The effect of soy bean on diabetic nephropathy

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The effect of soy bean on diabetic nephropathy

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<TABLE OF CONTENTS>

LIST OF FIGURES

LIST OF TABLES

ABSTRACT

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Diabetic nephropathy is one of the most frequent complications of diabetes mellitus which usually develops in 30-40% of patients with type 1 and type 2 diabetes mellitus and terminal renal failure occurs within 7 years after the onset of renal disease. Soy bean was shown to reduce urinary albumin excretion and total cholesterol in nondiabetic patients with nephrotic syndrome. However, reported studies that focused specifically on diabetic nephropathy are scarce and the available results are inconsistent. It was reported that soy bean consumption reduced urinary protein excretion in type 1 diabetic patients with diabetic nephropathy, whereas it was found an increase in urinary protein excretion when soy bean was consumed by type 2 diabetic patients. This study aims to investigate the effects of soy bean in diabetic nephropathy, particularly the effects of consuming of soy bean on histopathology of diabetic nephropathy, aquaporin (AQP) and osteopontin (OPN) expression. Male Sprague-Dawley rats were grouped into control, diabetic with red chow diet and diabetic with soy bean diet. Histology, the expression of osteopontin and aquaporin, renal function, Hb A1c were evaluated at the end of the study. In the diabetic rat with soy bean diet, the improvements on glomerular and tubulointerstitial lesions were demonstrated.

Osteopontin and aquaporin expression was suppressed in the kidney specimen of diabetic rats with soy bean.

In conclusion, soy bean could prevent weight loss due to diabetes mellitus and morphological destruction of kidney due to diabetes mellitus. Soy bean could improve glycemic control.
It could be assumed that long-standing controlled blood glucose with soy bean could prevent the progression of diabetes mellitus and therefore nephropathy could be prevented.

Key words: diabetic nephropathy, soy bean, aquaporin, osteopontin

The effects of soy bean on diabetic nephropathy

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I . INTRODUCTION

Diabetic nephropathy is one of the most frequent complications of diabetes mellitus which usually develops in 30-40% of patients with type 1 and type 2 diabetes mellitus. Terminal renal failure occurs within 7 years after the onset of renal disease. Renal disease is usually attributed to metabolic consequences of abnormal glucose regulation such as elevated blood and tissue levels of glycosylated proteins, to hemodynamic changes within the kidney tissue.[1] Diabetic nephropathy is characterized by a progressive accumulation of extracellular matrix components in the glomerular mesangium and tubular interstitium, which eventually leads to proteinuria and renal failure.[2] It is generally accepted that tubulo interstitial injury, along with glomerulosclerosis, is a major feature and an important predictor of renal dysfunction in diabetic nephropathy.[3] Tubulointerstitial fibrosis has long been recognized as an important histological parameter that correlates with chronic renal failure in a variety of renal diseases including diabetic nephropathy.[4,5]

The exact mechanisms underlying the evolution of diabetic nephropathy are complex and are not well defined.

Aquaporins (AQPs) are ubiquitously expressed pore-forming proteins located in renal proximal tubules and a part of the descending thin limbs. Aquaporins play a highly important role in the reabsorption of water from the renal tubular fluid. Immunohistochemical studies of biopsy samples from a wide range of renal diseases revealed a substantial and striking upregulation of AQP-1 in the glomeruli and also in the tubules of diseased kidneys.[6]

Osteopontin (OPN) is an arginine-glycine-aspartate containing adhesive glycoprotein that is expressed in a variety of organs including bone, kidney, vasculature, and epithelia. A functional role for OPN with respect to attracting macrophages has been recently documented in vivo and in vitro.[7,8] Osteopontin plays a pro-inflammatory role in the kidney. The up-regulation of OPN expression is also closely associated with macrophage influx in several models of kidney diseases.[9] Moreover, the extent of up-regulation of OPN expression in tubules correlates with the degree of macrophage accumulation and the magnitude of tubulointerstitial fibrosis and renal dysfunction.[10,11]

Restricting dietary protein intakes has long been known to reduce urinary albumin excretion. It is also beneficial for the prevention and treatment of diabetic nephropathy.[12,13]

Recently, instead of reducing protein intake, some interest has been directed toward manipulating the dietary protein quality, specifically by replacing animal protein with soy bean.[14] Soy bean was shown to reduce urinary albumin excretion and total cholesterol in nondiabetic patients with nephrotic syndrome.[15] Improvements in

renal function were shown in animal models of polycystic kidney disease.[16,17] Teixeira et al. found that a high soy bean diet was able to halt the increase in urinary albumin excretion typically seen in a type 2 diabetes mellitus mouse model, the *db/db* mouse.[18] Therefore, there is a growing body of evidence indicating that soy bean consumption may have beneficial effects for nephropathy in general.

However, reported studies that focused specifically on diabetic nephropathy are scarce, and the available results are inconsistent. Jibani et al[19] and Kontessis et al.[20] found that soy bean consumption reduced urinary protein excretion in type 1 diabetic patients with diabetic nephropathy, whereas Anderson et al. found an increase in urinary protein excretion when soy bean was consumed by type 2 diabetic patients with urinary protein excretion < 1000 mg/d and serum creatinine < 176.8 μmol/L (<2 mg/dL). [21]

The objective of this study was to investigate the effects of soy bean in diabetic nephropathy. In particular, the effects of consumption of soy bean on histopathology of diabetic nephropathy, aquaporin and osteopontin expression.

Ⅱ. MATERIALS & METHODS

Experiments were performed in accordance with the Principles of Laboratory Animal Care (National Institutes of Health, 1985, revised version). Eight to nine week old Male Sprague-Dawley rats weighing 250-300g (Samtako, Osan Korea) were fed a standard rat chow diet and had access to water ad libitum. At the beginning of the experimental period, ninety rats were assigned randomly into three subgroups which are control, diabetic with red chow diet, and diabetic with soy bean diet. Diabetes were induced by a single intraperitoneal injection of streptozotocin (STZ, 50mg/kg). One week after the STZ injection, blood glucose levels were determined in blood samples collected from the tail vein. Diabetes were confirmed by hyperglycemia (blood glucose concentration > 350 mg/dl). After diabetes were confirmed, soy bean feeding was started. Animals were sacrificed 4 weeks after confirming high blood glusoce level and biochemical analyses were done before the sacrifice. They were perfused with 4% paraformaldehyde and kidneys were removed.

1. Histology

The kidney specimens were fixed in 4% paraformaldehyde solution and embedded in paraffin. Sections were cut at 4 μm with a microtome and deparaffined with xylene. They were stained with Hematoxylin-Eosin (H-E) staining. Stained kidney sections were observed under a light microscope at 200 and 400 magnification.

2. Immunohistochemistry

Before paraffin embedding was performed, tissue blocks from whole kidneys were dehydrated in a graded series of ethanol (2

hours each in 70, 96, 99%, respectively) and xylene (overnight). Paraffin sections (4 μm thick) were cut on a Leica RM 2126 microtome and dried overnight at 37°C.

Sections were incubated with 10% normal goat serum for 20 min, and incubated with the rabbit anti-mouse AQP-1 antibody (1:100 dilution) and osteopontin (1:100 dilution) at room temperature for 1 hour. The immunoreactivity was visualized by incubation with a horseradish peroxidase-conjugated goat-anti-rabbit Ig*G* antibody (kit from Zymed) for 30 minutes at room temperature, followed by treatment with 3′-diaminobenzidine (DAB) 0.01% hydrogen peroxide (Sigma, USA). Immunoreactivity was detected using Zymed 2nd generation LAB-SA detection system (85-9043).

3. Electron Microscopy

Animals were perfused through the left ventricle with saline solution followed by 3% paraformaldehyde, 3% glutaraldehyde, and 0.1% picric acid. Kidney tissues were excised in 1 x 1 x 1 mm and immersed in fresh fixative for additional 2 hours at room temperature and then overnight at 4°C. After washing with PBS, the tissue were postfixed with 1% OsO4 in the same buffer for 2 hours at room temperature. Tissues were dehydrated in graded concentrations of ethanol and then embedded in Epon 812. Epon embedded sample were sectioned in 1 μm thickness (semi-thin section) and stained with 1% toluidine blue. After observation with light microscope, selected portions were trimmed and sectioned with ultramicrotome in thin section. Thin sections were stained with uranyl acetate and lead citrate and examined with Philips 500 electron microscope.

4. Biochemical analyses

Blood samples for the measurement of blood chemistry were drawn into prechilled EDTA-containing tubes and immediately placed on ice. All tubes were centrifuged within several minutes of collection and stored at -70°C until assay. Serum samples were assayed for blood urea nitrogen(BUN) and creatinine by using COBAS INTEGRA 400 (Roche, Sweden). Also, the hemoglobin A1c (Hb A1c) concentration was determined after hemolysis of the anticoagulated whole blood specimen. Hb A1c was determined immunoturbidimetrically. The ratio of both concentrations yields the final percent of Hb A1c result.

Ⅲ. RESULTS

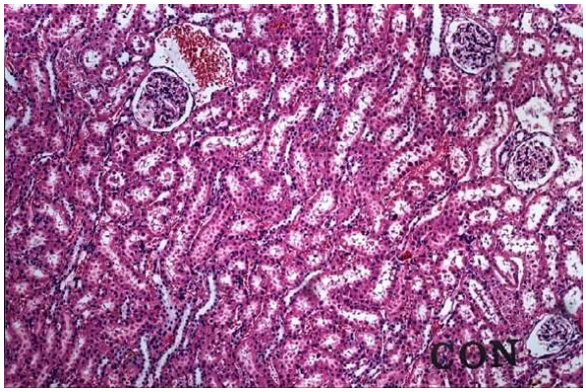
Rats that had received streptozotocin became diabetic in 70%. Diabetes was associated with reduced body weight when compared with the control rats. The change of body weight is shown in table 1.

Table 1. Weight changes of the rats

	beginning (g)	4 weeks after (g)	
Control group	273.5 ± 4.0	397.0 ± 13.6	P<0.001
DM group	270.3 ± 25.4	201.0 ± 32.5	P<0.01
DM soy group	275.5 ± 14.5	271.6 ± 30.5	

1. Histopathological finding

The kidney specimen of the diabetic group showed markedly severe destruction in glomerular and tubulo-interstitial lesions such as glomerular sclerosis, atrophy, interstitial expansion, and interstitial cellular infiltration (Fig. 1B) as compared with the control group (Fig. 1A). Also, collgen deposition was prominent and tubular spaces were obstructed (Fig. 1B). In the diabetic rat with soy bean diet, general morphology of glomerulus and tubulo-interstitial lesions were much improved and showed quite normal appearance (Fig. 1C).



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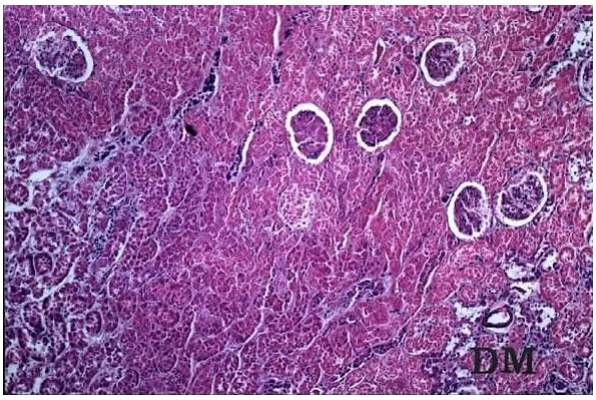

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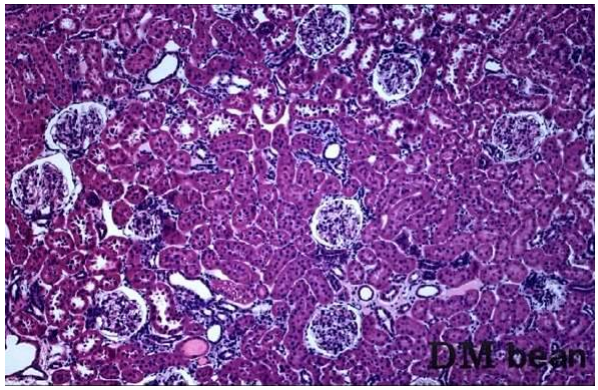


C

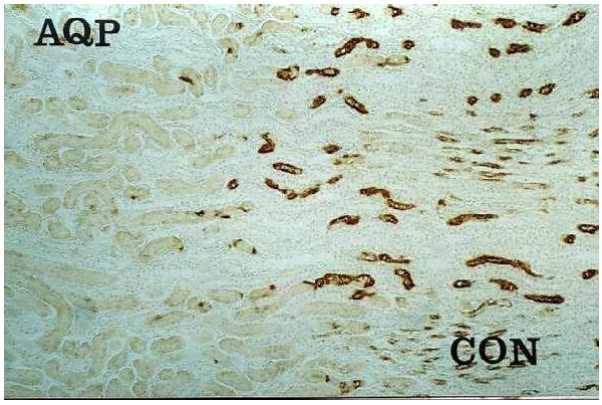
Figure 1. Photomicrographs of HE staining in the kidney of each group. A. Control rat. B. Diabetic rat. C. Diabetic rat with soy bean. The kidney specimen of the diabetic group showed markedly severe destruction in glomerular and tubulo-interstitial lesions such as glomerular sclerosis atrophy, interstitial expansion, and interstitial cellular infiltration (B) *G*eneral morphology of glomerulus and tubulo-interstitial lesions were much improved and showed quite normal appearance (C) (H-E stain, ×200).

2. Immunohistochemistry

AQP-1 is located on the basolateral and apical membranes of the proximal tubules and descending thin limb of the loop of Henle in the control group. It is absent from other parts of the nephron and the collecting ducts (Fig. 2A).

In the diabetic rats, AQP-1 expression was greatly increased in the glomerular endothelium. AQP-1 was also evident in the sclerosed glomeruli. AQP-1 staining was widespread and prominent in all viable proximal tubules (Fig. 2B).

AQP-1 expression was not found in glomeri in diabetic rats with soy bean diet (Fig. 2C).



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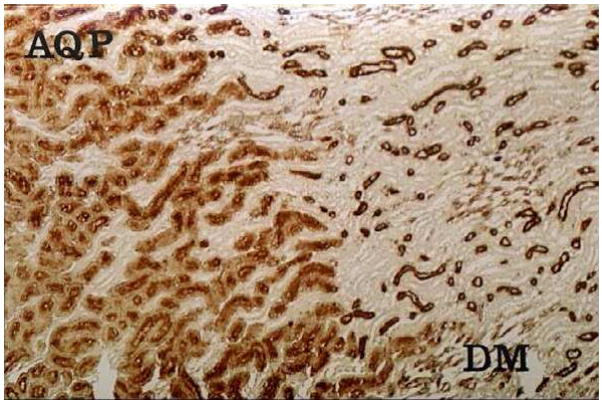

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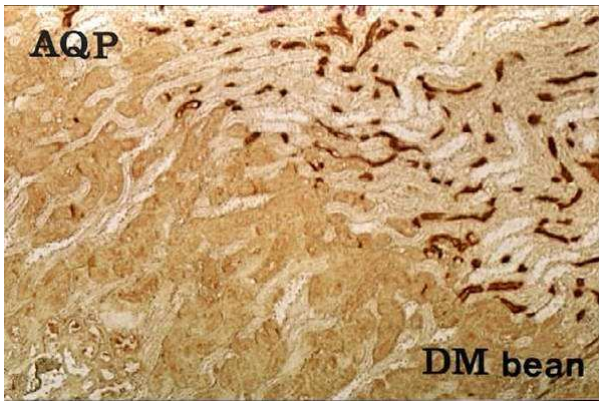
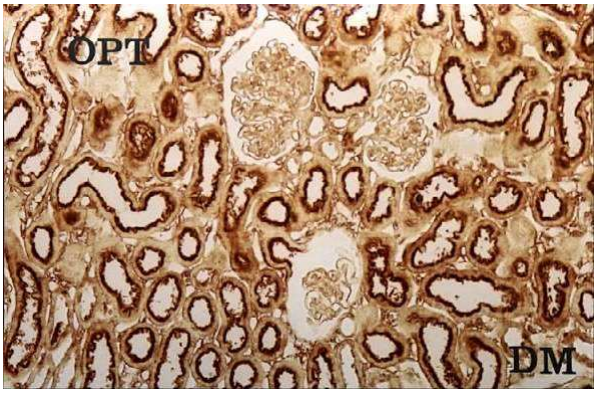


C

Figure 2. Photomicrographs of immunohistochemistry of aquaporin in the kidney of each group. A. Control rat. B. Diabetic rat. C. Diabetic rat with soy bean. AQP-1 is located on the basolateral and apical membranes of the proximal tubules and descending thin limb of the loop of Henle in the control group. It is absent from other parts of the nephron and the collecting ducts (A). In the diabetic rats, AQP-1 expression was greatly increased in the glomerular endothelium. AQP-1 was also evident in the sclerosed glomeruli. AQP-1 staining was widespread and prominent in all viable proximal tubules (B). AQP-1 expression was not found in glomeri in a diabetic rat with soy bean diet (C) (×200).

Immunostaining of osteopontin showed the typical distribution pattern in the renal cortex of control animals. Osteopontin was expressed in parietal epithelial cells of Bowman's capsule and rarely in the tubular epithelium (Fig. 3A). In diabetic rat, the osteopontin expression was increased in the renal cortex. A strong staining for osteopontin protein was found in the tubular epithelial cells of STZ-diabetic rats. No osteopontin staining was observed in glomerular or interstitial areas (Fig. 3B). In diabetic rats with soy bean diet, osteopontin expression was not found in the tubular epithelium such as in control group (Fig. 3C).

A



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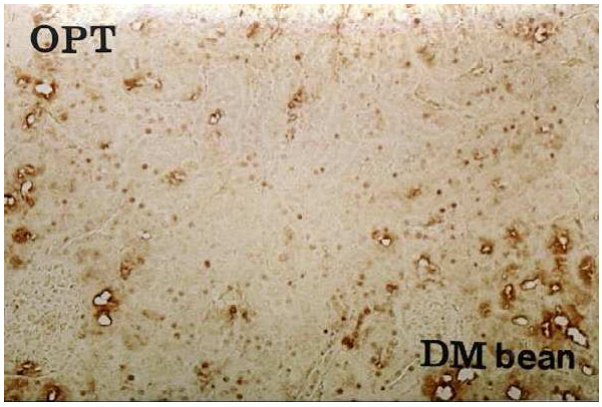

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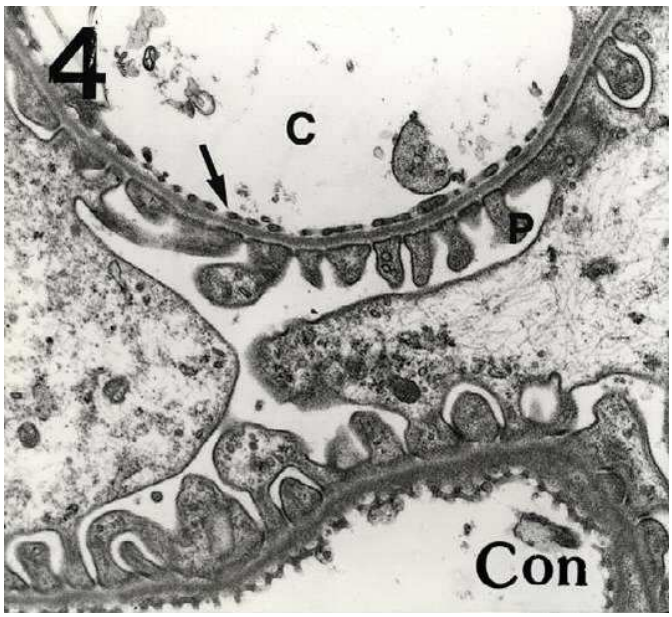
Figure 3. Photomicrographs of immunohistochemistry of osteopontin in the kidney of each group. A. Control rat. B. Diabetic rat. C. Diabetic rat with soy bean. Immunostaining of osteopontin showed the typical distribution pattern in the renal cortex of control rats. Osteopontin was expressed in parietal epithelial cells of Bowman's capsule and rarely in the tubular epithelium (A). The osteopontin expression was increased in the renal cortex. A strong staining for osteopontin protein was found in the tubular epithelial cells of a diabetic rat (B). In diabetic rats with soy bean diet, osteopontin expression was not found in the tubular epithelium (C) (×200).

3. Electron-microscopic finding

In the diabetic group, cells of tubules and glomerulus showed general destructive figures. Mitochondrias were destructed and formed vacuoles. Diaphragms of the endothelial cells of the glomerular capillaries showed irregularities and they were obstructed with the debris (Fig. 4B-1). Generally, all the basal lamina became thickened through the glomerulus and tubular cells (Fig. 4B-2).

In the DM with soy bean group, tubular cells showed normal structure. In proximal tubular cells, severe interdigitation figures were kept normal and long microvilli were intact. In the glomerulus, podocyte pedicles were normal in shape and interpedicular diaphragm were intact (Fig. 4C).



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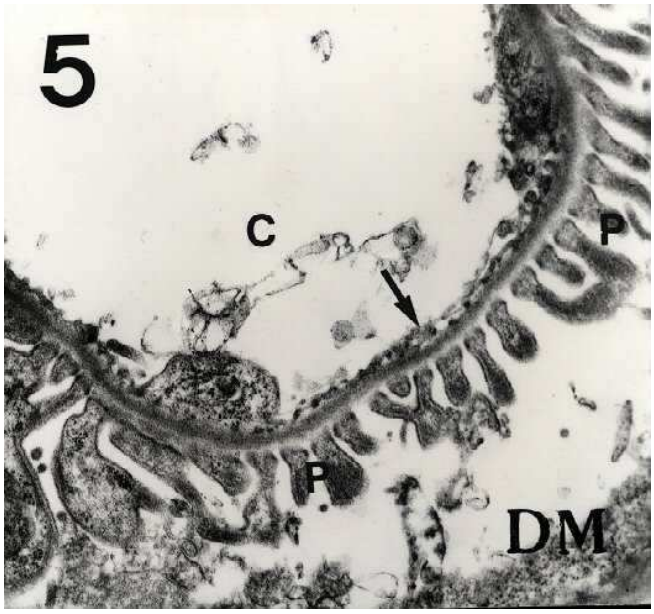
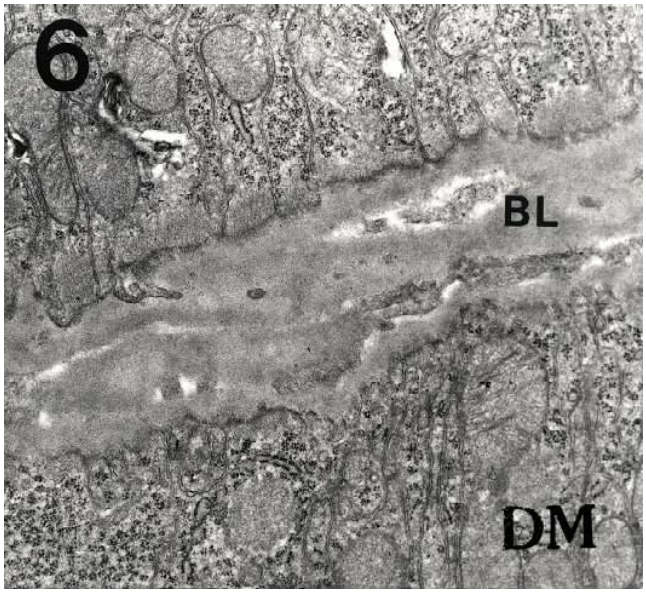


B-1



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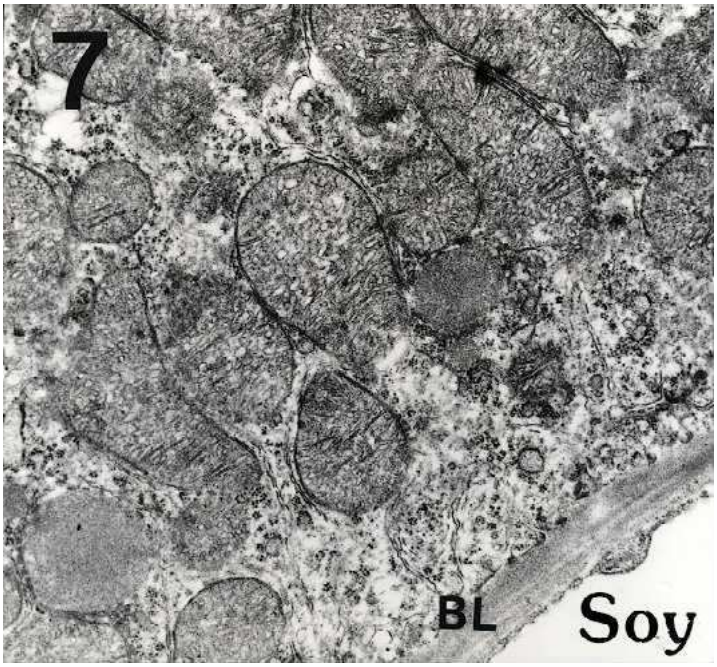

C

Figure 4. Photomicrographs of electron microscopic finding in the kidney of each group. A. Control rat. B-1,2. Diabetic rat. C. Diabetic rat with soy bean. Electron micrograph of a glomerular capillary, showing the fenestrated capillary endothelium C: capillary, P: Pedicle of podocyte, Arrow: fenestrated endothelium of type Ⅱ capillary (A). Cells of tubules and glomerulus showed general destructive figures. Diaphragms of the endothelial cells of the glomerular capillaries showed irregularities and they were obstructed with the debris (B-1). All the basal lamina became thickened through the glomerulus and tubular cells. BL: basal lamina (B-2). Tubular cells showed normal structure. In proximal tubular cells, interdigitation figures were kept normal and long microvilli were intact. BL: basal lamina (C).

4. Biochemical finding

Blood urea nitrogen, serum creatinine and hemoglobin A1c were measured and the results are shown in table 2. There was no significant difference in BUN and Creatinine mean values between the groups. The level of Hb A1c was lower in DM with soy group than in DM group.

Table 2. Change of Blood glucose

	1 week (mg/dl)	4 weeks (mg/dl)	
Control group	133.5 ± 7.6	173.0 ± 25.5	
DM group	427.8 ± 56.2	404.3 ± 64.0	
DM soy group	434.2 ± 19.8	268.0 ± 68.3	P<0.01

Table 3. Biochemical analysis in blood.

*G*roup	BUN (mg/dl)	Creatinine (mg/dl)	HbA1C (%)
Control group	21.8 ± 1.2	0.5 ± 0.03	3.6 ± 0.1
DM group	24.3 ± 0.9	0.5 ± 0.02	8.2 ± 0.4
DM soy group	35.4 ± 2.7	0.5 ± 0.02	6.9 ± 0.8

Reference values: BUN: 7.8-21.4 mg/dl; Creatinine: 0.6-1.5 mg/dl, HbA1C : 4.5-5.7%

IV. DISCUSSION

This study demonstrates that soy bean alters disease progression in the rat with diabetic nephropathy. Soy fed rats had less renal fibrosis and less renal injury. The earliest morphologic abnormalities in diabetic nephropathy are thickening of the glomerular basement membrane and expansion of the mesangium of the accumulation of the extracellular matrix. With time, matrix accumulation becomes diffuse and is evident as eosinophilic, PAS positive glomerulosclerosis on renal biopsy.[1] In this study, general morphology of glomerulus and tubulo-interstitial lesions of the diabetic rats with soy bean diet were much improved and seemed quite normal appearance compared with the findings of diabetic rats. Soy bean feeding is known to enhance the conversion of polyunsaturated fatty acids to docosahexaenoic acid.[22] Increased production of this complex lipid has been linked to benefits in a variety of inflammatory models and diseases, including renal disease.[23]

Aquaporin-1 (AQP-1) plays a critical role in the preservation of proximal tubule water handling and urinary concentration. AQP-1 is abundant in the proximal tubule and descending thin limb, where it is essential for constitutive water reabsorption at these sites. It is suggested that renal injury, regardless of etiology, produces increased stress on cell integrity, and increased expression of AQP-1 is an adaptive response to this.[24] The changes in AQP-1 immunostaining seen in this collection of rat renal biopsy specimens are similar to those documented in other studies. AQP-1 expression was increased in diabetic rat kidney. It is an interesting finding that soy bean attenuates renal aquaporin expression in diabetic kidney.

In agreement with previous studies, we found OPN expression was increased in the tubular epithelium of diabetic rat kidney. Osteopontin is a potent chemotactic and adhesive factor for macrophages[25]. There are overwhelming evidences that the up-regulation of tubular OPN expression is strongly associated with macrophage infiltration subsequent to tubulointerstitial injury in experimental studies[26] and in human patients with kidney diseases.[27] Diabetic nephropathy is not only a glomeular disease but is characterized by impaired tubular function as well.[28] The urinary excretion of low molecular weight proteins and tubular enzymes has been suggested to reflect disturbance and injury of proximal tubules and to proceed microalbuminuria.[29,30] Interstitial fibrosis occurs during the pathogenesis of diabetic nephropathy and has been shown to correlate with the development of reduced *G*FR.[31] Li et al suggested that up-regulation of OPN expression may play a role in tubulo interstitial injury associated with diabetic nephropathy and blockade of the renin angiotensin system by ramipril may confer renoprotection by decreasing OPN expression in non-insulin dependent diabetic nephropathy.[32] Since the up-regulation of OPN expression in the tubular epithelium in diabetic rat kidneys was significantly suppressed and general morphology of glomerulus and tubulo-interstitial lesions was much improved by soy bean intake, it is tempting to speculate that one of the mechanism of the renoprotective effect of soy bean may be related with decreasing OPN expression in diabetic nephropathy.

In the present study, the level of Hb A1c was lower in DM-Bean group than DM group. soy bean improves serum glucose and insulin levels, as well as insulin sensitivity in diabetes.[33,34] Although the exact mechanism has yet to be elucidated, it can not

be overlooked that the soluble fiber component of the soy bean may be the most important factor. Approximately 15 percent of the soy bean is insoluble carbohydrates and over 30 percent of the fiber in soy is of the soluble variety. And soy beans are slowly digested and have a low glycemic index.[35] Since factors implicated as triggers for increased matrix production in DM include the direct effects of hyperglycemia on mesangial cells, advanced glycosylation end-products and cell sorbitol accumulation[1], one of the mechanism of the renoprotective effect of soy bean may be related with glycemic control in diabetic nephropathy.

In conclusion, the results from this study show that soy bean could prevent morphological destruction of kidney due to diabetes mellitus. Further studies are required to determine the exact mechanism of renoprotective effect of soy bean.

Ⅴ. CONCLUSION

DM rats were treated with soy bean and the conclusions are as follows:

1. Soy bean could prevent weight loss due to diabetes mellitus.
2. Soy bean could prevent morphological destruction of kidney due to diabetes mellitus.
3. Soy bean could improve glycemic control.

It could be assumed that long-standing controlled blood glucose by soy bean could prevent the progression of diabetes mellitus and therefore nephropathy could be prevented.

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Abstract (in Korean)

대두가 당뇨병성 신증에 미치는 영향

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당뇨병성 신증은 당뇨병의 주요 합병증의 하나로 1, 2형 당뇨병 환자의 약 30-40%에서 발생하며 종국에는 신부전증에 이르게 된다. 대두는 당뇨병이 동반되지 않은 신증후군의 환자에서 요에서 알부민 배출과 혈중 콜레스테롤 수치를 감소시키는 것으로 보고되었다. 다낭성 신질환의 동물 모델에서도 신기능의 호전을 보였다고 한다. 하지만 대두가 당뇨병성 신증에 미치는 효과에 관한 연구는 일부에서는 요단백 배출을 줄이는 것으로, 다른 연구에서는 오히려 증가시키는 것으로 보고되어 논쟁의 여지가 있다. 이에 이 연구는 당뇨병성 신증에서 대두의 효과를 조사하고자 시행하였다. 특히 당뇨병성 신증의 조직학적 소견과 aquaporin, osteopontin 의 발현에 영향을 미치는지 알아보고자 하였다. Male Sprague-Dawley rats을 대조군, 일반 식이의 당뇨군, 대두 식이의 당뇨군으로 나누어 당뇨 발생 4주후에 조직학적 소견, osteopontin, aquaporin의 발현, 신기능, Hb A1c 등을 조사하였다. 대두를 투여한 당뇨군의 신장 조직 소견에서는 일반식이의 당뇨군에 비해 사구체와 세뇨간질 손상이 현저하게 적은 것을 관찰할 수 있었고, Osteopontin과 aquaporin 발현도 억제되어 있었다. 결론적으로 대두 투여는 당뇨병으로 인한 체중감소를 예방할 수 있었고 당뇨병에 의한 신장의 조직학적 손상을 막을 수 있었으며 이는 혈당조절을 향상시킬 수 있었던 것에 의한 것으로 추정된다.

핵심되는 말: 당뇨병성 신증, 대두, aquaporin, osteopontin