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A report of three cases of diabetic nephropathy satisfactorily treated with traditional herbal medicine

Hirozo GOTO,*[a] Yutaka SHIMADA,[a] Takahiro SHINTANI,[b] Naotoshi SHIBAHARA[c] and Katsutoshi TERASAWA[a]

[a] *Department of Japanese Oriental (Kampo) Medicine, Toyama Medical and Pharmaceutical University*
[b] *Department of Japanese Oriental (Kampo) Medicine, Kanebo Memorial Hospital*
[c] *Faculty of Medicine, and Department of Kampo Diagnostics, Toyama Medical and Pharmaceutical University*

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Abstract

We reported that three cases of diabetic nephropathy, who had overt proteinuria, were treated satisfactorily not only for their symptoms but also renal nephropathy with traditional herbal medicine over the long term. In Case 1, the level of S-Cr had changed from 1.2 to 2.0 mg/dl over 98 months, in Case 2 from 0.9 to 1.9 mg/dl over 70 months, and in Case 3 from 1.1 to 2.9 mg/dl over 81 months, acceptably moderate increases, meaning that the progression of their renal insufficiency was controlled over the long term. At the same time, the symptoms of hotness, numbness and edema were improved. Diabetic nephropathy with overt proteinuria is known to develop into renal failure after several years. In these cases, traditional herbal medicine was considered responsible for improving their QOL and prolonging the pre-dialysis period of diabetic nephropathy.

Key words diabetic nephropathy, QOL, traditional herbal medicine, Gosha-jinki-gan, Ompi-to, Keishi-bukuryo-gan.

Abbreviations BUN, blood urea nitrogen ; Bunsho-to (Fen-Qing-Tang), (分消湯) ; Chukenchu-to (Zhong-Jian-Zhong-Tang), (中建中湯) ; Daio (Da-Huang), (大黄), Rhei Rhizoma ; DM, diabetes mellitus ; Gosha-jinki-gan (Niu-Che-Shen-Qi-Gan), (牛車腎気丸) ; Hochu-ekki-to (Bu-Zhong-Yi-Qi-Tang), (補中益気湯) ; Karo-gaihaku-hakushu-to (Gua-Lou-Xie-Bai-Bai-Jiu-Tang), (栝楼薤白白酒湯) ; Keishi-bukuryo-gan (Gui-Zhi-Fu-Ling-Wan), (桂枝茯苓丸) ; Kumi-binro-to (Jiu-Wei-Bing-Lang-Tang), (丸味檳榔湯) ; Ninjin (Ren-Shen), (人参), Ginseng Radix ; Ompi-to (Wen-Pi-Tang), (温脾湯) ; PTCA, percutaneous transluminal coronary angiography ; Sanmotsu-ogon-to (San-Wu-Huang-Qin-Tang), (三物黄芩湯) ; S-Cr, serum creatine ; Shimbu-to (Zhen-Wu-Tang), (真武湯) ; Sokei-kakketsu-to (Shu-Jing-Huo-Xio-Tang), (疎経活血湯) ; Uzu-to (Wu-Tou-Tang), (烏頭湯).

Introduction

Diabetic nephropathy is a microangiopathy disease that is caused by chronic hyperglycemia. Clinical manifestations are proteinuria, renal dysfunction, hypertension and edema. When patients with long-term diabetes mellitus combined with retinopathy or neuropathy complain of the above symptoms, they are diagnosed as diabetic nephropathy. There are many such cases that advance to renal failure within several years.[1] Patients who are newly requiring hemodialysis due to diabetic nephropathy have been on the increase, and their prognosis, once they go into hemodialysis, is poor.[1] So this is one of the major problems and it is necessary to devise a countermove. However, there is no effective preventive method for diabetic nephropathy except to control hyperglycemia in the early stage by western medicine. In oriental medicine, there have been some reports that tradi-

*〒930-0194 富山市杉谷 2630
富山医科薬科大学医学部和漢診療学講座 後藤 博三
2630 Sugitani, Toyama 930-0194, Japan

tional herbal medicines are effective against renal failure.[2,3] So it is supposed that traditional herbal medicines can work to prevent progression to renal dysfunction by diabetes. Here we present three cases of diabetic nephropathy with proteinuria that were satisfactorily treated with traditional herbal medicines.

Case 1

A 74-year-old male visited our institution in 1991. His chief complaint was numbness of four limbs. Twelve years earlier a pacemaker was installed due to sinus syndrome. His father was suffering from diabetes mellitus.

Glycosuria was found at a medical examination in 1955. He consulted his family doctor, and his blood glucose was about 400 mg/dl. He was admitted and received medication, dietetic treatment (1800Kcal) and kinesitherapy. After this, he was admitted and discharged repeatedly, but his blood glucose control was poor due to his busy work schedule.

In 1988, he felt numbness in the four limbs and his HbA1c was 12 %, so insulin therapy was instracted for blood glucose control. But redness and abnormal sense in the palms and soles also occurred, so in October 1991 he came to our institution requesting treatment with traditional herbal medicine.

At the first medical examination, the complications of diabetes were positivity for proteiniuria, creatinine clearance of 53.8 ml/min on nephropathy, simple retinopathy by ophthalmoscopy, and vibration sense was decreased.

The physical characteristics were: body height 163 cm, body weight 74 kg, blood pressure 148/82 mmHg, red face, easy fatigue, pollakisuria, lower leg edema.

Pulse: minor of the deficiency type; weak and feeble pulse. It means the deficiency of KI.

Tongue: red dip, slight swelling, yellow fur.

Abdomen: slightly decreased abdominal tension, bilateral para-umbilical region tender on pressure, resistance resembling string of pearls in the midline of the lower abdomen. Laboratory data at first medical examination are shown in Table I.

When he came to our hospital, he was using insulin injection and dietetic treatment (1800Kcal) for diabetes control, and diuretics for his edema. He was administered Sanmotsu-ogon-to for his hotness of the four limbs and Gosha-jinki-gan for his edema.

Table I Background and laboratory findings

No.	Case 1	Case 2	Case 3
Sex	Man	Man	Man
Onset	1955	1964	1967
Complication			
Neuropathy	+	+	+
Retinopathy	+	+	+
Hypertension	+	−	+
Ischemic heart disease	+	+	−
Laboratory findings			
Data	(1991.10.8)	(1994.6.14)	(1993.4.27)
WBC (/μl)	6,350	8,510	6,090
RBC (×10⁴/μl)	491	442	376
Hb (g/dl)	15.7	14.0	12.2
Ht (%)	45.4	38.3	35.8
PLT (×10⁴/μl)	16.9	18.5	19.0
TP (g/dl)	7.0	7.5	6.2
Alb (g/dl)	4.2	4.2	3.6
T-Chol (mg/dl)	200	203	196
TG (mg/dl)	94	242	165
BUN (mg/dl)	23	23	22
Cr (mg/dl)	1.2	0.9	1.1
UA (mg/dl)	5.2	5.3	7.2
Na (mEq/l)	147	140	138
K (mEq/l)	3.8	4.2	4.7
Cl (mEq/l)	110	104	105
Ca (mg/dl)	9.5	9.1	8.4
IP (mg/dl)	3.3	2.6	3.1
Blood glucose (mg/dl)	62	195	146
HbA1c (%)	6.6	8.1	6.2
Urinalysis Protein	+	++	++
Blood	−	−	−

After two months, numbness in the four limbs had decreased. But in December 1991, he contracted Herpes Zoster, so we changed his formula to Uzu-to and Sokei-kakketsu-to for neuralgia. After this he became well. His renal function showed no change but edema of the lower limbs continued. We changed his formula to Kumi-binro-to and Shimbu-to in September 1992. Edema of the lower limbs decreased slightly and proteinuria decreased to a plus-minus status. In January 1994 he was operated for abdominal aortic aneurysm. As a result, the administration of Kampo formulas was halted for a while.

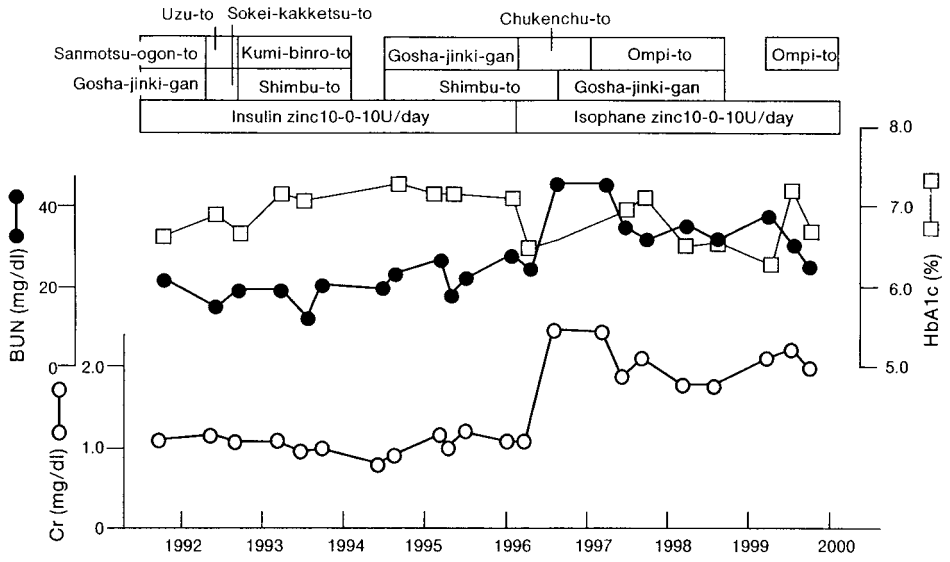

Figure 1 Clinical course in case 1

In July 1994, he was administered Shimbu-to and Gosha-jinki-gan for general fatigue again. In February 1996, he had lower abdominal pain and was diagnosed with ischemic colitis. So we changed his formula to Chu-kenchu-to from Gosha-jinki-gan. Furthermore, in June 1996, he felt chest distress. He was diagnosed with stenosis of the coronary artery and underwent percutaneous transluminal coronary angiography (PTCA). The effect of the contrast medium worsened his renal function, and serum creatine (S-Cr) was 2.4 mg/dl and blood urea nitrogen (BUN) was 45 mg/dl in October 1996. To improve his renal function, his formula was changed to Ompi-to. Following this, edema of the lower limbs remained, but his renal function improved to levels of S-Cr and BUN of 1.7 mg/dl and 28 mg/dl, respectively, in July 1997. When he stopped taking Kampo formulas in October 1997, his renal function became worse. So he again resumed Ompi-to in April 1999, and his renal function improved again (Figure 1).

Case 2

A 79-year-old male visited our institution in 1994. His chief complaint was renal dysfunction by diabetis nephropathy. His sister was suffering from diabetes mellitus.

Glycosuria was presented at a medical examination in 1964. He received dietetic treatment (1600Kcal) and medication with glibenclamide from 1979. The dose of glibenclamide was increased gradually but blood glucose control worsened to HbA1c 8.0 %. In 1984, he felt numbness of bilateral lower limbs, and in 1991 he was diagnosed with diabetis retinopathy. In 1994, edema of the lower limbs set in. In June 1994, he came to our institution for treatment of his renal dysfunction with traditional herbal medicine.

His physical characteristics were: body height 159 cm, body weight 60 kg, blood pressure 136/82 mmHg, red face, easy fatigue, thirst, athenopia, lower leg edema.

Pulse: minor of a mild excess-type; strong pulse. It means the excess of KI.

Tongue: red dip, white fur.

Abdomen: slightly enhanced abdominal tension, bilateral para-umbilical region tender on pressure, resistance resembling string of pearls in the midline of the lower abdomen. Laboratory data at first medical examination are shown in Table I.

When he visited our hospital, he was using glibenclamide for diabetes control. We administered Hochu-ekki-to for easy fatigue and Gosha-jinki-gan for edema. In September 1994, we changed Hochu-ekki-to to Keishi-bukuryo-gan because of signs of blood stasis. Then his condition of edema and easy fatigue

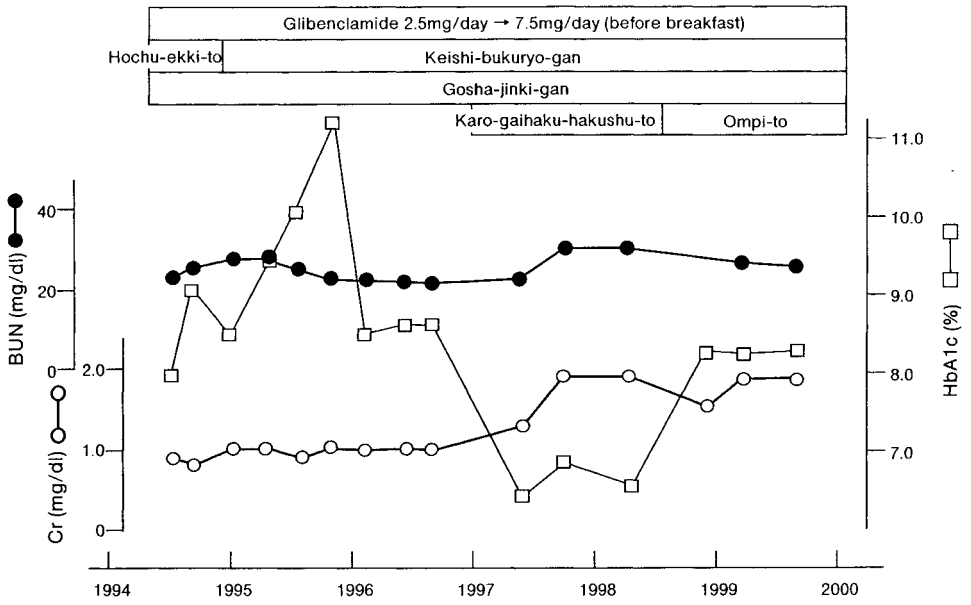

Figure 2 Clinical course in case 2

improved. However, as diabetes mellitus (DM) control was poor, he was admitted to our hospital from November 26 to December 12. His DM control then improved. During his hospitalization, his complications of diabetes were: proteiniuria 1.9 g/day, creatinine clearance 66.4 ml/min, S-Cr 1.7 mg/dl and BUN 28 mg/dl on nephropathy, simple retinopathy by ophthalmoscopy, vibration sense and decreased neuroconductive velocity. After discharge, in January 1997, he was diagnosed with angina pectoris and was examined by PTCA. The effect of the contrast medium worsened his renal function ; the level of S-Cr was 1.3 mg/dl and that of BUN 22 mg/dl in May 1997. After re-PTCA, his renal function decreased gradually. The level of S-Cr was 1.9 mg/dl, so we administered Ompi-to, and his renal function has since been stable (Figure 2).

Case 3

A 78-year-old male visited our institution in 1993. His chief complaint was renal dysfunction by diabetic nephropathy. Twelve years earlier he was diagnosed with hypertension. His father was suffering from diabetes mellitus.

Glycosuria was discovered during a medical examination in 1967. He received dietetic treatment (1600Kcal). In 1975 he suffered from thirst and pollakisuria, and he consulted his family doctor. His blood glucose was about 400 mg/dl and he received dietetic treatment again. His body weight decreased from 75 kg to 55 kg and DM control improved. But then DM control became worse gradually. In 1988, he entered the hospital for diabetes mellitus, hypertension, diabetic nephropathy and retinopathy. From then, with the help of medications, his DM control was good. But from 1993, his renal function worsened gradually. He was informed by his doctor that he would need hemodialysis in the future. In April 1993, he came to our institution for the treatment of renal dysfunction with traditional herbal medicine. His physical characteristics were : body height 154 cm, body weight 55 kg, blood pressure 140/74 mmHg, easy fatigue, nycturia.

Pulse: Pulsus intentus minor of a mild excess-type. Pulsus intentus is wiry pulse. It is a sign of cold condition.

Tongue: red dip, yellow fur.

Abdomen: balanced state of abdominal tension, hypertonic rectus abdominis muscle, resistance resembling string of pearls in the midline of the lower abdomen. Laboratory data from the first medical examination are shown in Table I.

We administered Gosha-jinki-gan for edema and

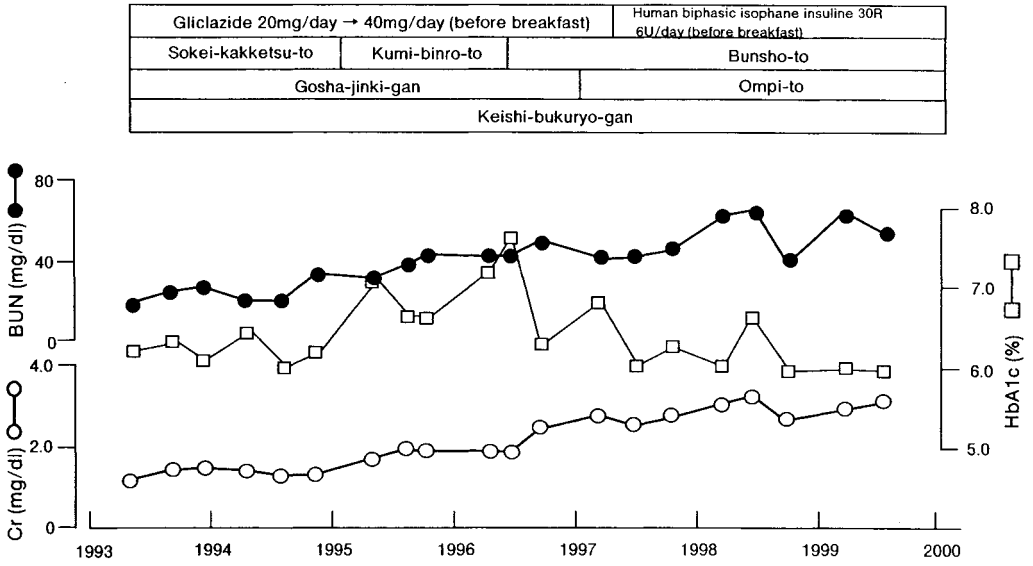

Figure 3 Clinical course in case 3

Sokei-kakketsu-to for numbness of the lower limbs. In order to evaluate the state of his diabetes mellitus, he was admitted in our hospital in July 1993. Improvement in his DM control was achieved. During his hospital stay, his complications of diabetes were: proteiniuria 3.3 g/day, creatinine clearance 54.8 ml/min, S-Cr 1.3 mg/dl and BUN 17 mg/dl concerning nephropathy, simple retinopathy by ophthalmoscopy, vibration sense and decreased neuroconductive velocity. He used glibenclamide, and his blood glucose control improved to HbA1c 6.3 %. When numbness of his lower limbs was improved, we changed Sokei-kakketsu-to to Kumi-binro-to with Daio for his edema in 1995. Edema of his lower limbs was also improved.

His edema and DM control became gradually worse in 1996, and he was hospitalized again in July 1996. He had proteiniuria of 3.0 g/day, creatinine clearance of 31.2 ml/min, the level of S-Cr was 1.8 mg/dl and that of BUN was 29 mg/dl. So we changed from Kumi-binro-to to Bunsho-to with Daio. His edema decreased slightly, but his renal function became worse. We changed from Gosha-jinki-gan to Ompi-to in December 1996, and then his renal function became a little better. But his renal dysfunction worsened gradually again to 3.3 mg/dl of S-Cr. So we increased the volume of Ninjin in Ompi-to in August 1998. As a result, the level of S-Cr decreased to 2.3 mg/dl and DM control was good at about HbA1c 6.0 % at the latest measurement (Figure 3).

Discussion

Traditional herbal medicine was often used for diabetes mellitus to cure several symptoms. In these cases, the symptoms of hotness, numbness and edema were improved. It is supposed that effective treatment of symptoms brings about improved QOL for the patients and may affect some control over blood glucose. Among the reports of the effects of traditional herbal medicine on diabetes mellitus, there are some that claim an effect of decreasing blood glucose[4] and a favorable effect on neuropathy.[5] But any effect on diabetic nephropathy has not been clear.

Now it has become possible to diagnose diabetic nephropathy in its early stage by measuring microalbuminuria. It is also reported that strict control of blood glucose can suppress the appearance of microalbuminuria.[6] But when proteinuria and renal dysfunction exist, strict control of blood glucose cannot suppress the progression of renal dysfunction. Then, after several years, renal function becomes decadent,[1] and its prognosis is very poor. So it is extremely important, and also very difficult, to suppress the progres-

Table II Changes in progression of renal dysfunction

Case No.	Blood Pressure (mmHg)	Duration (month) of Kampo treatment	Before treatment			After treatment		
			Cr (mg/dl)	BUN (mg/dl)	UA (mg/dl)	Cr (mg/dl)	BUN (mg/dl)	UA (mg/dl)
1	148/82	98	1.2	23	5.2	2.0	27	6.7
2	136/82	70	0.9	23	5.3	1.0	24	5.8
3	140/74	81	1.1	22	7.2	2.9	49	7.2

sion of diabetic nephropathy. To protect against its advance, the main methods are the use of ACE-inhibitor[7] and protein restrict diet.[8] Nevertheless, it is difficult to prevent the advance of renal dysfunction over the long term.

There have already been some reports about traditional herbal medicines being useful for nephropathy and chronic renal failure. Especially Daio, Ompi-to and Gosha-jinki-gan and Sairei-to are reported to be effective for nephropathy and nephrotic syndrome.[3,9,10] Therefore is this study, the mechanisms of Daio and Ompi-to were studied. Clinically they have anabolic and anticatabolic effects for the metabolism of nitrogen, and have an inhibiting effect on methylguanidine.[11] Basically, they were reported to have an antiperoxidation effect,[12] a decreasing effect on transforming growth factor-β[13] and a protective effect for apoptosis.[14] In total, these effects work to protect renal function, and it is suggested that they work to suppress renal dysfunction as well.

Table II shows the changes of renal function in the three cases before and after Kampo treatment. These three cases were diagnosed with diabetic nephropathy, based on long-term diabetes mellitus and the presence of diabetic retinopathy and proteinuria. Their condition was diagnosed as overt nephropathy because they presented overt proteinuria and renal dysfunction, and their prognosis was judged to be poor. But these three cases then maintained their renal function for 6 to 9 years. It is considered that the traditional herbal medicines they were administered worked to protect against renal dysfunction by diabetes mellitus.

In our three cases, the blood glucose levels did not decrease. Therefore, the protective effect on renal function was thought to be not by improvement of blood glucose but rather a direct effect on the kidney.

In this study, traditional herbal medicine was believed not only to improve their QOL but also to prolong the pre-dialysis period of diabetic nephropathy. The future of this protective effect of Kampo formulas against diabetic nephropathy will require further investigations with larger study populations.

Supplementary notes

All Kampo formulas used for these patients consisted of hot water and extracts that were prepared from a mixture of several dried traditional herbal

Table III Crude drugs of mainly used prescriptions

Prescription	Crude drugs (g/day)
Ompi-to (Wen-Pi-Tang)	Glycyrrhizae Radix 4.0, Zingiberis Rhizoma 3.0, Ginseng Radix 2.0, Rhei Rhizoma 1.0-3.5, Aconiti Japonici Tuber 2.0-2.5
Gosha-jinki-gan (Niu-Che-Shen-Qi-Wan)	Rehmanniae Radix 5.0, Corni Fructus 3.0, Dioscoreae Rhizoma 3.0, Alismatis Rhizoma 3.0, Hoelen 3.0, Moutan Cortex 3.0, Cinnamomi Cortex 1.0, Achyranthis Radix 3.0, Plantaginis Semen 2.0, Aconiti Japonici Tuber 1.0-2.0
Keishi-bukuryo-gan (Gui-Zhi-Fu-Ling-Wan)	Cinnamomi Cortex 0.2, Paeoniae Radix 0.2, Persicae Semen 0.2, Hoelen 0.2, Moutan Cortex 0.2, Honey 1.0

medicines. This mixture was heated in 600 ml of water and reduced to 300 ml. The aqueous extract, called the "decoction", was taken 3 times a day before meals. The components and indications for main Kampo formulas are summarized in Table III. If two Kampo formulas were administered, they were taken alternatively every other day.

Acknowledgment

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和文抄録

顕性蛋白尿期にある糖尿病性腎症の患者に漢方治療を施行した。その結果，随伴する諸症状の改善のみならず長期間，腎機能低下の進行を抑制した3症例を経験したので報告した。

症例1では，98ヶ月の観察でS-Cr値は1.2から2.0 mg/dl，症例2では70ヶ月の観察で，S-Cr値は0.9から1.9 mg/dl，症例3では81ヶ月の観察で，S-Cr値は1.1から2.9 mg/dl，と長期間腎機能低下の進行を抑制した。同時に，手足の火照りやしびれ感，下肢の浮腫などの症状の軽快も認めた。持続的に蛋白尿を認める顕性腎症期に至った糖尿病性腎症は数年の経過で，末期腎不全から血液透析に至ると言われている。今回の症例から和漢薬は，糖尿病性腎症における腎機能障害に対して腎機能障害の進行抑制作用を有する可能性が示唆された。このことから，和漢薬は糖尿病に随伴する諸症状を緩和し，QOLを改善するのみでなく，血液透析導入までの期間を延長し，予後を改善したと考えられた。

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