protein restriction, at the state of enalapril treatment, against the development of renal lesions. At present, dietary protein restriction is being seriously considered as a therapy to prevent progressive renal failure in humans. However, because of difficulty with patient compliance, it may not be possible to adequately restrict protein intake in patients with chronic renal failure.

Salt restriction led to a modest decline in systemic blood pressure and imposed less severe dietary restrictions on experimental animals and patients than protein restriction, yet it might convey a similar degree of protection from renal damage.

This study was undertaken to test the effects of moderate dietary sodium restriction on the development of renal failure in the remnant kidney model. It was also used to evaluate the influence of dietary sodium intake on the progression of renal failure during antihypertensive therapy in the remnant kidney model.

Materials and Methods

Male Sprague-Dawley rats (Korean National Institute of Safety Research) weighing 200 to 250 grams were studied in all experiments. Rats were allowed to adapt the laboratory for 7 days prior to surgery. Subtotal (5/6) nephrectomy was performed using methods as described in a previous study[8]. Following surgery, the rats were kept for seven days on a diet containing 18.5% casein and 0.49% sodium, to allow them to recover from surgical stress and acute renal failure. They were then matched for body weight and randomly assigned to experimental groups.

The first study analyzed the effects of dietary sodium on 5/6 nephrectomized rats. The treatment groups were as follows: 5/6 nephrectomy and a 0.49% sodium diet (NN); 5/6 nephrectomy and a 0.25% sodium diet (LN). The second study evaluated the effects of dietary sodium on antihypertensive drugs-treated 5/6 nephrectomized rats. The treatment groups were as follows; 5/6 nephrectomy, a 0.49% sodium diet and enalapril (NNE); 5/6 nephrectomy, a 0.49% sodium diet and nicardipine (NNN); 5/6 nephrectomy, a 0.25% sodium diet and enalapril (LNE); 5/6 nephrectomy, a 0.25% sodium diet and nicardipine (LNN).

The diet used in the first and second studies contained 0.49% sodium, as in the usual laboratory chow; sodium was reduced to 0.25% for a normal-low sodium diet. Both diets contained 18.5% casein, 18% corn starch, 50.73% dextrose, 3.58% corn oil, 5.32% cellulose, 1.85% mineral mixture, 1.0% vitamin mixture, 0.3% DL-Methionine, and 0.2% choline chloride. Except for sodium and chloride, the electrolyte contents of the diets were similar. Phosphorus and calcium concentrations were kept identical. The two diets were given ad libitum. The pilot study showed that the change in sodium diet from 0.49% to 0.25% induced no significant difference in food intake and growth.

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 drugs administered.

These were housed in individual metabolic cages at constant humidity and temperature and with a 12 hour light-dark cycle, and had free access to tap water.

Baseline studies included systolic blood pressure measurements, 24 hour urine collection for protein and creatinine, and serum creatinine. Biweekly determinations of systolic blood pressure were made on awake, quiet, and 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 weeks, 12 weeks, 16 weeks, and 24 weeks after surgery, 24 hour urine was collected for protein and creatinine excretion rate. Urine protein concentration was measured by spectrophotometer 4010 (Germany). Creatinine concentration in blood and urine was determined using an autoanalyzer (Hitachi 7150 auto chemistry analyzer, Japan). Creatinine clearance was calculated using the standard formula. Glomerular filtration rate after ablation was estimated by determining the clearance of creatinine using the final 24-hour urine collection and a sample of blood collected on the same day.

At the time of sacrifice at 4 weeks, 12 weeks, 16 weeks, and 24 weeks after ablation, the animals were anesthetized with ether, blood samples were drawn, and immediately afterwards the remnant kidneys were removed, weighed, and each of them processed separately. They were fixed in 4 g/100 ml (10%) buffered formaldehyde solution, embedded in paraffin, cut at 3-μm and stained with hematoxylin/eosin and periodic acid-Schiff reagent. Sections including superficial and juxtamedullary glomeruli were evaluated. In each tissue specimen, a minimum of 50 glomeruli were examined. Partly cut glomeruli were not included in counting. All sections were evaluated using a blind technique. The prevalence of glomerular injury was quantitatively assessed in a blinded fashion by one observer. Mesangial matrix expansion scores were measured as the same method in a previous study[8].

The glomerular volume was measured by the method of Wiebel and Gomez[11], which involves determining a mean glomerular profile area and calculating mean volume from the following formula: glomerular volume=area$^{1.5}$ $\times$ 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. Histologic sections were examined at a mean magnification of 150$\times$, determined by a stage micrometer. A grid with points 0.5 cm apart was used for point counting. A total of at least 50 glomeruli per animal were scored.

All results were expressed as means$\pm$SD. 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. Statistical significance was defined as $P<0.05$.

Results

The effect of salt restriction on awake systolic blood pressure is shown in Table 1. The NN rats developed systemic hypertension which was already present six weeks after reduction of renal mass. Blood pressure tended to be lower in LN rats. At the time of 16 weeks after ablation, the mean value of systolic blood pressure was 200$\pm$6 mmHg in NN rats, a value significantly greater than that of 178$\pm$7 mmHg in the LN rats. After surgery, the LNE, LNN, NNE, and NNN rats reduced blood pressure.

Table 2 shows the impact of salt restriction on urinary protein excretion. The LN, LNE, LNN, NNE, and NNN rats had significantly less proteinuria than the NN rats at 16 weeks ($P<0.05$). At 16 weeks, LN rats developed proteinuria (78$\pm$16mg/day), which were lessened in LNE rats (35$\pm$9 mg/day), and LNN rats (41 $\pm$15 mg/day)($P<0.05$). At 24 weeks, LN rats developed proteinuria (82$\pm$10 mg/day), which were lessened in LNE rats (54$\pm$3 mg/day) ($P<0.05$) and not lessened in LNN rats (76$\pm$11 mg/day) ($P>0.05$).

Creatinine clearance at 24 weeks averaged only 1.11 $\pm$0.2 ml/min in LN rats, a value significantly less than that of 1.6$\pm$0.19 ml/min seen in LNE rats ($P<0.05$) but not different than that of 1.15$\pm$0.1 ml/min observed in LNN rats. Rats on a 0.25% sodium diet didn't reach the end stage renal failure at 24 weeks after nephrectomy.

Comparison of the LN and NN rats demonstrated no significant growth of remnant kidney associated with a 0.25% sodium diet (LN; 2.15$\pm$0.03g at 24 weeks vs. NN; 1.99$\pm$0.12 at 16 weeks, $P>0.05$)(Table 3). Although the LNE rats (1.86$\pm$0.04g) at 24 weeks had a numerally large mean kidney weight than the NNE rats (1.58$\pm$0.14g) at 16 weeks, it did not achieve statistical significance. Remnant kidney weights at 24 weeks in the LNN rats were not significantly different from those observed in the NNN rats at 16 weeks.

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

Group	Untreated		Enalapril		Nicardipine	
Diet	0.49% Na	0.25% Na	0.49% Na	0.25% Na	0.49% Na	0.25% Na
2wks	141±10	138± 1	135± 7	136±3	133±5	136±1
4wks	147± 6	138± 1	135± 4	138±1	138±5	131±1
6wks	160± 6	153± 1	148± 5	145±3	148±6	142±4
8wks	175±11	155± 2**	151±10*	149±5	158±7*	143±6
10wks	173± 4	156±11**	158± 6*	152±2	147±6*	145±5
12wks	180± 6	155± 6**	159± 7*	148±5	153±8*	137±5
14wks	192± 5	166± 8**	151± 4*	143±5*	149±7*	138±3*
16wks	200± 6	178± 7**	159± 5*	146±9*	159±7*	138±4*

* $P < 0.05$ vs. untreated rats on the same diet
** $P < 0.05$ vs. the same group of rats on a 0.49% sodium diet

Mesangial expansion scores were significantly less in the LN rats compared to those in the NN rats (LN: 12 weeks; 1.97±0.02, 24 weeks; 2.06±0.03 vs. NN: 12 weeks; 2.29±0.09, 16 weeks; 2.55±0.16, $P<0.05$) (Table 4). The LNE and NNE rats were not significantly different in mesangial expansion scores after 12 weeks. There were no different mesangial expansion scores in LNN and NNN rats after 12 weeks. Mesangial expansion scores were not significantly different among three groups on a 0.25% sodium diet at all times. The LN, LNE, and LNN rats could be sacrificed at 24 weeks and had evidence of less severe renal lesions.

The results of the morphometrical analysis are reported in Table 5. Glomerular volumes at 24 weeks in the LN rats were significantly less compared to those at 16 weeks in the NN rats (LN: 24 weeks; $1.58\pm0.18\times10^6$ μm^3 vs. NN: 16 weeks; $1.98\pm0.16\times10^6$ μm^3, $P<0.05$). Comparison of the LNE and NNE rats at the sacrifice showed a reduction in mean glomerular volume associated with a 0.25% sodium diet (LNE: 24 weeks; $1.51\pm0.08\times10^6$ μm^3 vs. NNE: 16 weeks; $1.81\pm0.22\times10^6$ μm^3, $P<0.05$). The LN, LNE, and LNN rats did not show significant increase in glomerular volume from 12 weeks to the end of the study. There were not significantly different glomerular volume among LN, LNE, and LNN groups at all times.

Table 2. Proteinuria (mg/day) at 16 and 24 weeks after renal ablation according to dietary sodium content

	0.49% Na 16 wks.	0.25% Na 16 wks.	0.25% Na 24 wks.
Untreated	101±15	78±16**	82±10
Enalapril	67±15*	35± 9*,**	54± 3*
Nicardipine	78±12*	41±15*,**	76±11*

* $P < 0.05$ vs. untreated rats on the same diet
** $P < 0.05$ vs. the same group of rats on a 0.49% sodium diet

Table 3. Remnant kidney weight (g) at 16 and 24 weeks after renal ablation according to dietary sodium content

	0.25% Na 16 wks.	0.25% Na 24 wks.
Untreated	1.99±0.12	2.15±0.03
Enalapril	1.58±0.14*	1.86±0.04*
Nicardipine	1.75±0.17*	1.96±0.05*

* $P < 0.05$ vs. untreated rats on the same diet
** $P < 0.05$ vs. the same group of rats on a 0.25% sodium diet.

Table 4. Mesangial expansion score changes according to dietary sodium content

Group	Untreated		Enalapril		Nicardipine	
Diet	0.49% Na	0.25% Na	0.49% Na	0.25% Na	0.49% Na	0.25% Na
4wks	1.67±0.07	1.69±0.07	1.63±0.07	1.71±0.06	1.65±0.05	1.72±0.03
12wks**	2.29±0.09	1.97±0.02	1.96±0.04*	1.99±0.07	1.96±0.01*	1.97±0.02
16wks**	2.55±0.16		1.99±0.16*		2.04±0.05*	
24wks**		2.06±0.03		2.02±0.03		2.02±0.01

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

Table 5. Glomerular volume ($\times 10^6$ μm^3) changes according to dietary sodium content

Group	Untreated		Enalapril		Nicardipine	
Diet	0.49% Na	0.25% Na	0.49% Na	0.25% Na	0.49% Na	0.25% Na
4wks	1.09±0.11	0.98±0.17	0.97±0.16	0.84±0.11	1.07±0.16	0.88±0.10
12wks**	1.50±0.11	1.39±0.18	1.35±0.08	1.50±0.12	1.39±0.15	1.46±0.06
16wks**	1.98±0.16		1.81±0.22		1.65±0.17	
24wks**		1.58±0.18		1.51±0.08		1.49±0.07

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

Discussion

The purpose of the present study was to examine the effect of a small change in dietary sodium, remaining within the normal range on the early development of glomerulosclerotic lesion and proteinuria in the remnant kidney models. The two sodium diets used were isocaloric, and had the same contents of phosphorus, calcium and protein. They had the same amounts in order to exclude any possible effect of these factors on any beneficial effect from a normal-low sodium diet. Both sodium diets remained within the range normally used in laboratories. The sodium content of the normal-low sodium diet used was about four times higher than the minimal content required for normal growth[12].

The experimental data related to the effects of dietary sodium manipulation on progressive renal scarring is limited. Only a few studies have investigated the effect of dietary sodium on progressive renal failure and have shown equivocal results. In uninephrectomized rats, a high salt intake increases compensatory renal growth and accelerates the development of glomerular sclerosis[13], while a low sodium diet prevents glomerular sclerosis of the remaining kidney[14]. A protective effect of salt restriction on progressive renal scarring in uninephrectomized spontaneously hypertensive rats has been observed[16]. In subtotally nephrectomized rats, Purkerson *et al*[17] failed to observe any effect of salt restriction or supplementation on the underlying nephropathy. Daniels and Hostetter[18] demonstrated that severe sodium restriction (0.06% vs. 0.46%) reduces urinary protein loss, glomerulosclerosis and glomerular hypertrophy in the ligation model, despite unchanged systemic and glomerular hypertension. They suggested that these protection effects seemed to be independent of changes in systemic or glomerular hypertension and may be related to a reduction in glomerular hypertrophy. Dworkin's groups have shown that the inhibition of compensatory growth by dietary sodium restriction had similar protective effects in both the remnant model[19] and in the uninephrectomized spontaneously hypertensive rats[16]. However, these studies used the

remnant kidney model from ligation of branches of renal arteries. A shortcoming of this model is the severe, persistent hypertension which appears immediately after ligation, and which may play a role in renal deterioration. It has been strongly suggested that the early hypertension, following arterial ligation results from ischemia of renal tissue adjacent to infarcted areas and not from nephron reduction and renal insufficiency. One study showed that dietary salt restriction improved the consequences of nephron loss in the excision remnant kidney model[20].

Few reports have examined the effect of moderate sodium restriction on the progression of renal failure. Terzi et al[20] reported that even a much less severe sodium reduction induces a marked decrease in renal lesions in the excision remnant kidney model. The marked reduction in glomerular hypertrophy and tubular dilatation and the absence of arteriolar alterations were found.

In the excision remnant kidney model we have used for several years, blood pressure remains near normal during the first weeks or months after surgery and sometimes until end-stage renal disease. Hypertension in this model is the consequence rather than the cause of renal damage, since its development follows that of glomerular sclerosis. In the subtotally nephrectomized rats fed a normal rat chow containing 0.49% sodium, damage of the kidneys persisted and progressed. Heavy persistent proteinuria and compensatory renal hypertrophy developed after nephrectomy. End-stage renal failure could not be observed even though 16 weeks had passed after 5/6 nephrectomy in the previous experimental settings. This finding was unexpected and contrasted with all previous reports using the ligation model. This led us to conduct this experimental study 24 weeks after nephrectomy. Comparison of biological data taken after similar duration and of parameters measured at sacrifice of the rats on a 0.49% sodium diet and a 0.25% sodium diet was used to analyze the consequence of different sodium feeding.

In the present study, sodium restriction resulted in a marked protection of the remnant kidney. At sacrifice, despite their longer survival, subtotally nephrectomized rats on a normal-low sodium diet had lower blood pressure, protein excretion, remnant kidney weight, and mesangial expansion scores, and smaller glomerular volume. This evidence affords slower progression of renal disease than rats on a normal-high sodium diet. Little change of kidney weight, mesangial expansion scores, and glomerular volume from 12 weeks after ablation suggested a lack of renal and glomerular hypertrophy.

A protective effect of moderate salt restriction may be related to inhibition of compensatory renal growth. Our findings are in agreement with other authors[16,18,19]. In keeping with this hypothesis, high dietary sodium enhances in vivo renal hyperplasia and hypertrophy[21], whereas sodium deficiency slows kidney growth[22] as well as compensatory growth of other organs[23]. It is probable that this protection effect of salt restriction is attributable to a modest decline in systemic pressure. In the excision model hypertension is improved by sodium restriction[24] in accordance with our study. Whether this can be ascribed mainly to less hypertension may be questioned. Another report suggests that a sodium diet does not act exclusively through blood pressure control[18]. Benstein *et al*[15] observed that sodium restricted diet (0.09% vs. 0.45%) has a protective effect in uninephrectomized spontaneously hypertensive rats, which does not depend on blood pressure, plasma renin concentration, or glomerular hemodynamics. A possible explanation for the discrepancies observed lies in the differences between the two models of renal ablation.

The present study compared the effect of enalapril with two levels of dietary sodium (0.49% vs. 0.25%) in excision remnant kidney model and demonstrated that rats on a 0.25% sodium diet and enalapril developed less systemic hypertension, proteinuria, renal injury and glomerular volume than those of rats on a 0.49% sodium diet and enalapril. Thus, enalapril provided particularly successful in reducing proteinuria and glomerular injury when combined with dietary salt restriction. Our data is consistent with the findings of Terzi et al[20]. However, they reported that angiotensin converting enzyme inhibitor (ACEI) may be ineffective on blood pressure and renal deterioration and a moderate sodium restriction is sufficient to slow renal progression and to restore the actions of ACEI. The protective effect of both a normal-

low sodium diet and ACEI correlates with a substantial attenuation of renal enlargement, with lower glomerular hypertrophy and prominent reduction of tubular dilatation[20]. One study has compared the effect of enalapril with two levels of dietary sodium (0.6% vs. 0.1%) after arterial ligation. Salt restriction enhanced the antihypertensive action of enalapril and may have caused a further reduction in glomerular capillary pressure[25]. Proteinuria and glomerular injury were particularly well reduced by combined enalapril and salt restriction. It found that enalapril was beneficial in the two conditions, with a greater effect on the low sodium diet, in accordance with our study.

Our study showed that proteinuria was particularly well controlled by combined enalapril and salt restriction. In man sodium depletion is necessary to obtain an optimal antiproteinuric effect of ACEI. Heeg *et al*[26] found that proteinuria was reduced in those receiving lisinopril during sodium restriction, while the antiproteinuric effect virtually disappeared after the patients changed to a high salt intake. Thus, the antiproteinuric effect of the ACEI lisinopril is strongly dependent on dietary sodium restriction[27].

The present study also compared the effect of nicardipine with two levels of dietary sodium (0.49% vs. 0.25%) in the excision remnant kidney model. Comparison of rats on a normal-high sodium diet and nicardipine, rats on a normal-low sodium diet and nicardipine demonstrated that rats on a normal-low sodium diet and nicardipine developed less systemic hypertension, proteinuria, renal injury, and glomerular volume than those rats on a normal-high sodium diet and nicardipine. Nicardipine effect on the progression of chronic renal failure in excision remnant kidney model is improved by moderate sodium restriction, which is less than that of enalapril effect. The mechanisms through a normal-low sodium diet plus nicardipine cause improvement in the early change of chronic renal failure that cannot be answered by the present study. Taken together, the results of the studies appear consistent with the possibility that the renoprotective property of a dietary salt restriction and antihypertensive therapy is in some sense driven by reducing high blood pressure, and limit renal hypertrophy.

Finally, it should be noted that the degree of reduction in renal damage produced by moderate salt restriction in this model is similar in magnitude to that observed in remnant kidney rats that are fed a low protein diet in a previous study[2]. At present, dietary protein restriction is a therapeutic maneuver applicable to patients with progressive renal failure. However, because of difficulty with patient compliance, it may not be possible to adequately restrict protein intake in all patients at risk for developing end stage renal disease. On the other hand, moderate salt restriction should impose less severe dietary restrictions on patients than does protein restriction, yet might convey a similar degree of protection from renal damage. Therefore, we believe that clinical trials on the effects of moderate dietary salt restriction on progressive renal failure in humans are warranted.

In summary, feeding remnant kidney rats a low salt diet prevents the increase in renal and glomerular size that follow renal ablation. Salt restricted rats also display less blood pressure, proteinuria, and glomerular damage than rats on standard chow. These findings suggest that the inhibition of compensatory renal growth and a modest decline in blood pressure is mechanisms by which salt restriction retards progressive renal damage. Enalapril provided particularly successful in reducing proteinuria and glomerular injury when combined with salt restriction.

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< 한 글 요 약 >

식이 sodium 제한 및 식이 sodium 제한에 따른 항고혈압제의 투여가 만성신부전증의 진행에 미치는 영향에 관한 실험적 연구

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목 적 : 만성신부전유발 백서에서 식이 sodium 제한이 만성신부전의 진행속도 및 혈압조절에 어떠한 영향을 주는지, 또한 항고혈압제제 (enalapril: E, nicardipine: N) 와 병행 투여하였을 때 항고혈압제제 단독투여보다 만성신부전의 진행속도 및 혈압조절에 어떠한 영향을 주는 지를 연구하였다.

방 법 : 5/6 신절제술로 만성신부전을 유발시킨 백서를 수술 제 7일부터 무작위로 0.49% sodium 식이군, 0.25% sodium 식이군, 0.49% sodium 식이 enalapril군, 0.49% sodium 식이 nicardipine군, 0.25% sodium식이 enalapril군, 0.25% sodium식이 nicardipine군으로 나누고 신절제술 4 주, 12 주, 16 주 혹은 24 주에 혈압, 24시간 단백뇨의 변화, 신 조직의 mesangial expansion score (MES) 및 사구체용적의 변화를 비교 분석하였다.

결 과 : 1) 0.25% sodium 식이군은 0.49% sodium 식이군보다 혈압의 감소를 보였고 0.25% sodium 식이 enalapril군, 0.25% sodium 식이 nicardipine군, 0.49% sodium 식이 enalapril군, 0.49% sodium 식이 nicardipine 군에서는 혈압의 감소가 관찰되었다. 2) 16주째 0.25% sodium 식이 enalapril군, 0.25% sodium 식이 nicardipine군, 0.49% sodium 식이 enalapril군, 0.49% sodium 식이 nicardipine 군은 0.49% sodium 식이군보다 의의있는 단백뇨의 감소를 보였다 (P<0.05). 0.25% sodium 식이군의 16주째 뇨단백은 78±16 mg 이었고 0.25% sodium 식이 enalapril 군, 0.25% sodium 식이 nicardipine군은 각각 35±9 mg, 41±15 mg으로 enalapril, nicardipine 에 의해 뇨단백의 감소를 관찰할 수 있었고, 0.25% sodium 식이군의 24주째 뇨단백은 82±10 mg 이었고 0.25% sodium 식이 enalapril 군, 0.25% sodium 식이 nicardipine군은 각각 54±3 mg, 76±11mg 으로, enalapril 에 의해서만 24 시간 단백뇨의 의의있는 감소를 관찰할 수 있었다. 3) 24주째 백서를 희생하여 크레아티닌 청소률을 관찰한 결과 심한 신부전은 관찰되지 않았고, 0.25% sodium 식이 대조군에 비해 0.25% sodium 식이 enalapril군에서 사구체여과율이 증가됨을 관찰할 수 있었다. 4) 신절제술후 남아 있는 신조직무게를 비교하여 보면 24주째 0.25% sodium 식이군, 0.25% sodium 식이 enalapril군, 0.25% sodium 식이 nicardipine군에서 16주째 0.49% sodium 식이군, 0.49% sodium 식이 enalapril군, 0.49% sodium 식이 nicardipine 군보다 의의있게 신조직무게가 증가됨을 관찰할 수 없었다. 5) 0.25% sodium 식이군은 0.49% sodium 식이군과 비교하여 MES 의 현저한 감소를 보였고 (0.25% sodium 식이군: 12주; 1.97±0.02, 24주; 2.06±0.03 vs. 0.49% sodium 식이군: 12주; 2.29±0.09, 16주; 2.55±0.16, P<0.05) 12주 이후에 관찰한 MES는 0.25% sodium 식이군, 0.25% sodium 식이 enalapril군, 0.25% sodium 식이 nicardipine군 세군간의 통계적인 차이는 없었다. 6) 24주에 시행한 0.25% sodium 식이군의 사구체용적은 16주에 시행한 0.49% sodium 식이군의 사구체용적보다 현저하게 감소되어있었다 (0.25% sodium 식이군:24주; $1.58\pm0.18\times10^6$ μm^3 vs. 0.49% sodium 식이군:16주; $1.98\pm0.^{16}\times10^6$ μm^3, P<0.05). 24주 0.25% sodium 식이 enalapril군의 사구체용적($1.51\pm0.08\times10^6$ μm^3)은 16주 0.49% sodium 식이 enalapril군의 사구체용적($1.81\pm0.22\times10^6$ μm^3)과 비교하여 현저한 감소를 보였다. 12 주, 24 주에 관찰한 0.25% sodium 식이군, 0.25% sodium 식이 enalapril군, 0.25% sodium 식이 nicardipine군의 사구체용적은 세군간에 의의있는 차이는 없었다.

결 론 : 식이 sodium 제한은 대상성 신비대의 감소를 통해 신손상을 감소시켰고 혈압의 감소에도 도움을 주었다. 식이 sodium 제한과 항고혈압제재 특히 enalapril 을 병행투여하였을 때 항고혈압제재 단독투여보다 뇨단백 및 신조직의 대상성 비대를 감소시켰다. 따라서 만성신부전증에서 경도의 저sodium식이가 만성신부전으로의 진행을 지연시키며 혈압의 감소에도 도움이 됨을 알 수 있었다.