Use of Allopurinol in Slowing the Progression of Renal Disease Through Its Ability to Lower Serum Uric Acid Level

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• ***Background:*** **Hyperuricemia is associated strongly with the development of hypertension, renal disease, and progression. Allopurinol decreases serum uric acid levels by inhibiting the enzyme xanthine oxidase. We hypothesized that administrating allopurinol to decrease serum uric acid levels to the normal range in hyperuricemic patients with chronic kidney disease may be of benefit in decreasing blood pressure and slowing the rate of renal disease progression in these patients.** ***Methods:*** **We conducted a prospective, randomized, controlled trial of 54 hyperuricemic patients with chronic kidney disease. Patients were randomly assigned to treatment with allopurinol, 100 to 300 mg/d, or to continue the usual therapy for 12 months. Clinical, hematologic, and biochemical parameters were measured at baseline and 3, 6, and 12 months of treatment. We define our study end points as: (1) stable kidney function with less than 40% increase in serum creatinine level, (2) impaired renal function with creatinine level increase greater than 40% of baseline value, (3) initiation of dialysis therapy, and (4) death.** ***Results:*** **One patient in the treatment group dropped out because of skin allergy to allopurinol. Serum uric acid levels were significantly decreased in subjects treated with allopurinol, from 9.75 ± 1.18 mg/dL (0.58 ± 0.07 mmol/L) to 5.88 ± 1.01 mg/dL (0.35 ± 0.06 mmol/L; $P < 0.001$). There were no significant differences in systolic or diastolic blood pressure at the end of the study comparing the 2 groups. There was a trend toward a lower serum creatinine level in the treatment group compared with controls after 12 months of therapy, although it did not reach statistical significance ($P = 0.08$). Overall, 4 of 25 patients (16%) in the allopurinol group reached the combined end points of significant deterioration in renal function and dialysis dependence compared with 12 of 26 patients (46.1%) in the control group ($P = 0.015$).** ***Conclusion:*** **Allopurinol therapy significantly decreases serum uric acid levels in hyperuricemic patients with mild to moderate chronic kidney disease. Its use is safe and helps preserve kidney function during 12 months of therapy compared with controls. Results of this study need to be confirmed with an additional prospective trial involving a larger cohort of patients to determine the long-term efficacy of allopurinol therapy and in specific chronic kidney disease subpopulations.** ***Am J Kidney Dis*** **47:51-59.**

INDEX WORDS: Uric acid; chronic kidney disease (CKD); allopurinol; hyperuricemia.

ELEVATED SERUM uric acid levels have been related to increased risk for the development of hypertension[1,2] and cardiovascular diseases.[3] There is also increasing evidence to show that hyperuricemia may have a pathogenetic role in the progression of renal diseases, rather than merely reflecting decreased renal uric acid excretion. Syrjanen et al[4] and Ohno et al[5] showed that an increased serum uric acid level at the time of diagnosis is a predictor of renal progression in patients with immunoglobulin A nephropathy, although a causal relationship could not be derived from these studies. A high uric acid level also correlated with the development of renal insufficiency in patients with type 2 diabetes[6] and individuals with normal kidney function.[7,8] In a recent cohort study performed in Japan, hyperuricemia was associated with a greater incidence of patients developing end-stage renal disease (ESRD) and an independent predictor of ESRD in women.[9]

Allopurinol decreases serum uric acid levels by inhibiting the enzyme xanthine oxidase. In experimental rat models, hyperuricemia-induced functional and structural injury of the kidney were prevented by allopurinol treatment, which maintained serum uric acid levels in the normal range.[10,11] For animal models of established renal diseases, correction of the hyperuricemic state can significantly improve blood pressure control, decrease proteinuria, and decrease the amount of glomerulosclerosis, tubulointerstitial fibrosis, and vasculopathy.[12] Hence, strategies to

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control and decrease serum uric acid levels may have a beneficial effect on improving kidney function or slowing the progression of renal diseases in clinical practice. We therefore conducted a prospective, randomized, controlled study to investigate the renal effects of allopurinol treatment in hyperuricemic patients with chronic kidney disease.

METHODS

Eight hundred fifty-two patients were followed up in our renal clinic from April 2003 to April 2004 and screened for eligibility to participate in the study. Included subjects had to fulfill the following inclusion criteria: (1) presence of renal disease, defined as daily proteinuria greater than 0.5 g and/or an elevated serum creatinine (Cr) level greater than 1.35 mg/dL (>120 μmol/L) at baseline; and (2) in stable clinical condition in terms of general health and renal function (baseline serum Cr level and daily proteinuria had not increased by > 40% within the 3 months before screening).

We excluded patients with a history of gouty arthritis, renal stones, and advanced chronic kidney disease (serum Cr > 4.50 mg/dL [>400 μmol/L]). Patients already on allopurinol or azathioprine treatment for any reason at the screening visit, those with a known history of allopurinol hypersensitivity, women of childbearing age and unwilling to use effective means of contraception, and pregnant or lactating women also were excluded.

Two hundred seventy-six patients satisfied these criteria and were screened for fasting serum uric acid level. Hyperuricemia is defined as a serum uric acid level greater than 7.60 mg/dL (>0.45 mmol/L). Obstructive uropathy or renal stones were excluded by means of ultrasonography in all recruited subjects.

Randomization and Treatment Protocol

Patients were randomly assigned acording to a computer-generated list into either the treatment or control group. Treatment-group patients were administered a starting allopurinol dose of 100 mg/d or 200 mg/d, depending on baseline renal function (allopurinol, 200 mg/d, if serum Cr ≤ 1.70 mg/dL [≤150 μmol/L], and 100 mg/d, if serum Cr > 1.70 mg/dL [>150 μmol/L]). The dose was adjusted according to serum uric acid level, aiming to maintain uric acid levels within the normal range. Dosages of antihypertensive drugs, lipid-lowering agents, and steroid or cytotoxic drugs were continued and adjusted according to the individual patient's clinical conditions.

Follow-Up Assessment

Subjects were followed up every 4 weeks for the first 6 months and then every 8 weeks, for a total of 12 months. During each follow-up session, systolic (SBP) and diastolic blood pressure (DBP) were recorded, and daily urinary protein excretion, hemoglobin level, white blood cell count, platelet count, serum Cr level, alanine aminotransferase level, fasting total cholesterol level, low-density lipoprotein cholesterol level, high-density lipoprotein cholesterol level, triglyceride level, fasting uric acid level, and C-reactive protein level were checked.

Adverse Events

Any adverse event considered to be related to the use of allopurinol was recorded during the follow-up assessment. For minor adverse events, allopurinol would be withheld temporarily until symptoms resolved; allopurinol therapy then would be restarted and the patient closely monitored, and the drug would be discontinued if adverse effects recurred. For serious adverse events, including Stevens-Johnson syndrome and hepatitis, allopurinol therapy would be discontinued at once and the study would be terminated. The study was approved by the institutional ethics committee, and each participating patient gave written informed consent before enrollment.

Outcome Analysis

Patient's clinical outcome was analyzed after the 1-year study period. We defined study end points as follows: (1) stable renal function indicates a serum Cr level at the end of study that increased by less than 40% compared with baseline; (2) worsening of renal function, serum Cr level increased by greater than 40% compared with baseline, but not yet requiring dialysis; (3) end-stage renal disease requiring dialysis therapy; and (4) death.

Statistical Analysis

All statistical analyses were performed using the SPSS program, version 11.0 (SPSS Inc, Chicago, IL) for Windows XP. Unless otherwise stated, values are expressed as mean ± SD. Categorical data were compared by means of chi-square test, and continuous variables, by means of Student *t*-test. Comparison of various parameters between baseline and different intervals was performed by means of paired Student *t*-test. Analysis of variance test was used when parameters of more than 2 groups were compared. Statistical significance is defined as 2-tailed *P* less than 0.05.

RESULTS

Between April 2003 and April 2004, a total of 54 patients were enrolled in the study. Mean age of the allopurinol group was 47.7 ± 12.9 years, and of the control group, 48.8 ± 16.8 years. Male-female ratios were 9:4 and 13:15 for the treatment and control groups, respectively. Diabetes mellitus constituted 24% (treatment group) and 27% (control group) in our study population, and the majority of patients had preexisting hypertension (84%, treatment group; 73%, control group). Baseline characteristics, causes of renal disease, laboratory parameters, and medications used in our study patients are listed in Table 1.

All except 3 subjects completed the study. One patient in the treatment group was withdrawn prematurely because she developed a urticarial

Table 1. Baseline Demographic Characteristics

	Treatment Group	Control Group	*P*
No. of patients	25	26	
Age (y)	47.7 ± 12.9	48.8 ± 16.8	0.78
Sex (female:male)	9:4	13:15	0.09
Body weight (kg)	70.5 ± 10.4	65.4 ± 12.7	0.12
Renal pathology			
Diabetes mellitus	6	7	
SLE	1	2	
IgA nephropathy	5	3	
FSGS	5	3	
MN	1	3	
MCGn	0	1	
MPGn	0	1	
Chronic Gn	7	6	0.73
Hypertension			
(mm Hg)	21 (84)	19 (73)	0.30
SBP	138 ± 20	135 ± 19	0.68
DBP	79 ± 10	71 ± 14	0.25
Cr (mg/dL)	1.64 ± 0.63	1.86 ± 0.69	0.27
Proteinuria (g/d)	2.39 ± 2.88	2.39 ± 2.20	0.99
Medications			
Lipid-lowering			
Statins	6 (23)	11 (44)	0.11
Antihypertensive			
Beginning of study			
ACE inhibitor	15 (57.7)	14 (56)	0.90
ARB	8 (30.8)	5 (20)	0.38
End of study			
ACE inhibitor	14 (56)	15 (57.7)	0.77
ARB	9 (36)	4 (15.4)	0.11

NOTE. Values expressed as mean ± SD or number (percent). To convert serum Cr in mg/dL to μmol/L, multiply by 88.4.

Abbreviations: SLE, systemic lupus erythromatosus; FSGS, focal segmental glomerulosclerosis; MN, membranous nephropathy; MCGn, minimal change glomerulonephritis; MPGn, membranoproliferative glomerulonephritis; chronic Gn, presumed chronic glomerulonephritis with no renal biopsy done; ACE, angiotensin-converting enzyme; ARB, angiotensin II receptor blockers.

skin rash a few days after the initiation of allopurinol treatment, and the rash subsided promptly on drug withdrawal. Two patients in the control group defaulted their scheduled follow-ups and were considered drop outs. Thus, there were 25 patients in the treatment group and 26 patients in the control group for analysis.

Blood Pressure Control

SBPs of all subjects at the start and end of the study are shown in Fig 1. In the treatment group, baseline SBP was 138 ± 20 mm Hg, and after 12 months of allopurinol treatment, there was a significant decrease in SBP to 127 ± 21 mm Hg ($P = 0.02$; Fig 2). DBP also was noticed to have a nonsignificant decrease from 79 ± 10 to 75 ± 10 mm Hg at the end of the study ($P = 0.12$). For the control group, SBPs and DBPs measured at baseline were 135 ± 19 and 71 ± 14 mm Hg, respectively; there were no changes after 12 months of follow-up (SBP, 135 ± 32 mm Hg; $P = 0.90$; DBP, 71 ± 13 mm Hg; $P = 0.89$). When we compared blood pressures between the 2 groups, there was no significant difference in either SBP or DBP ($P = 0.31$ and $P = 0.21$, respectively). There was also no difference between the 2 groups in terms of number and types of antihypertensive drugs used.

Biochemical and Hematologic Parameters

By the end of the study, serum uric acid levels were significantly decreased in subjects treated with allopurinol, from 9.75 ± 1.18 mg/dL (0.58 ± 0.07 mmol/L) to 5.88 ± 1.01 mg/dL (0.35 ± 0.06 mmol/L; $P < 0.001$), whereas serum uric acid levels for subjects in the control group remained elevated throughout the study period (9.92 ± 1.68 mg/dL [0.59 ± 0.10 mmol/L] at baseline and 10.08 ± 1.68 mg/dL [0.60 ± 0.10 mmol/L] at the end of the study). There were no changes in serum alanine aminotransferase, serum lipid (total cholesterol, low-density lipoprotein cholesterol, high-density lipoprotein cholesterol, and triglyceride), C-reactive protein, or hemoglobin levels or white blood cell and platelet counts after the 12-month study period in both groups, as listed in Table 2.

Renal Function and Proteinuria

Serum Cr levels of all subjects at the start and end of the study are shown in Fig 3. Baseline serum Cr levels were similar in the 2 groups (1.64 ± 0.63 mg/dL [146 ± 56 μmol/L] in the treatment group and 1.86 ± 0.69 mg/dL [164 ± 61 μmol/L] in the control group; $P = 0.27$). In the treatment group, there was no significant change in serum Cr levels after 12 months (1.99 ± 0.92 mg/dL [176 ± 81 μmol/L]; $P = 0.15$), whereas in the control group, there was worsening by the end of the study (2.89 ± 0.96 mg/dL [255 ± 85 μmol/L]; $P = 0.003$; Fig 4). Deterioration in renal function in the control group became significant by the third month of follow-up and continued during the study period

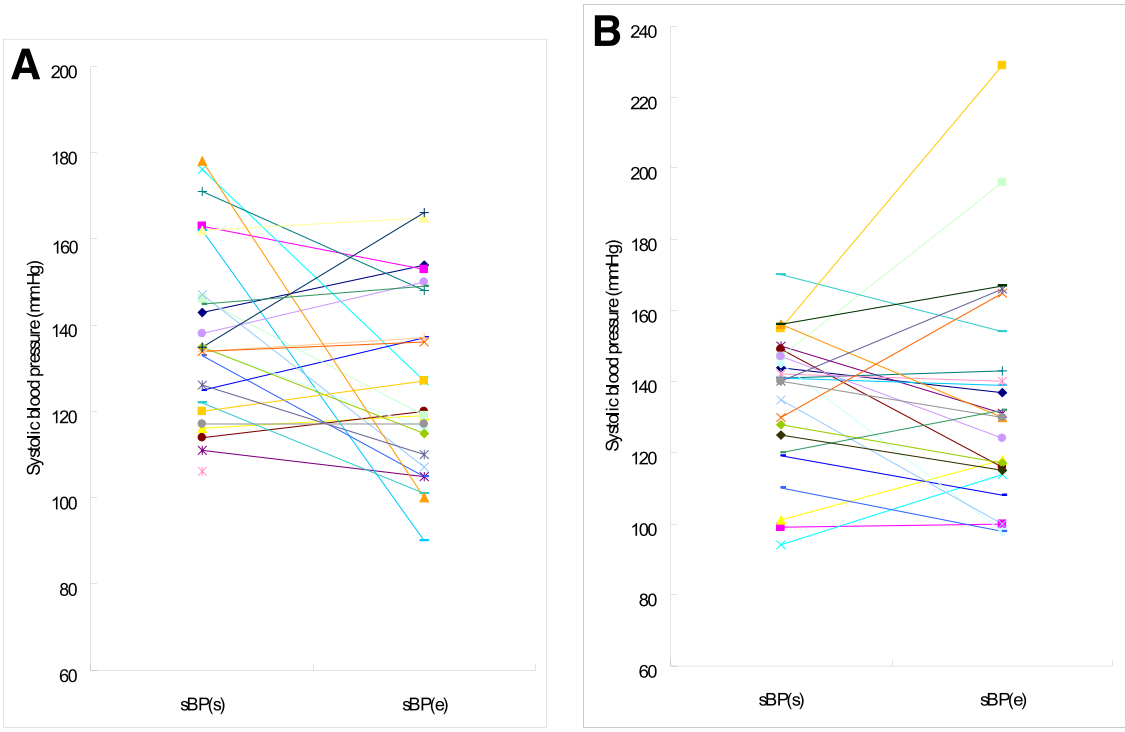

Fig 1. Plot of SBPs of all patients in the (A) treatment group and (B) control group at the start, sBP(s), and end, sBP(e), of the study.

(Fig 5). When we compared serum Cr levels of the 2 groups after treatment for 12 months, there was a trend toward a lower serum Cr level in the treatment group compared with controls, although it did not reach statistical significance ($P = 0.08$). For proteinuria, baseline protein excretion in the treatment group (2.39 ± 2.88 g/d) was similar to that in the control group (2.39 ± 2.20 g/d). Proteinuria at the end of allopurinol treatment was 2.53 ± 4.85 g/d ($P = 0.90$), and for the control group, 2.16 ± 1.93 g/d after the 12-month follow-up ($P = 0.55$). There was also no statistical difference between the 2 groups at the end of the study.

Subgroup Analysis

We divided the treatment group into 3 categories according to uric acid level at the end of the study:

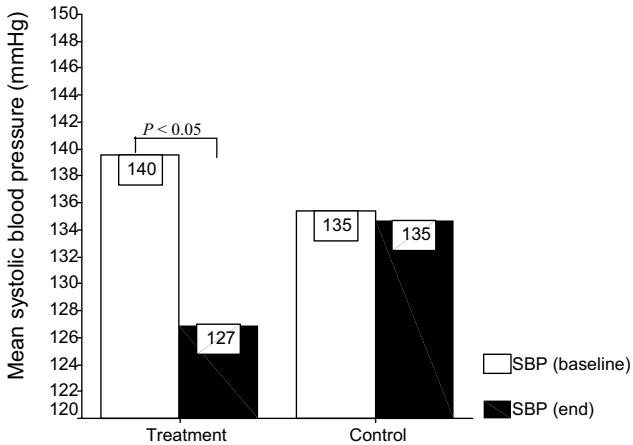

Fig 2. Mean SBP at baseline and end of treatment.

Table 2. Biochemical and Hematologic Parameters of the Treatment and Control Groups

	Treatment Group		Control Group	
	Baseline	12 Months	Baseline	12 Months
Uric acid (mg/dL)	9.75 ± 1.18	5.88 ± 1.01*	9.92 ± 1.68	10.08 ± 1.68
Alanine aminotransferase (IU/L)	22 ± 11	36 ± 16	19 ± 9	19 ± 10
Total cholesterol (mg/dL)	235.5 ± 57.9	200.8 ± 46.3	196.9 ± 42.5	200.8 ± 46.3
Low-density lipoprotein cholesterol (mg/dL)	146.7 ± 50.2	108.1 ± 46.3	115.8 ± 42.5	112.0 ± 38.6
High-density lipoprotein cholesterol (mg/dL)	50.2 ± 15.4	50.2 ± 11.6	54.1 ± 15.4	54.1 ± 15.4
Triglycerides (mg/dL)	221.2 ± 106.2	177.0 ± 88.5	150.4 ± 79.6	159.3 ± 88.5
C-Reactive protein (mg/L)	9.7 ± 14.6	8.8 ± 12.4	3.8 ± 4.8	1.6 ± 2.1
Leukocyte count (10^9/L)	12.9 ± 1.6	12.3 ± 2.3	12.1 ± 2.4	11.8 ± 2.6
Hemoglobin (g/dL)	8.0 ± 2.2	8.8 ± 3.2	8.2 ± 2.8	8.6 ± 2.9
Platelet count (10^9/L)	252 ± 58	249 ± 93	283 ± 100	255 ± 116

NOTE. To convert serum uric acid in mg/dL to mmol/L, multiply by 0.0595; total, low-density lipoprotein, and high-density lipoprotein cholesterol in mg/dL to mmol/L, multiply by 0.02586; hemoglobin in g/dL to g/L, multiply by 10.

*$P < 0.05$.

(1) 3.36 to 4.99 mg/dL (0.2 to 0.299 mmol/L), (2) 5.00 to 6.70 mg/dL (0.3 to 0.399 mmol/L), and (3) 6.71 to 7.60 mg/dL (0.4 to 0.45 mmol/L), and correlation analysis was performed among these 3 groups with regard to percentage of decrease in SBP and serum Cr level. No clinical correlation

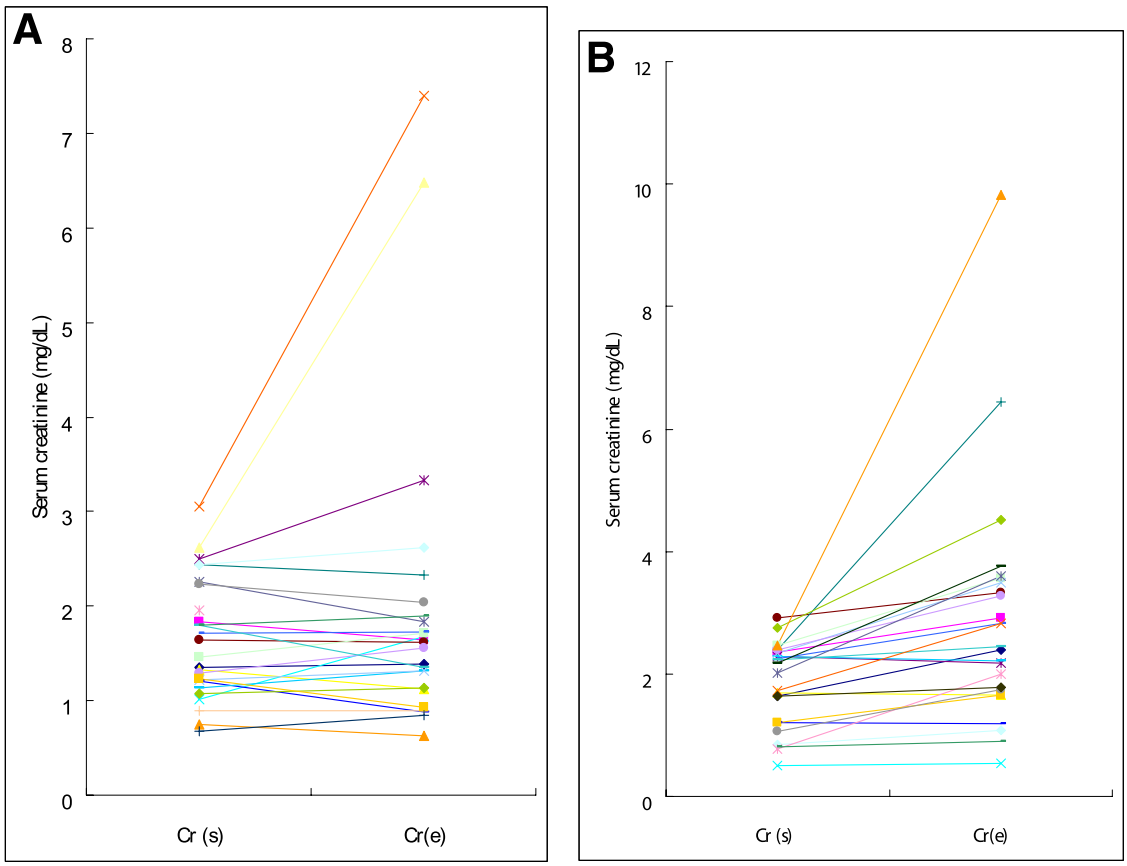

Fig 3. Plot of serum Cr levels of all patients in the (A) treatment group and (B) control group at the start, Cr(s), and end, Cr(e), of the study. To convert serum Cr in mg/dL to μmol/L, multiply by 88.4.

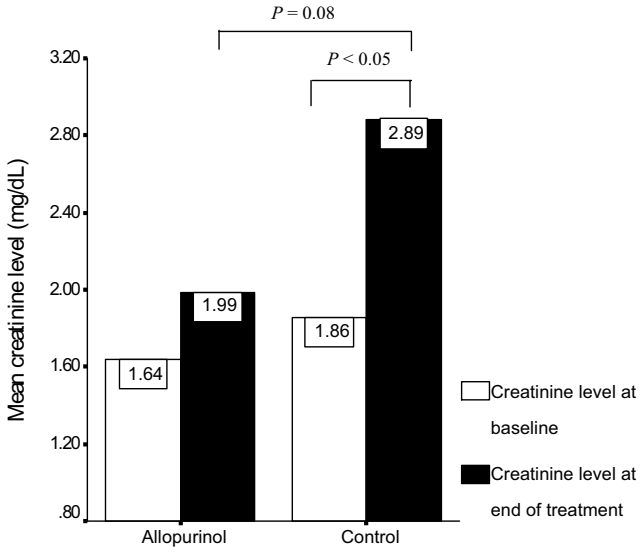

Fig 4. Mean serum Cr levels at baseline and end of treatment. To convert serum Cr in mg/dL to μmol/L, multiply by 88.4.

could be shown among the 3 categories of target uric acid levels in relation to either percentage of decrease in SBP ($P = 0.24$) or percentage of change in serum Cr level ($P = 0.32$).

Outcome

In the treatment group, 84% of patients (21 of 25 patients) in the treatment group maintained stable renal function throughout the study, 12% (3 of 25 patients) had worsening of renal function, and 4% (1 of 25 patients) reached end-stage renal failure. In the control group, patients with stable renal function constituted 53.8% (14 of 26 patients); worsening of renal function, 42.3% (11 of 26 patients); and need for dialysis therapy, 3.8% (1 of 26 patients). Significantly more patients in the control group showed deterioration in kidney function at the end of the study ($P = 0.015$). There were no deaths in either patient group during the study.

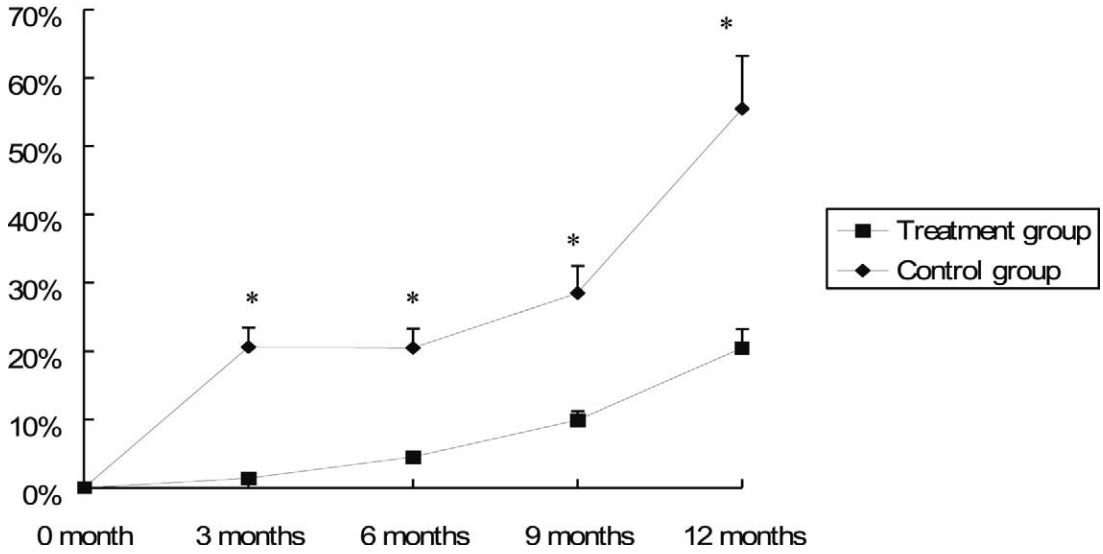

Fig 5. Mean percentage of change in Cr levels in the treatment and control groups. *$P < 0.05$ compared with baseline.

DISCUSSION

Uric acid is a product of purine metabolism. After being filtered, uric acid is both reabsorbed and excreted in the proximal tubule through a voltage-sensitive urate channel and a urate-anion exchange mechanism. Hyperuricemia can be a result of either increased production or decreased excretion. In patients with renal disease, there is decreased uric acid urinary excretion, and whether this will give rise to hyperuricemia depends on the gastrointestinal excretory compensation.[13] The prevalence of elevated serum uric acid levels in our patients with renal diseases was 19.6%. This is an underestimation of the proportion of patients with coexisting hyperuricemia and renal disease because we excluded from our study patients with advanced stages of renal disease, in whom we would expect a more significant decrease in urinary uric acid excretion.

Hyperuricemia has been related to high blood pressure. It was reported that up to 50% to 70% of hyperuricemic patients had hypertension,[14] and conversely, 25% of hypertensive patients had elevated uric acid levels.[15] Increased blood pressure can cause a decrease in renal blood flow and stimulate urate reabsorption. Moreover, hypertension can cause microvascular disease and local tissue ischemia, leading to increased adenosine triphosphate degradation to adenine and xanthine and increased generation of xanthine oxidase, which, in turn, would result in increased uric acid production.[16,17] In addition, tissue ischemia liberates lactate, which competes with urate for excretion in the proximal renal tubule through the organic-anion exchanger,[18] creating a vicious cycle and an additional increase in serum uric acid levels. Conversely, increased serum uric acid levels also can induce high blood pressure. This is thought to be mediated through activation of the renin-angiotensin system, either directly, by decreasing neuronal nitric oxide synthase in the juxtaglomerular apparatus,[19] or indirectly, through decreasing renal perfusion by stimulating the afferent arteriolar vascular smooth cell proliferation[20] or through the induction of cyclo-oxygenase-2 in the macula densa and arterioles.[21]

In experimental rat models, controlling uric acid levels with allopurinol prevented the development of hypertension and renin and neuronal nitric oxide synthase level changes.[19] In the present study, although we showed that SBP decreased in the treatment group after allopurinol treatment, blood pressure was not significantly different from the control group. The reason may be the selection of our subjects. All our patients had established renal diseases with impaired renal function, and most patients had long-standing hypertension at the time of recruitment. Structural damage to the arteries and kidneys had been incurred, and the high blood pressure at this point probably was multifactorial in pathogenesis. Thus, although serum uric acid level was normalized, hypertension probably was irreversible. Therefore, it seems that to ameliorate the hypertensive effect of hyperuricemia, early treatment with allopurinol may be necessary, and once the disease has been established, the effect of decreasing serum uric acid levels may be limited.

There are no large-scale studies investigating the relationship between hyperuricemia and proteinuria. Kang et al[22] found that hyperuricemic rats showed greater proteinuria, greater blood pressure, and greater serum Cr levels than controls, which were treated with allopurinol to decrease serum uric acid levels. However, in the present study, we could not show a benefit of using allopurinol in decreasing the amount of proteinuria in hyperuricemic patients. We think the reason may be similar to what we have observed in blood pressure control in our subjects; and whether earlier treatment with allopurinol may have a more significant hypoproteinuric effect needs further investigation.

An elevated uric acid level has been associated with a greater incidence of end-stage renal disease, and hyperuricemia is an independent predictor of end-stage renal disease in women.[9] In our study, we showed that allopurinol is able to slow the progression of renal diseases. The precise mechanism is not known, but probably related to multiple factors. Uric acid has a number of detrimental effects. It can cause endothelial dysfunction, which can be improved with allopurinol,[23] and it can also activate circulating platelets and impair endothelial nitric oxide production.[23,24] Hyperuricemia has been shown to cause an increase in glomerular hydrostatic pressure, caused by direct uric acid stimulation of vascular smooth muscle cell proliferation in the

afferent arterioles, which induces a more rigid vessel wall and loss of the autoregulatory and protective mechanisms. Arterial pressure then is transmitted directly to the glomerulus, causing glomerular hypertension, resulting in glomerular hypertrophy and sclerosis.[25] Allopurinol therefore may, by diminishing serum uric acid levels, serve as an agent to decrease glomerular hydrostatic pressure indirectly and thus help alleviate renal damage. As discussed, hyperuricemia is associated with an elevated blood pressure, which may further jeopardize renal function, and this also may be prevented by the early use of allopurinol.

Furthermore, uric acid per se is proinflammatory. It can stimulate the synthesis of monocyte chemoattractant protein 1,[26] interleukin 1β, interleukin 6, and tumor necrosis factor α, which may contribute to the development of vascular diseases and atherosclerosis.[27] Therefore, decreasing uric acid levels to normal may have anti-inflammatory effects. Xanthine oxidase is a superoxide-producing enzyme, and its activity can be inhibited completely by the use of allopurinol. In experimental models, allopurinol prevented vascular complications through its antioxidating effects and limiting the generation of free radicals.[28] However, in a recent randomized placebo-controlled trial, allopurinol could not show its superiority over placebo in the reduction of lipid peroxidation and total oxidative stress in patients with diabetes.[29] Therefore, whether allopurinol manifests its beneficial effects through its antioxidating properties is still not conclusive.

Uric acid is now recognized to be a mediator of renal disease and progression. Hyperuricemia induces high blood pressure, renal afferent arteriopathy, increased glomerular hydrostatic pressure, and renal scarring. We showed that using allopurinol to decrease serum uric acid levels is safe and may be beneficial in decreasing SBP and slowing the rate of deterioration in renal function, but this beneficial effect had no correlation with the level of decrease in serum uric acid levels. Another important point to note is that the results of our study may be limited by the concomitant use of antihypertensive drugs. Although there were no differences in the use of angiotensin-converting enzyme inhibitors and angiotensin receptor blockers in the 2 studied groups at the beginning and end of the trial, we could not completely delineate the beneficial effect contributed by the antihypertensive medications in the decrease in blood pressure and preservation of kidney function. Our results clearly have to be confirmed in a larger prospective trial to determine the long-term efficacy of allopurinol therapy in these patients.

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