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

## - Clinical evaluation of the effect of traditional herbal medicines containing Daio (Rhei Rhizoma) on the progression of diabetic nephropathy with overt proteinuria -

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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 a 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.

We also studied the effect of traditional herbal medicines containing Daio (Rhei Rhizoma) on the long-term progression of diabetic nephropathy with overt proteinuria in 8 patients [mean age 60 (45-73) years; duration of diabetes 18 (7-36) years]. An average of 7.4 (5-12) kinds of traditional herbal prescriptions was used for each patient. At the beginning of the study mean HbA1c was 8.2% and mean serum creatinine was 1.0±0.3 mg/dl. After a mean of 107 ±25 months, the mean serum creatinine level had significantly increased to 4.8±2.6 mg/dl. The mean serum creatinine levels of 5 patients not advancing to dialysis treatment increased from 1.2±0.3 to 3.2±1.0mg/dl, and those of 3 patients requiring dialysis increased from 0.8±0.1 to 7.5±2.1mg/dl. The mean rate of decline of creatinine clearance in the measurable 4 patients was 0.78±0.40 ml/min/month.

Diabetic nephropathy with overt proteinuria is reported to develop into renal failure after 6-7 years. In this study, traditional herbal medicines with Daio were considered to be effective in prolonging the pre-dialysis period of diabetic nephropathy.

**Key words** diabetic nephropathy, traditional herbal medicine, Daio, Gosha-jinki-gan, Ompi-to, Keishi-bukuryo-gan, Hochu-ekki-to.

**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), 九味檳榔湯; 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

In recent years, together with the increase of patients with diabetes mellitus, the number of patients with diabetic nephropathy has also been increasing. As a result, patients newly requiring hemodialysis due to diabetic nephropathy have also been increasing. It is sup-

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posed that one of the causes of diabetic nephropathy is the factor of heredity. Furthermore, the control of blood glucose is especially important in the early stage. It is reported that strict control of blood glucose can suppress the appearance of microalbuminuria.[1] However, once proteinuria and renal dysfunction are present, even stringent blood glucose control cannot suppress the progression of renal dysfunction. Then, after several years, renal function becomes decadent, and its prognosis is very poor.[2] It is therefore crucial, albeit very difficult, that the progression of diabetic nephropathy be somehow suppressed or delayed. To protect against its advance, the main methods are the use of ACE-inhibitors[3] and protein-restricted diet.[4] Nevertheless, it is a major challenge to prevent the advance of renal dysfunction over the long term.

In oriental medicine, there have already been some reports about traditional herbal prescriptions being useful for nephropathy[5] and chronic renal failure.[6] Especially Daio, Ompi-to[7] and Daio-Kanzo-to[8] are reported to be effective against renal failure. The mechanisms of Daio and Ompi-to have been studied, revealing that they possess anabolic and anticatabolic effects on the metabolism of nitrogen and have an inhibiting effect on methylguanidine.[7]

Thus, it is considered that traditional herbal medicines can function 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. We studied the effect of traditional herbal medicines containing Daio in 8 patients, focusing on the progression of diabetic nephropathy with overt proteinuria.

## Case presentation[9]

### 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 four limbs and his HbA1c was 12%, so insulin therapy was instructed for blood glucose control. But redness and abnormal sensations 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, it was found that the complications of diabetes were positive for proteiniuria, creatinine clearance of 53.8ml/min on nephropathy, simple retinopathy by ophthalmoscopy, and also vibration sense was decreased.

Physical characteristics of the patient were: body height 163cm, body weight 74kg, 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,

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 | − | − | − |

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 hotness of the four limbs and Gosha-jinki-gan for his edema.

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 on an abdominal aortic aneurysm. As a result, the administration of Kampo formulas was halted for a while.

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 Chukenchu-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).

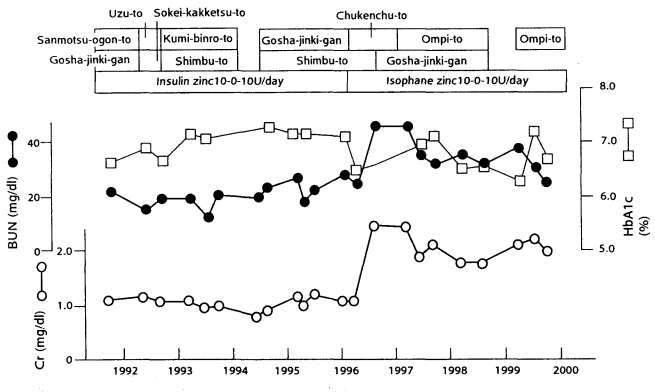


Figure 1. Clinical course in case 1

**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 diabetic 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.

Physical characteristics of the patient were: body height 159cm, body weight 60kg, 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 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: proteinuria 1.9g/day, creatinine clearance 66.4ml/min,

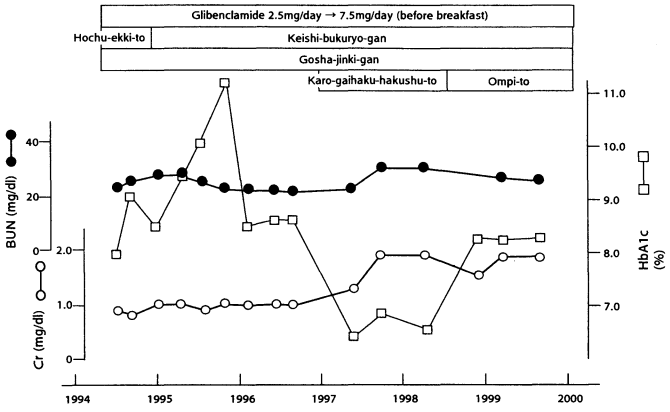


Figure 2. Clinical course in case 2

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 (1600 Kcal). In 1975 he suffered from thirst and pollakisuria, and he consulted his family doctor. His blood glucose was about 400mg/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. Physical characteristics of the patients were: body height 154cm, body weight 55kg, 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 Sokei-kakketsu-to for numbness of the lower limbs. In order to evaluate the state of his diabetes mellitus, he was admitted to our hospital in July 1993. Improvement in his DM control was achieved. During his hospital stay, his complications of diabetes were: proteinuria 3.3g/day, creatinine clearance 54.8ml/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 proteinuria of 3.0g/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

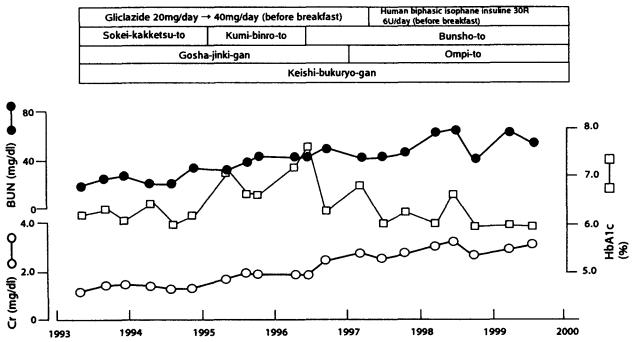


Figure 3. Clinical course in case 3

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).

## Patients and Methods[10)]

Eight type II diabetes patients [mean age 60 (45-73) years; male:female = 6:2; duration of diabetes 18 (7-36) years] with diabetic nephropathy and overt proteinuria were investigated in this study. Type II diabetes was defined by the following diagnostic criteria: age of patients at the time of diagnosis >40 years, and patients initially treated with diet alone or in combination with oral antidiabetic drugs. The diagnosis of diabetic nephropathy was established by renal biopsy in 2 patients. None of the other patients had evidence of pyuria, hematuria, or urinary tract infection, and all had normal kidneys on ultrasound. At the beginning of the study, 5 of the patients were receiving oral antidiabetic drugs, and the other 3 were already being treated by conventional insulin therapy. Salt intake was restricted to approximately 9g/day in all cases. Dietary protein restriction to 0.8g/kg body weight was prescribed for all patients.

Antihypertensive therapy was given to 3 patients at the beginning of the study and to all patients in due course. Six patients received double-, and the other 2 triple-drug therapy. The antihypertensive drugs used were calcium antagonists, diuretics and ACE inhibitors. Six of the patients temporarily received ACE inhibitors, but they were discontinued when serum creatinine increased to 4.0 mg/dl.

All traditional herbal medicines used for these patients consisted of hot water and extracts that were prepared from a mixture of several dried crude drugs. This mixture was heated in 600ml of water and reduced to 300ml. The aqueous extract, called the "decoction", was taken 3 times a day before meals. The components of the main traditional herbal prescriptions are summarized in Table II.

We added Daio to every decoction from a minimum of 0.5g/day. Because Daio induces diarrhea, it was increased gradually till the patients evacuated their bowels two or three times a day. As a result, Daio was used at 1.0-5.0g/day.

Traditional herbal prescriptions were selected by diagnosis based on oriental medicine, and they were changed and/or increased according to the state of the patients. As a result, 5-12 kinds of traditional herbal prescriptions were used (mean 7.4 kinds). Among them, Ompi-to was used for 5, Hochu-ekki-to for 6, Gosha-jinki-gan for 4, and Keishi-bukuryo-gan for 6 patients. In addition, antihypertensive drugs, diuretics and anticoagulants *etc.*, which were being used before the traditional herbal therapy, were continued. Further, according to the advance of nephropathy, western drugs were added and increased.

Certain parameters were controlled at least every 3 months; in the fasting state, creatinine, urea nitrogen, potassium, calcium, inorganic phosphate and uric acid in serum were measured by autoanalyser.

The data were presented as mean $\pm$ standard error.

Table II. Crude drugs of the mainly 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 |
| Hochu-ekki-to (Bu-Zhong-Yi-Qi-Tang) | Astragali Radix 4.0, Atractylodis Lanceae Rhizoma 4.0, Ginseng Radix 4.0, Angelicae Radix 4.0, Bupleuri Radix 2.0, Cimicifugae Rhizoma 2.0, Zingiberis Rhizoma 1.0, Zizyphi Fructus 2.0, Aurantii Nobilis Pericarpium 2.0, Glycyrrhizae Radix 1.5 |
| 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 |

Table III. Patients' characteristics at entry into the study

| Patient No. | Sex | Age (years) | Duration of diabetes (years) | Body mass index (kg/m$^2$) | Antidiabetic treatment | Complication (N/R/HT/IHD) | HbA1c (%) | Urinary protein (g/day) | S-Cr (mg/dl) | BUN (mg/dl) | Cr-clearance (ml/min) |
|---|---|---|---|---|---|---|---|---|---|---|---|
| 1 | M | 65 | 36 | 27.9 | Insulin | +/+/+/+ | 6.6 | (30 mg/dl) # | 1.2 | 23 | 53.8 |
| 2 | M | 73 | 30 | 23.7 | Oral agent | +/+/−/+ | 8.1 | 0.9 | 0.9 | 23 | 76.4 |
| 3 | M | 71 | 26 | 23.2 | Oral agent | +/+/+/− | 6.2 | 3.0 | 1.1 | 22 | 70.0 |
| 4 | M | 58 | 14 | 25.2 | Insulin | +/+/+/+ | 11.4 | (100 mg/dl) # | 1.6 | 21 | 55.2 |
| 5 | F | 61 | 8 | 24.6 | Oral agent | +/+/−/− | 9.4 | (30 mg/dl) # | 1.0 | 12 | 74.7 |
| 6 | F | 50 | 7 | 27.0 | Oral agent | +/+/−/+ | 8.9 | 1.1 | 0.7 | 13 | 82.6 |
| 7 | M | 45 | 14 | 23.9 | Oral agent | +/+/−/− | 7.2 | 3.5 | 0.8 | 11 | 78.5 |
| 8 | M | 55 | 10 | 19.6 | Insulin | +/+/−/− | 7.4 | 2.8 | 0.8 | 12 | 69.6 |
| Mean ± S.D. | | 60 ± 10 | 18 ± 11 | 24.4 ± 2.5 | | | 8.2 ± 1.7 | 2.3 ± 1.2 | 1.0 ± 0.3 | 17 ± 5.5 | 70.1 ± 10.5 |

N: Neuropathy, R: Retinopathy, HT: Hypertension, IHD: Iscemic heart decease, S-Cr: Serum creatinine, BUN: Blood urea nitrogen
# indicates measurement by qualitative analysis

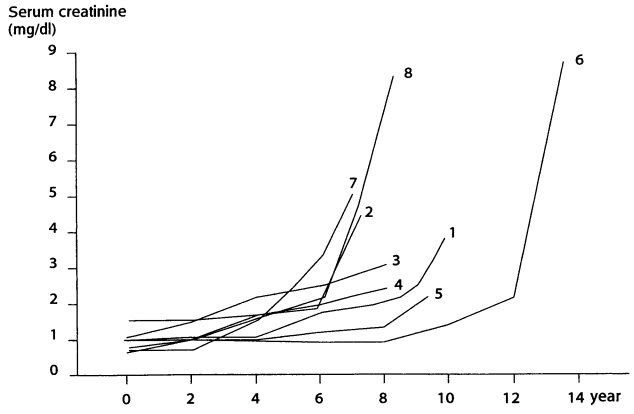


Figure 4. The individual course of serum creatinine in the type II diabetic patients

Statistical comparisons were performed using the paired t-test. The level of statistical significance was defined as $p<0.05$.

## Results

Table III shows the patients' characteristics at the time of admission into the study. At the beginning of the study, mean HbA1c was 8.2%. Every patient had diabetic neuropathy and retinopathy. Three of the patients had hypertension and 4 had ischemic heart disease. Mean serum creatinine was 1.0 (0.7-1.6) mg/dl.

Figure 4 shows the course of serum creatinine levels of all 8 patients. The mean serum creatinine level was significantly increased from 1.0±0.3 to 4.8±2.6 mg/dl ($p<0.01$) within a mean of 107±25 months. Three of the 8 patients required dialysis treatment (No.6-8). The mean serum creatinine level of the patients not advancing to dialysis (No.1-5) was increased from 1.2±0.3 to 3.2±1.0 mg/dl. The mean serum creatinine level of those requiring dialysis (No.6-8) was increased from 0.8±0.1 to 7.5±2.1 mg/dl.

The rate of decline of creatinine clearance of the 4 patients in whom (No.3,6,7,8) this could be measured was 0.66,0.45,1.36 and 0.64 ml/min/month, respectively, and their mean rate of decline was 0.78±0.40 ml/min/month.

Individual laboratory data at the first and last investigations (or the introduction of dialysis treatment) are shown in Table IV. Mean blood urea nitrogen rose from 17±5.5 to 66±25 mg/dl ($p<0.01$), serum calcium decreased from 9.3±0.5 to 8.2±0.7 mg/dl ($p<0.05$), inorganic phosphate rose from 3.2±0.3 to 4.1±0.5 mg/dl ($p<0.01$), serum uric acid rose from 5.1±1.2 to 6.8±1.5 mg/dl ($p<0.01$), and serum potassium remained unchanged during the study.

## Discussion

Traditional herbal medicines have often been used for diabetes mellitus to cure several symptoms. General malaise, pollakisuria, hotness, numbness and edema showed improvement. It is supposed that effective treatment of symptoms results in improved quality of life (QOL), possibly accompanied by at least a minimal degree of control over blood glucose levels. Among the

Table IV. Laboratory data

| Patient No. | Observation time (months) | S-Cr (mg/dl) | | BUN (mg/dl) | | K (mEq/l) | | Ca (mg/dl) | | Pi (mg/dl) | | Uric acid (mg/dl) | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | Baseline | Follow-up | Baseline | Follow-up | Baseline | Follow-up | Baseline | Follow-up | Baseline | Follow-up | Baseline | Follow-up |
| 1 | 120 | 1.2 | 3.8 | 23 | 62 | 3.8 | 4.2 | 9.5 | 8.5 | 3.3 | 4.1 | 5.2 | 8.5 |
| 2 | 84 | 0.9 | 4.5 | 23 | 54 | 4.2 | 4.8 | 9.1 | 7.8 | 2.6 | 4.8 | 5.3 | 8.1 |
| 3 | 99 | 1.1 | 3.0 | 22 | 69 | 4.7 | 4.0 | 8.4 | 8.1 | 3.1 | 4.3 | 7.2 | 6.5 |
| 4 | 98 | 1.6 | 2.6 | 21 | 42 | 4.0 | 4.4 | 9.0 | 9.0 | 3.2 | 3.6 | 5.8 | 7.0 |
| 5 | 110 | 1.0 | 2.1 | 12 | 36 | 5.0 | 5.4 | 9.9 | 8.7 | 3.4 | 3.8 | 5.1 | 7.5 |
| 6 | 161 | 0.7 | 8.6 | 13 | 82 | 4.5 | 4.4 | 9.3 | 9.0 | 3.3 | 3.4 | 3.8 | 7.3 |
| 7 | 83 | 0.8 | 5.1 | 11 | 69 | 3.9 | 4.7 | 9.7 | 7.5 | 3.4 | 4.8 | 4.7 | 6.1 |
| 8 | 97 | 0.8 | 8.8 | 12 | 117 | 3.9 | 4.3 | 9.8 | 7.1 | 2.9 | 3.8 | 3.4 | 3.7 |
| Mean ± S.D. | 107 ± 25 | 1.0 ± 0.3 | 4.8 ± 2.6 | 17 ± 5.5 | 66 ± 25 | 4.3 ± 0.4 | 4.5 ± 0.4 | 9.3 ± 0.5 | 8.2 ± 0.7 | 3.2 ± 0.3 | 4.1 ± 0.5 | 5.1 ± 1.2 | 6.8 ± 1.5 |
| Paired t-test | | ** | | ** | | NS | | * | | ** | | * | |

Symbols (*and**) indicate significant differences from the data before traditional herbal medicines treatment at $p<0.05$ and 0.01, respectively.

reports regarding the effects of traditional herbal medicines on diabetes mellitus, there are some that claim an effect of decreasing blood glucose[11] and a favorable effect on neuropathy.[12]

However, any effect on diabetic nephropathy has not yet been established. Now it has become possible to diagnose diabetic nephropathy in its early stage by measuring microalbuminuria. It has also been reported that strict control of blood glucose can suppress the appearance of microalbuminuria.[1] Unfortunately, in the presence of proteinuria and renal dysfunction, strict control of blood glucose can no longer delay the progression of renal dysfunction.

There have been some studies that observed the disease from the appearance of persistent proteinuria to the beginning of dialysis. The mean periods were 74 (40-119) months[2] and $6.5 \pm 5.1$ years.[13] The mean rate of decline in creatinine clearance was $10.9 \pm 4.9$ ml/min/year.[2]

There have been no reports about the long-term course of diabetic nephropathy treated with traditional herbal medicines. In this study, during an average observation period of 107 months, the mean serum creatinine level was significantly increased from 1.0 to 4.8 mg/dl. Three of the 8 patients required dialysis treatment. Further, the mean rate of decline in creatinine clearance of 4 patients was 9.4 ml/min/year. Considering this course of renal function over such a long term, it can be suggested that traditional herbal medicines have a certain inhibitory effect on the advance of diabetic nephropathy with overt proteinuria.

In the present study, none of the 8 patients showed a decrease in blood glucose level by traditional herbal medicines. 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.

There have already been some reports about traditional herbal medicines being useful for nephropathy and chronic renal failure. Especially Daio, Ompi-to,[7] Goshajinki-gan[14] and Sai-rei-to[15] have been reported to be effective for nephropathy and nephrotic syndrome.

The mechanisms of Daio and Ompi-to have been examined. Clinically they have anabolic and anticatabolic effects on the metabolism of nitrogen and have an inhibiting effect on methylguanidine.[7] Basically, they were reported to have an antiperoxidation effect,[16] a decreasing effect on transforming growth factor-$\beta$[17] and a protective effect for apoptosis.[18]

Furthermore, it has also been indicated that coagulation factors were involved in the worst aspects of diabetic nephropathy.[19] Therefore, Keishi-bukuryo-gan, which has been successfully used to improve blood circulation,[20,21] was suggested to exert a favorable effect on coagulation factors. In total, these effects worked to protect renal function, and it is suggested that they work to suppress renal dysfunction as well.

As for the abnormality of electrolytes in renal dysfunction, serum potassium did not change significantly. As traditional herbal medicines consist of crude drugs, it was a matter of concern that they might influence the

serum potassium level. But in this study, traditional herbal medicines were thought to have little effect on the serum potassium level, as no patients were using anti-hyperkalemic drugs. Mean serum calcium decreased and inorganic phosphate rose significantly. However, such changes were considered to take place with common renal failure.[6] Finally, other side effects that would call for the cessation of the use of traditional herbal medicines were not encountered in this study.

In conclusion, traditional herbal medicines were believed not only to improve the QOL of the patients in our series, but also to suppress the advance of renal insufficiency by diabetic nephropathy with overt proteinuria. Of course, the future of this protective effect provided by traditional herbal medicines against diabetic nephropathy will require further investigations with larger study populations.

## 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2.0mg/dl，症例2では70ヶ月の観察で，S-Cr値は0.9から1.9mg/dl，症例3では81ヶ月の観察で，S-Cr値は1.1から2.9mg/dlと長期間腎機能低下の進行を抑制した。

さらに，顕性蛋白尿期の糖尿病性腎症患者8症例［平均年齢60（45－73）才，糖尿病罹患期間18（7－36）年］に対する大黄含有漢方方剤の効果を検討した。各症例において平均7.4（5－12）方剤を用いた。和漢薬治療開始時のHbA1cは8.2％で，平均血清クレアチニン値は1.0±0.3mg/dlであった。各症例は，糖尿病性神経症と網膜症を有しており，3症例で高血圧症を4症例で虚血性心疾患を合併していた。平均107±25ヶ月後，血清クレアチニン値は4.8±2.6mg/dlと有意に上昇した。透析導入に至らなかった5症例の平均血清クレアチニン値は1.2±0.3から3.2±1.0mg/dlと上昇し，透析導入に至った3症例は，平均血清クレアチニン値が0.8±0.1から7.5±2.1mg/dlと上昇した。クレアチニンクリアランスを測定することのできた4症例において，その平均上昇率は，0.78±0.40ml/min/monthであった。

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6－7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。今回の検討から大黄含有漢方方剤は，糖尿病性腎症における腎機能障害の進行を抑制し血液透析導入までの期間を延長したと考えられた。

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## References

1) The diabetes control and complication trial research group: The effect of intensive treatment of diabetes on the development and progression of long-term complications in insulin-dependent diabetes mellitus. *N. Engl. J. Med.* **329**, 977-986, 1993.
2) Biesenbach, G. and Zazgornik, J.: High mortality and poor quality of life during predialysis period in type II diabetic patients with diabetic nephropathy. *Renal Failure* **16**, 263-272, 1994.
3) Lewis, E.J., Hunsicker, L.G., Bain, R.P. and Rohde, R.D.: The effect of angiotensin-converting-enzyme inhibition on diabetic nephropathy. *N. Engl. J. Med.* **329**, 1456-1462, 1993.
4) Pedrini, M.T., Levey, A.S., Lau, J., Chalmers, T.C. and Wang, P.H.: The effect of dietary protein restriction on the progression of diabetic and nondiabetic renal diseases: A meta-analysis. *Ann. Intern. Med.* **124**, 627-632, 1996.
5) Morimoto, K., Takahashi, M., Watanabe, S., Tekigi, T., Yokoyama, S., Mori, N., Hibi, I., Hatanaka, Y., Horikawa, K., Imafuku, T. and Itoh, T.: A study of therapeutic effect of Sairei-to in primary chronic glomerulonephritis. *Kidney and Dialysis* **31**, 125-131, 1991.
6) Mitsuma, T., Yokozawa, T., Oura, H. and Terasawa, K.: Rhubarb therapy in patients with chronic renal failure (part 2). *Jpn. J. Nephrol.* **29**, 195-207, 1987.
7) Mitsuma, T., Yokozawa, T., Oura, H., Terasawa, K. and Narita, K.: Clinical evaluation of Kampo medication, mainly with Wen-Pi-Tang, on the progression of chronic renal failure. *Jpn. J. Nephrol.* **41**, 769-777, 1999.
8) Akamatsu, A. and Takara, M.: Rhubarb therapy for chronic renal failure. *Kidney and Dialysis* **23**, 183-191, 1987.
9) Goto, H., Shimada, Y., Shintani, T., Shibahara, N.and Terasawa, K.: A report of three cases of diabetic nephropathy satisfactorily treated with traditional herbal medicine. *J. Trad. Med.* **17**, 198-204, 2000.
10) Goto, H., Shimada, Y., Tanikawa, K., Sato, S., Hikiami, H., Sekiya, N., and Terasawa, K.: Clinical evaluation of the effect of Daio (Rhei Rhizoma) on the progression of diabetic nephropathy with overt proteinuria. *Am. J. Chin. Med.* (in press)
11) Hirabayashi, M. and Fujinuma, H.: Effects of Ba-Wei-Di-Huang-Wan (Hachimi-jio-gan) on diabetic neuropathy and blood sugar level, Clinical case report. *Thera. Res.* **13**, 1671-1675, 1992.
12) Sato, Y.: Diabetic neuropathy. *Internal Medicine* **67**, 616-620, 1991.
13) Ordonez, J.D. and Hiatt, R.A.: Comparison of type II and type I diabetics treated for end-stage renal disease in a large prepaid health plan population. *Nephron* **51**, 524-529, 1989.
14) Ida, T., Matsuda, O., Suenaga, M., Kuriyama, R., Yoshiyama, N., Tomura, N., Shu, R., Tomita, K. and Maruyama, F.: The effect of Gosyajinkigan on diabetic nephropathy. *Kidney and Dialysis* **34**, 115-117, 1993.
15) Aida, K., Tawata, M., Tsuchiya, K. and Onaya, T.: The effect of

Saireito (Kampo medicine) on diabetic nephropathy. *Therapeutic Research* **16**, 263-266, 1995.

16) Hattori, T., Fujitsuka, N., Kurogi, A. and Shindo, S.: Protective effect of Onpi-to (TJ-8117) on the expression of apoptosis in 5/6 nephrectomized rats. *Jpn. J. Nephrol.* **39**, 377-386, 1997.

17) Hattori, T., Fujitsuka, N., Kurogi, A. and Shindo, S.: Effect of Onpi-to (TJ-8117) on TGF-$\beta$1 in rats with 5/6 nephrectomized chronic renal failure. *Jpn. J. Nephrol.* **38**, 475-483, 1996.

18) Yokozawa, T., Dong, E., Lui, Z.W., Oura, H. and Nishioka, I.: Antiperoxidation activity of Wen-Pi-Tang in vitro. *Nat. Med.* **50**, 243-246, 1996.

19) Kubo, K.: Coagulation factors in type 2 diabetes mellitus: Association with nephropathy. *J. Japan. Diab. Soc.* **44**, 329-334, 2001.

20) Kohta, K., Hikiami, H., Shimada, Y., Matsuda, H., Hamazaki, T. and Terasawa, K.: Effects of Keishi-bukuryo-gan on erythrocyte aggregability in patients with multiple old lacunar infarction. *J. Med. Pham. Soc. WAKAN-YAKU* **10**, 251-259, 1993.

21) Hikiami, H., Kohta, K., Sekiya, N., Shimada, Y., Itoh, T. and Terasawa, K.: Erythrocyte deformity in "oketsu" syndrome and its relations to erythrocyte viscoelasticity. *J. Trad. Med.* **13**, 156-164, 1996.