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ORIGINAL ARTICLE

Beneficial effect of *Astragalus membranaceus* on estimated glomerular filtration rate in patients with progressive chronic kidney disease

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Summary *Background/Purpose:* Several types of herbal preparations have been used as supplementary therapies for the treatment of progressive chronic kidney disease (CKD), but the scientific evidence for their use is scarce. The aim of the present study was to determine the effects of *Astragalus membranaceus* on renal outcome in patients with progressive CKD. *Methods and Results:* The study population consisted of 35 patients with CKD stages 4 and 5 whose estimated glomerular filtration rate (eGFR) decreased over a 3-month period before the start of *A membranaceus* treatment despite the use of conventional therapy (from 14.6 ± 6.28 mL/min/1.73 m^2 to 11.6 ± 5.24; mean $\pm$ SD, $p < 0.05$). Similarly, the eGFR of 15 patients with CKD stage 4 decreased over the same period despite conventional therapy (from 20.8 ± 4.59 to 16.7 ± 4.17; $r = -1.298$; $p < 0.05$), but increased after the initial period of 3 months of supplementary treatment with *A membranaceus* (to 18.6 ± 5.67; $r = 0.973$; $p < 0.05$) and remained at that level at 6 months (17.8 ± 5.60) and 12 months (16.3 ± 5.89). However, in 20 patients with CKD stage 5, the beneficial effect of *A membranaceus* was limited to the first 3 months only (-3 months: 10.5 ± 2.7, baseline: 8.0 ± 2.75, 3 months: 8.4 ± 2.96, 6 months: 6.8 ± 2.45). *A membranaceus* had no significant effects on other laboratory parameters. Only seven patients (1 in stage 4 and 6 in stage 5) required dialysis within 12 months of *A membranaceus* treatment, whose eGFR at baseline was relatively low (7.4 ± 1.06). *Conclusion:* The results suggest that *A membranaceus* can maintain stable levels of eGFR and delay the initiation of renal replacement therapy in patients with progressive CKD stage 4.

至今已有數種草藥製劑被應用於進行性慢性腎病(CKD)的補充療法，然而此用途仍缺乏相關的科學理據。本研究旨在探討膜莢黃耆(Astragalus membranaceus)對進行性CKD患者的腎臟效應。研究對象為35位第4或5期CKD患者，即使在常規治療下(不包括A membranaceus)，其腎絲球過濾率估

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算值(eGFR)仍在3個月內明顯下降(從14.6 ± 6.28 mL/min/1.73 m² 至 11.6 ± 5.24; mean ± SD, $p < 0.05$)。其中15人為第4期CKD患者，eGFR於該段期間明顯下降(從20.8 ± 4.59至16.7 ± 4.17; $r = -1.298$; $p < 0.05$)，但在膜莢黃耆補充療法開始後3個月回升(至18.6 ± 5.67; $r = 0.973$; $p < 0.05$)，並維持穩定於6個月(17.8 ± 5.60)及12個月(16.3 ± 5.89)。另外20位為第5期CKD患者，膜莢黃耆對其效益僅可見於首3個月(−3個月: 10.5 ± 2.7, 基線: 8.0 ± 2.75, 3個月: 8.4 ± 2.96, 6個月: 6.8 ± 2.45)。至於其他實驗室項目，膜莢黃耆並不具明顯效應。在膜莢黃耆的12個月治療期間，僅7人(第4期：1人；第5期：6人)需接受透析治療，其基線eGFR均偏低(7.4 ± 1.06)。因此，對於第4期進行性CKD患者，膜莢黃耆有助維持eGFR於穩定水平，並延遲腎臟替代療法的開始時間.

Introduction

With increasing numbers of patients undergoing renal replacement therapy, the cost of chronic kidney disease (CKD) is rising worldwide.[1] The number of patients requiring dialysis therapy in Japan has also increased almost linearly, about 10,000 a year, since surveys began in 1983, reaching 297,126 at the end of 2010. Therefore, it is important to establish strategies to delay the progression to end-stage kidney disease in CKD patients. However, despite significant advances in conventional medicine, no specific treatment is available for patients with stages 4 and 5 CKD. There is definitely a need for the use of combinations of different treatment modalities to control the progression of CKD, highlighting the importance of research on discovering new pharmacological agents for CKD.[2] In Japan, not only traditional herbalists but also nephrologists have occasionally used herbal medicine for treatment of patients with CKD, including some imported from China, as part of combination therapy.[3] Traditional herbalists usually prescribe a blend of several herbs such as *Astragalus membranaceus*, *Angelica sinensis*, *Angelica acutiloba*, *Salvia miltiorrhiza*, and *rhubarb* to patients with renal disease. Among these herbal medicines, formulations containing *A membranaceus* have often been used for renal disorders based on their diuretic action and reduction of proteinuria.[4,5] In addition, *A membranaceus* is believed to have beneficial effects on other conditions such as diabetes mellitus[6,7] and cardiovascular,[8,9] digestive,[10,11] hepatic,[12] neurological,[13,14] and allergic diseases.[15] Several recent experimental studies using animal models of diabetic nephropathy[6] and unilateral ureteral obstruction (UUO) renal fibrosis[16] have highlighted the potency of *A membranaceus*. To our knowledge, however, there are only a few clinical case reports in the English literature on the effects of *A membranaceus* when used alone for membranous nephropathy.[17,18]

The objective of our prospective study was to assess the efficacy of *A membranaceus* in progressive CKD when used in combination with conventional therapy. As it is not randomized, we set up the primary endpoint to decline rate of eGFR before and after treatment with *A membranaceus*. Since several species of herbs are usually prescribed in combination, the present study is the first clinical trial on the use of *A membranaceus* alone.

Patients and methods

Patients

Of the 41 patients who were initially enrolled in this study, six were unable to continue treatment with *A membranaceus* for 3 months, and their data were excluded from the analysis. The reasons for cessation of treatment were revocation of consent ($n = 3$), start of dialysis therapy ($n = 1$), diarrhea ($n = 1$), and change of hospital ($n = 1$). Therefore, the study population eventually consisted of 35 patients (15 with CKD stage 4 and 20 with CKD stage 5) who were treated with *A membranaceus* daily for more than 3 months.

Study design

Outpatients with progressive CKD stage 4 to 5 who consented to undergo treatment with *A membranaceus* were enrolled in this study. Progressive CKD in this study was defined as reduction in the estimated glomerular filtration rate (eGFR) over a period of 3 months preceding enrollment in the study despite the use of conventional therapy. We compared the slope of eGFR decline before and after treatment with *A membranaceus*. All enrolled patients were already being treated for CKD-related complications such as hypertension, renal anemia, metabolic acidosis, and mineral bone disease with antihypertensive drugs, erythropoietin, xanthine oxidase inhibitors, sodium bicarbonate, vitamin D analogs, and absorbant AST120.[19] During the study, the patients were advised to continue to take all their medications wherever possible. The trial protocol was approved by the institutional review board of Juntendo University Hospital, and all patients gave written informed consent. Whenever a patient demanded a revocation of consent, we excluded that patient's information from our study.

The *A membranaceus* used in this study was inspected and certified according to the regulations established by the Japanese Pharmacopeia. Participants were treated with 2.5 g *A membranaceus* twice a day, together with conventional therapy. There was no prohibited combination of drugs. The primary outcome measurement was retardation of CKD progression as assessed by the slope of eGFR. The eGFR for each patient was estimated using the four-variable Modifications of Diet in Renal Disease study equation.[20]

The following information was recorded every 4 weeks at each visit to Juntedo University Hospital: body weight, blood pressure, hemoglobin (Hb), serum creatinine, blood urea nitrogen (BUN), uric acid (UA), Na, K, Cl, albumin, low-density lipoprotein cholesterol, e-GFR, and urinary protein excretion (mg/g·Cr).

Statistical analyses

Data are expressed as mean ± SD. Statistical comparison of data before and after treatment with *A membranaceus* was performed using the Mann−Whitney *U*-test, and the analysis of changes in eGFR was performed using the paired

Table 1 Clinical characteristics of the patients.

	All patients ($n = 35$)	CKD stage 4 ($n = 15$)	CKD stage 5 ($n = 20$)
Age (y)	64.1 ± 13.1	62.4 ± 15.7	66.8 ± 12.6
Females/males	22/13	9/6	13/7
Body weight (kg)	62.4 ± 11.9	61.2 ± 11.4	64.6 ± 12.9
Body mass index (kg/m^2)	24.0 ± 3.9	23.3 ± 4.0	24.5 ± 3.8
Systolic blood pressure (mmHg)	130.5 ± 16.4	129.9 ± 17.3	131.2 ± 18.3
Diastolic blood pressure (mmHg)	75.3 ± 9.6	75.0 ± 13.2	78.2 ± 10.2
eGFR (mL/min/1.73 m^2)	11.69 ± 5.49	16.74 ± 4.17	8.03 ± 2.69
Treatment (%)			
ACEI or ARB	65.7	66.7	65.0
Vitamin D analog	14.3	6.7	20.0
Sodium bicarbonate	28.6	13.3	40.0
Diuretics	31.4	46.7	20.0
Primary disease	Hypertensive nephrosclerosis		$n = 13$
	Chronic glomerulonephritis		$n = 10$
	Diabetic nephropathy		$n = 5$
	Polycystic kidney disease		$n = 4$
	Chronic interstitial nephritis		$n = 2$
	Vesicoureteral reflux		$n = 1$

Data are mean ± SD or number of patients.
ACEI = angiotensin converting enzyme inhibitor; ARD = angiotensin II receptor blocker; CKD = chronic kidney disease; eGFR = estimated glomerular filtration rate.

t-test (StatView version 5.0; SAS Institute Inc., Tokyo, Japan). A p value <0.05 was considered statistically significant. The correlation coefficient between before and after treatment with *A membranaceus* was expressed as $r = .$

Results

Demographic and clinical characteristics of the patients

In these patients, the primary kidney diseases were nephrosclerosis ($n = 13$), chronic glomerulonephritis ($n = 10$), diabetic nephropathy ($n = 5$), autosomal dominant polycystic kidney disease ($n = 4$), chronic interstitial nephritis ($n = 2$), and vesicoureteral reflux ($n = 1$). This group consisted of 22 (63%) males and 13 (47%) females aged 40–94 years ($64.1 ± 13.1$). Table 1 lists the demographic and clinical characteristics, blood pressure, laboratory findings, and drug usage of these patients.

Changes in eGFR and proteinuria

For the entire group of 35 patients, the mean eGFR at 3 months before the administration of *A membranaceus*

Table 2 Serial changes in various clinical and laboratory parameters during combination treatment including *Astragalus membranaceus* in the entire patients populations.

	−3 mo	0 mo	3 mo	6 mo	9 mo	12 mo
n	35	35	35	26	20	16
Systolic blood pressure (mmHg)	135 ± 15.0	131 ± 16.4	136 ± 17.5	133 ± 17.1	128 ± 12.5	126 ± 13.0
Diastolic blood pressure (mmHg)	77 ± 10.1	75 ± 9.6	76 ± 8.7	76 ± 7.9	76 ± 8.5	75 ± 9.1
Hemoglobin (g/dL)	10.9 ± 1.6	11.0 ± 1.5	10.8 ± 1.4	10.6 ± 1.6	10.2 ± 2.4	10.6 ± 1.3
BUN (mg/dL)	47.4 ± 18.6	48.7 ± 18.1	54.2 ± 23.1	52.0 ± 23.4	43.4 ± 17.8	47.6 ± 14.1
Serum creatinine (mg/dL)	3.87 ± 1.65	4.03 ± 1.73	3.87 ± 1.88	3.63 ± 1.65	3.30 ± 1.47	3.29 ± 1.40
eGFR (mL/min/1.73 m^2)	14.56 ± 6.28	11.55 ± 5.24*	12.81 ± 6.68	13.54 ± 6.65	14.42 ± 6.45	13.89 ± 6.09
Uric acid (mg/dL)	7.26 ± 1.49	7.51 ± 1.41	7.79 ± 1.65	7.21 ± 1.43	7.28 ± 1.10	7.81 ± 0.90
Albumin (g/dL)	3.89 ± 0.43	3.92 ± 0.46	3.97 ± 0.82	3.86 ± 0.56	3.81 ± 0.52	3.86 ± 0.48
LDL-C (mg/dL)	100.5 ± 25.2	102.5 ± 25.1	99.5 ± 29.8	94.5 ± 34.3	91.6 ± 26.5	89.8 ± 24.0
Na (mmol/L)	140.4 ± 2.2	139.6 ± 3.3	139.8 ± 2.7	140.7 ± 1.7	139.8 ± 2.1	139.7 ± 2.9
K (mmol/L)	4.8 ± 0.5	4.8 ± 0.6	4.7 ± 0.5	4.7 ± 0.5	5.0 ± 0.5	4.9 ± 0.6
Cl (mmol/L)	106.5 ± 3.5	106.8 ± 4.5	106.6 ± 3.9	107.1 ± 2.7	106.8 ± 3.2	106.5 ± 4.4
Proteinuria (g/g·Cr)	2.44 ± 2.39	1.87 ± 1.83	2.14 ± 2.17	3.08 ± 4.71	4.38 ± 5.97	1.38 ± 1.29

Data are mean ± SD.
*$p < 0.05$, compared with the value at −3 months. For abbreviations, see Table 1.
BUN = blood urea nitrogen; LDL-C = low-density lipoprotein cholesterol.

Table 3 Effects of combination treatment including *Astragalus membranaceus* on various clinical and laboratory data according to severity of underlying kidney disease.

	CKD stage 4					CKD stage 5				
	−3 mo	0 mo	3 mo	6 mo	12 mo	−3 mo	0 mo	3 mo	6 mo	12 mo
n	15	15	15	14	13	20	20	20	12	3
Systolic BP (mmHg)	134 ± 14.1	130 ± 14.3	133 ± 17.1	132 ± 14.8	125 ± 10.7	135 ± 15.8	130 ± 17.9	137 ± 18.4	134 ± 20.2	124 ± 17.2
Diastolic BP (mmHg)	78 ± 11.3	78 ± 8.2	76 ± 9.8	76 ± 8.1	76 ± 8.9	78 ± 11.1	74 ± 10.2	76 ± 8.8	76 ± 7.7	74 ± 11.4
Hemoglobin (g/dL)	11.8 ± 1.5	11.9 ± 1.3	11.6 ± 1.5	11.5 ± 1.5	11.0 ± 1.3	10.2 ± 1.4	10.1 ± 1.0	10.0 ± 0.7	9.4 ± 1.4	9.6 ± 0.6
BUN (mg/dL)	36.2 ± 8.9	36.5 ± 8.4	41.0 ± 15.2	40.9 ± 12.8	43.9 ± 15.8	60.4 ± 17.4	59.1 ± 18.2	65.6 ± 18.0	65.4 ± 25.6	77.4 ± 14.7
Creatinine (mg/dL)	2.48 ± 0.59	2.57 ± 0.63	2.43 ± 0.89	2.58 ± 1.06	3.00 ± 1.65	4.69 ± 1.44	5.09 ± 1.54	4.95 ± 1.69	6.13 ± 2.37	5.04 ± 1.20
eGFR (mL/min/1.73 m^2)	20.82 ± 4.59	16.66 ± 4.17*	18.64 ± 5.67	17.80 ± 5.60	16.28 ± 5.89	10.47 ± 2.70	8.02 ± 2.75	8.42 ± 2.96	6.82 ± 2.45	7.93 ± 2.95
Uric acid (mg/dL)	7.01 ± 1.44	7.25 ± 1.79	7.29 ± 1.84	6.92 ± 1.73	7.67 ± 1.03	7.68 ± 1.11	7.71 ± 1.07	8.14 ± 1.33	7.58 ± 1.07	7.94 ± 1.08
Albumin (g/dL)	3.89 ± 0.35	3.97 ± 0.37	4.06 ± 0.35	4.08 ± 0.37	3.91 ± 0.46	3.95 ± 0.42	3.92 ± 0.53	3.94 ± 0.45	3.72 ± 0.67	3.82 ± 0.51
LDL-C (mg/dL)	100.5 ± 25.2	102.5 ± 25.1	99.5 ± 29.8	94.5 ± 34.3	88.7 ± 20.6	100.5 ± 25.2	102.5 ± 25.1	99.5 ± 29.8	94.5 ± 34.3	90.7 ± 24.6
Na (mmol/L)	140.6 ± 1.5	141.0 ± 2.4	140.5 ± 1.8	140.4 ± 1.3	140.3 ± 2.8	139.8 ± 2.9	139.6 ± 2.7	139.2 ± 3.3	141.3 ± 1.8	137.8 ± 3.3
K (mmol/L)	4.7 ± 0.6	4.7 ± 0.6	4.7 ± 0.4	4.8 ± 0.4	5.0 ± 0.5	4.9 ± 0.4	4.9 ± 0.6	4.7 ± 0.6	4.7 ± 0.6	4.8 ± 1.0
Cl (mmol/L)	106.9 ± 2.9	106.7 ± 1.8	106.7 ± 3.1	107.6 ± 1.9	106.9 ± 3.1	106.2 ± 4.1	107.0 ± 5.8	106.5 ± 4.6	105.9 ± 3.8	104.2 ± 5.8
Proteinuria (g/g·Cr)	1.83 ± 2.79	1.14 ± 1.43	1.39 ± 1.78	1.79 ± 2.24	1.71 ± 2.29	2.80 ± 1.91	2.32 ± 2.50	2.86 ± 2.50	4.96 ± 7.26	9.64 ± 23.21

Data are mean ± SD.
*$p < 0.05$, compared with the value at −3 months. For abbreviations, see Table 1.
BUN = blood urea nitrogen; LDL-C = low-density lipoprotein cholesterol.

was $14.6 ± 6.3$ mL/min/1.73 m^2 and decreased even with conventional therapy to $11.6 ± 5.2$ mL/min/1.73 m^2 at study enrollment ($r = -1.232$, $p = 0.0026$). The eGFR recovered to $12.8 ± 6.7$ mL/min/1.73 m^2 after 3 months of treatment ($r = 0.896$), although BUN and UA tended to increase slightly. We could measure 24-hour creatinine clearance in 13 patients. *A membranaceus* also improved creatinine clearance in the same way as eGFR (-3 M; $13.2 ± 4.1$ mL/min, 0 M; $9.4 ± 2.9$ mL/min, $+3$ M; $10.5 ± 4.1$ mL/min, $+6$ M: $9.8 ± 4.3$ mL/min, respectively) in these patients. Other laboratory data remained unchanged throughout the study (Table 2). Among the 35 patients, CKD was classified as stage 4 in 15. The eGFR at baseline in this group was $20.8 ± 4.6$ mL/min/1.73 m^2, which decreased to $16.7 ± 4.2$ at baseline despite conventional therapy ($r = -1.329$, $p < 0.05$). However, after 3 months of treatment that included *A membranaceus*, the eGFR increased to $18.6 ± 5.7$ mL/min/1.73 m^2 ($r = 0.973$) and remained stable for the next 12 months ($16.3 ± 5.9$ mL/min/1.73 m^2) (Table 3). This effect was not noted in 20 patients with CKD stage 5, with the exception of a small increment in eGFR at 3 months (Table 3). No changes in BUN, hemoglobin, total protein, albumin, low-density lipoprotein cholesterol, UA, and urinary protein excretion were noted during the entire study in the two groups (Table 3). There were also no differences in primary disease, age, and sex between the two groups. During this study, seven patients underwent renal replacement therapy within 12 months of *A membranaceus* treatment. Their eGFR at baseline was significantly low ($7.4 ± 1.1$ mL/min/1.73 m^2) (Table 4). On the other hand, 16 patients who continued *A membranaceus* treatment for more than 12 months had a relatively high eGFR at baseline ($14.2 ± 5.4$ mL/min/1.73 m^2). Furthermore, 13 patients with CKD stage 4 who continued *A membranaceus* treatment for more than 24 months, showed eGFR at 24 months of $13.3 ± 5.24$ mL/min/1.73 m^2 and thus required no dialysis therapy. Unfortunately, we could not follow up two patients who changed hospitals at 6−12 months.

The clinical courses of eGFR in each patient of 3 months before to 3 months after treatment with *A membranaceus* are shown in Fig. 1A. Although they already underwent treatment with conventional therapy, the slope of eGFR started to decline ($r = -1.232$) even before treatment. After *A membranaceus* treatment for 3 months, the slope of eGFR was significantly improved ($r = 0.896$). However, this effect did not continue after 6 months. The mean values of eGFR of 3 months before to 12 months after treatment with *A membranaceus* are shown in Fig. 1B. The improved eGFR reverted to the level of −3 months after the treatment, for 6 months. The amount of proteinuria tended to decrease after treatment with *A membranaceus* for 3 months, but it was not statistically significant. On the other hand, increment of eGFR and decrement of proteinuria for 3 months were well correlated ($r = 0.802$, Fig. 1C).

Adverse events

Twelve adverse events in 10 patients were reported. They included skin eruptions ($n = 5$, 12.2%), digestive symptoms

Table 4 Serial changes in serum creatinine and estimated glomerular filtration rate (eGFR) in seven patients who underwent renal dialysis within 12 months of combination treatment including *Astragalus membranaceus*.

	−3 mo	0 mo	3 mo	6 mo
n	7	7	7	6
Creatinine (mg/dL)	4.75 ± 0.72	5.28 ± 0.75	5.17 ± 0.75	5.84 ± 1.16
eGFR (mL/min/1.73 m^2)	10.78 ± 1.27	7.42 ± 1.06	7.45 ± 1.82	6.61 ± 1.82

Data are mean $\pm$ SD.

($n = 3$, 7.3%), anemia ($n = 2$, 4.9%), and stomatitis ($n = 2$, 4.9%). All events were mild to moderate in severity. Two patients discontinued *A membranaceus* treatment temporarily due to skin rashes on the legs and gastritis, but they resumed and continued treatment without any further adverse events, suggesting that these adverse events were rather associated with the uremic state.

Discussion

Since there are no specific therapies for recovery of renal function after reaching the end stage of CKD, multidisciplinary treatment and diet therapy including protein restriction are considered to delay the progression of CKD.[2] In Japan, not only herbalists but general practitioners also sometimes use Chinese herbal preparations as complementary therapies to reduce the rate of progression of CKD. In general and traditional medicine, the prescribed herbs are often polyherbal formulas, because it is generally believed that herbs have synergistic effects. Among several herbs, *A membranaceus* is often present in polyherbal formulas prescribed for renal diseases because of its anti-inflammatory and diuretic actions. For this reason, we chose *A membranaceus* to study the effects of a single herbal therapy in patients with CKD stages 4 and 5 whose eGFR was decreasing in the previous 3 months, in place of a multidisciplinary therapy. Since *A membranaceus* has been inspected and certified by the Japanese government health authorities and included in the health insurance system, the cost of treatment is less than that with other medicines such as oral adsorbent AST120,[19] which is sometimes used for the same purpose.

In this study, *A membranaceus* significantly increased eGFR in patients with progressive CKD stage 4, but the effectivity period was limited to about 1 year, because otherwise *A membranaceus* might prolong the initiation of renal replacement therapy for at least 1 year.

Progressive CKD was defined as a reduction in the eGFR value over a period of 3 months preceding enrollment in this study despite conventional therapy. We classified the stage of CKD by eGFR at the start of *A membranaceus* treatment.

What is the underlying mechanism(s) of action of *A membranaceus* on renal function? Previous studies reported that the combination of two herbs, *A membranaceus* and *Angelica sinensis*, increased the densities of aminopeptidase P-positive glomerular and peritubular capillaries, similar to enalapril treatment in five of six nephrectomized rats.[21] The authors concluded that upregulation of renal cortical vascular endothelial growth factor in the treatment group reduced capillary loss and improved microstructural dysfunction.[21] In another study, the same herbal combination also enhanced nitric oxide production via activation of endothelial NO synthase and scavenging reactive oxygen species in a mouse UUO model.[22] Based on a histopathological examination, the enhanced production of NO was considered to explain the improvement observed in ischemic microvasculature and attenuation of interstitial fibrosis.[22] Since *A membranaceus* contains a relatively high amount of flavonoids which have strong antioxidative action, it may exert these positive effects on eGFR. In another study using the rat UUO model, treatment with *A membranaceus* reduced the mRNA expression levels of TGF-β1 and smooth muscle actin, which rectified the decrease in fibronectin and type I collagen depositions, suggesting that the renoprotective effects of the two herbal medicines might be related to inhibition of myofibroblast action.[16] Motomura et al[23] demonstrated that astragalosides, especially astragaloside V isolated from the root of *Astragalus radix*, inhibited the formation of advanced glycation end products (including both *N*-carboxymethyl-lysine and pentosidine) *in vitro*. In rats with streptozotocin-induced diabetes, treatment with *A membranaceus* improved renal function by reducing nuclear factor-kappa B and increasing IκB mRNA levels in the renal cortex.[24] Although we could not investigate the mechanisms of action of *A membranaceus* in our clinical study, the results confirmed that *A membranaceus* was able to maintain the eGFR during the study period. The effects of *A membranaceus* were similar regardless of the underlying mechanism of CKD. The significant temporal increment of eGFR was not recognized in patients with CKD stage 5, suggesting that the number of residual nephrons is critical for the effect of *A membranaceus*. The beneficial effects of *A membranaceus* allowed a delay in the initiation of renal replacement therapy in patients with progressive CKD stage 4. Hence, early commencement of *A membranaceus* treatment might enhance the beneficial effects with a clearer impact on the disease process. The reason why *A membranaceus* improved eGFR but had no effect on BUN and UA was not clear. Since most patients took loop diuretics, the effect of diuretics may be one of the reasons.

Several adverse events of *A membranaceus* were observed within the first month of treatment. However, these side effects were mild, and recovery was noted following discontinuation of the herbal preparation. Accordingly, daily treatment with *A membranaceus* for up to 24 months seems to be safe.

In conclusion, *A membranaceus* should be effective in the treatment of progressive CKD, but a randomized control
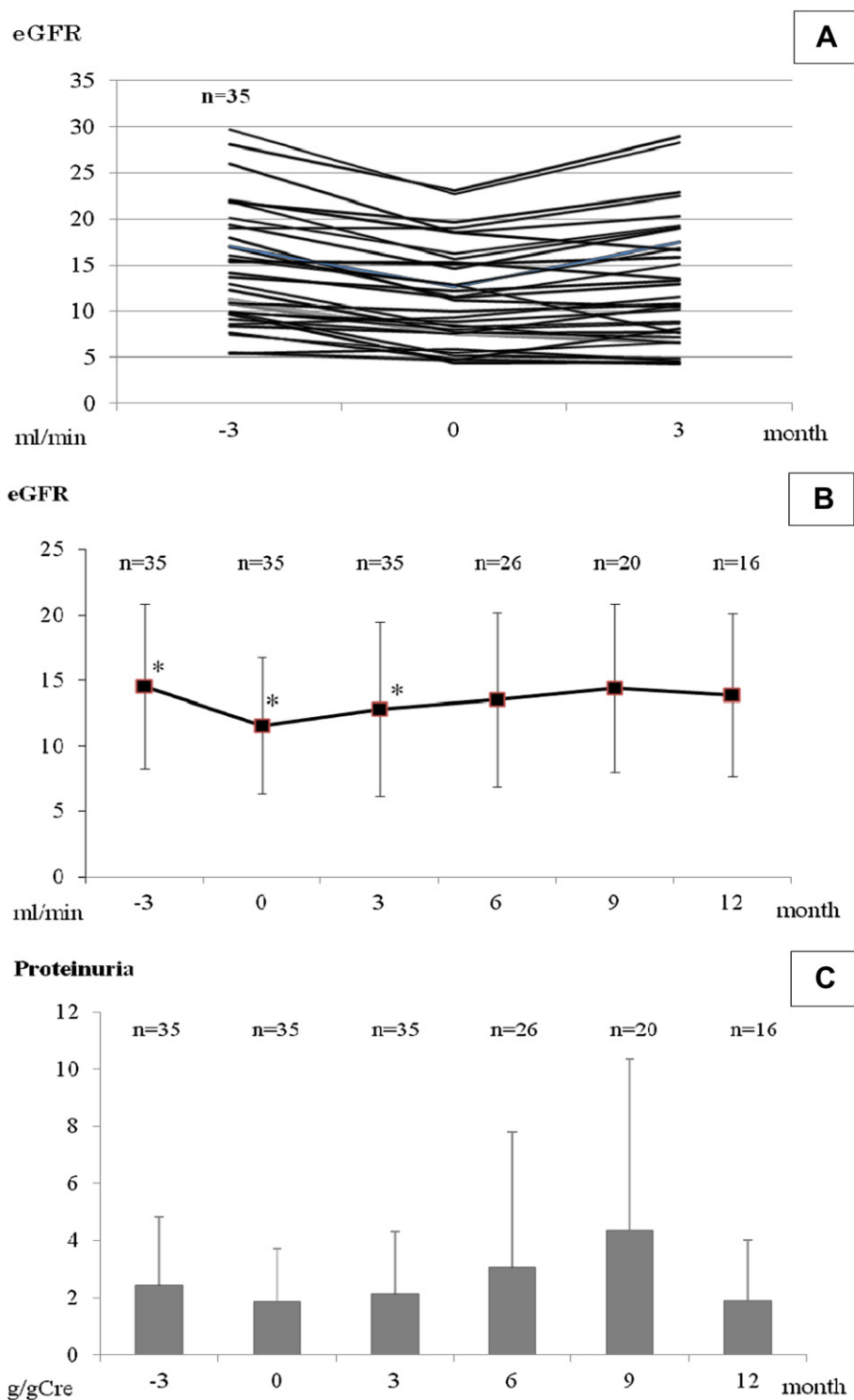
Figure 1 (A) Estimated glomerular filtration rate (eGFR)-time plot for 35 patients 3 months before, at the start of, and 3 months after treatment with *Astralagalus membranaceus*. (B) The mean eGFR values of patients from 3 months before to 12 months after treatment with *A membranaceus*. Asterisk indicates significance (<0.05) compared with the value at 3 months before treatment with *A membranaceus*. (C) Proteonuria-time plot for patients from 3 months before to 12 months after treatment with *A membranaceus*.

study is needed to confirm the exact effects of this herbal preparation.

Acknowledgments

References

1. Trivedi H, Pang M, Campbell A, Saab P. Slowing the progression of chronic renal failure: economic benefits and patients' perspectives. *Am J Kidney Dis* 2002;**39**:721—9.
2. Patient Registration Committee. JSDT. An overview of regular dialysis treatment in Japan (as of 31 December 2002). *Ther Apher Dial* 2004;**8**:358—62.
3. Wojcikowski K, Johnson D, Gobe G. Herbs or natural substances as complementary therapies for chronic kidney disease: ideas for future studies. *J Lab Clin Med* 2006;**147**:160—6.
4. Ma J, Fan S, Chen J, Gu Y, Lin S. Messenger RNA expressions of vasopressin system and aquaporin-2 in adriamycin-induced nephrotic rats and effects of *Astragalus membranaceus*. *Chin Med J* 1999;**112**:1068—72.
5. Ni Z, Zhang Q, Qian J, Wang L. Effect of Astragalin on matrix secretion and beta 1 integrin mRNA expression in human mesangial cells. *Chin Med J* 1999;**112**:1063—7.
6. Zhang J, Xie X, Li C, Fu P. Systematic review of the renal protective effect of *Astragalus membranaceus* (root) on diabetic nephropathy in animal models. *J Ethnopharmacol* 2009;**126**:189—96.
7. Liu M, Wu K, Mao X, Wu Y, Ouyang J. *Astragalus* polysaccharide improves insulin sensitivity in KKAy mice: regulation of PKB/GLUT4 signaling in skeletal muscle. *J Ethnopharmacol* 2010;**127**:32—7.
8. Cai Q, Li X, Wang H. *Astragali* and *Angelica* protect the kidney against ischemia and reperfusion injury and accelerate recovery. *Chin Med J* 2001;**114**:119—23.
9. Su D, Yan H, Zhang B, Wu D, Dai Y. Effects of *Astragalus membranaceus* on cardiac function and SERCA2a gene expression in myocardial tissues of rats with chronic heart failure. *Zhong Yao Cai* 2009;**32**:85—8.
10. Sheng B, He D, Zhao J, Chen X, Nan X. The protective effects of the traditional Chinese herbs against renal damage induced by extracorporeal shock wave lithotripsy: a clinical study. *Urol Res* 2011;**39**:89—97.
11. Liu J, Hu X, Yang Q, Yu Z, Zhao Z, Yi T, et al. Comparison of the immunoregulatory function of different constituents in radix astragali and radix hedysari. *J Biomed Biotechnol* 2010;**2010**:1—12.
12. Wang J, Li J, Shi L, Lu X, Cheng W, Chen Y. Preventive effects of a fractioned polysaccharide from a traditional Chinese herbal medical formula (Yu Ping Feng San) on carbon tetrachloride-induced hepatic fibrosis. *J Pharm Pharmacol* 2010;**62**:935—42.
13. Chan W, Durairajan S, Lu J, Wang Y, Xie L, Kum W, et al. Neuroprotective effects of astragaloside IV in 6-hydroxydopamine-treated primary nigral cell culture. *Neurochem Int* 2009;**55**:414—22.
14. Lu MC, Yao CH, Wang SH, Lai YL, Tsai CC, Chen YS. Effect of *Astragalus membranaceus* in rats on peripheral nerve regeneration: *in vitro* and *in vivo* studies. *J Trauma* 2010;**68**:434—40.
15. Matkovic Z, Zivkovic V, Korica M, Plavec D, Peacanic S, Tudoric N. Efficacy and safety of *Astragalus membranaceus* in the treatment of patients with seasonal allergic rhinitis. *Phytother Res* 2010;**24**:175—81.
16. Zuo C, Xie X, Qiu H, Deng Y, Zhu D, Fan J. *Astragalus mongholicus* ameliorates renal fibrosis by modulating HGF and TGF-beta in rats with unilateral ureteral obstruction. *J Zhejiang Univ Sci B* 2009;**10**:380—90.
17. Ahmed M, Hou S, Battaglia M, Picken M, Leehey D. Treatment of idiopathic membranous nephropathy with the herb *Astragalus membranaceus*. *Am J Kidney Dis* 2007;**50**:1028—32.
18. Leehey D, Casini T, Massey D. Remission of membranous nephropathy after therapy with *Astragalus membranaceus*. *Am J Kidney Dis* 2010;**55**:772.
19. Maeda K, Hamada C, Tomino Y, Hayashi T, Shou I, Horikoshi S, et al. Long-term effects of the oral adsorbent, AST-120, in patients with chronic renal failure. *J Int Med Res* 2009;**37**:205—13.
20. Matsuo S, Imai E, Tomino Y, Yasuda Y, Nitta K, Yamagata K, et al. Collaborators developing the Japanese equation for estimated GFR. Revised equations for estimated GFR from serum creatinine in Japan. *Am J Kidney Dis* 2009;**53**:982—92.
21. Song J, Meng L, Li X, Lis S, Qu L. A combination of Chinese herbs, *Astragalus membranaceus* var. *mongholicus* and *Angelica sinensis*, improved renal microvascular insufficiency in 5/6 nephrectomized rats. *Vascul Pharmacol* 2009;**50**:185—93.
22. Meng L, Qu L, Li X, Cai S, Wang H, Li X. A combination of Chinese herbs, *Astragalus membranaceus* var. *mongholicus* and *Angelica sinensis*, enhanced nitric oxide production in obstructed rat kidney. *Vascul Pharmacol* 2007;**47**:174—83.
23. Motomura K, Fujiwara Y, Nohara T, Kiyota N, Tsurushima K, Takeya M, et al. Astragalosides isolated from the root of *Astragalus radix* inhibit the formation of advanced glycation end products. *J Agric Food Chem* 2009;**57**:7666—72.
24. Zhang Y, Wu C, Cheng J. Merit of *Astragalus* polysaccharide in the improvement of early diabetic nephropathy with an effect on mRNA expressions of NF-kappaB and IkappaB in renal cortex of streptozotocin-induced diabetic rats. *J Ethnopharmacol* 2007;**114**:387—92.