The effect of allopurinol on the progression of chronic kidney disease

Aygul Ozdemir, Ayca Inci*  
Antalya Training and Research Hospital, Nephrology Department, Antalya, Turkey

A R T I C L E   I N F O
Article Type: Original

A B S T R A C T

Introduction: Hyperuricemia has been associated with the development of hypertension, cardiovascular, and renal disease.

Objectives: We conducted a prospective study to investigate the benefits of allopurinol treatment in hyperuricemic patients with chronic kidney disease (CKD) stage 3.

Patients and Methods: Our study includes a total of 132 patients (41 females and 91 males) with CKD grade 3 who are followed up by the pre-dialysis polyclinic. Around 67 of these patients administered allopurinol while 65 patients were not administered. The therapy protocol for the patients was allopurinol 150 mg/d and the duration of the follow-up was 12 months. Clinical records of the patients were screened, to start with 3, 6, 9 and 12 months, eGFR (estimated glomerular filtration rate) values were calculated.

Results: The patients' eGFR with allopurinol treatment was increased compared with baseline values. 12th month increased by 1.02 ± 8.89 mL/min/1.73 m² from baseline in eGFR, but it was not statistically significant (P = 0.352). In the control group 12th month showed a decrease in baseline GFR value of 2.59 ± 7.9 mL/min/1.73 m² (P = 0.012). The 3, 6, 9, 12th months compared with baseline in the allopurinol treatment group showed a significant decrease in uric acid value (P < 0.05).

Conclusion: Decreased renal progression was observed by reduction of serum uric acid levels at stage 3 hyperuricemic CKD with allopurinol. The annual decline in GFR in hyperuricemic patients, is more than normouricemic patients.

Keywords:
Chronic kidney disease  
Allopurinol  
Uric acid  
Glomerular filtration rate  
Hyperuricemia

Implication for health policy/practice/research/medical education: Hyperuricemia has been associated with the development of hypertension, cardiovascular, and renal disease. We conducted a prospective study to investigate the benefits of allopurinol treatment in hyperuricemic patients with chronic kidney disease stage three and showed that with allopurinol administration annual decline in glomerular filtration rate in hyperuricemic patients, is slower than normouricemic patients.


Introduction
Chronic kidney disease (CKD) is described as the presence of a renal disease lasting for more than 3 months, which is detected with biochemical analysis, urine analysis or imaging methods regardless of presence of reduced glomerular filtration rate (GFR) (1). Systemic hypertension, abnormalities of calcium-phosphate metabolism, hyperparathyroidism, intraglomerular hypertension, hyperlipidemia, acidosis, hyperuricemia and anemia are the important factors contributing to progression of chronic renal disease (2,3). Serum uric acid level increases as urinary excretion of uric acid decreases in patients with CKD. Elevated serum uric acid level increases the risk for hypertension and cardiovascular disease development (4-6). Chronic hyperuricemia has a pathogenetic role in interstitial inflammation and renal disease progression (7). Allopurinol decreases serum uric acid levels by inhibiting xanthine oxidase enzyme. Limited number of studies conducted with hyperuricemic chronic renal disease patients indicate that allopurinol may be effective for slowing renal disease progression (8). However sufficient number of studies are not available in literature.

Objectives
In our study, we planned to investigate the effect of allopurinol...
Patients and Methods
A total of 132 chronic renal disease patients (41 female, 91 male) who were aged between 18-70 years, followed up by Nephrology Department of Antalya Research and Training Hospital between March 2011-September 2012, whose estimated GFR (eGFR) was 30-60 mL/min/1.73 m², who had hyperuricemia (serum uric acid >7 mg/dL) were enrolled in the study. Of them, 67 were receiving allopurinol and 65 were not. Patient selection was done based on age, gender, cause of renal failure, baseline eGFR and uric acid values. Patients in both groups were on a salt restricted and protein restricted (0.6 g/kg daily) diet in the course of the study. All participants were receiving angiotensin converting enzyme inhibitor or angiotensin receptor blocker antihypertensives and alpha-ketoacid. Presence of coronary artery disease, diabetes mellitus, hypertension and vitamin D use ratios were similar in both groups. Serum blood urea nitrogen (BUN), creatinine, albumin and uric acid levels tested with 3 months of intervals and eGFR values were calculated using MDRD formula. Patients who receiving 150 mg daily allopurinol for 2 months were included in the study.

Ethical issues
The research followed the tenets of the Declaration of Helsinki. The research was approved by ethical committee of Antalya Training and Research Hospital (Antalya, Turkey). The goals of the study were explained to participants and all of them accepted to participate and were assured the confidentiality of their individual information as well as the voluntary nature of participating in the study.

Statistical analysis
Frequency, ratio, mean, standard deviation values were used as descriptive statistics. Distribution of variables was controlled with Kolmogorov–Smirnov test. Independent samples t test and Mann-Whitney U test were used for analysis of quantitative data. Paired samples t test was used for repeated measurements. Chi-square test was used for analysis of qualitative data and Fisher’s exact test was used for analysis of quantitative data. Paired samples t test and Mann-Whitney U test were used for analysis of repeated measurements. Chi-square test was used for analysis of qualitative data and Fisher’s exact test was used for analysis of quantitative data. Paired samples t test and Mann-Whitney U test were used for analysis of repeated measurements. Chi-square test was used for analysis of qualitative data and Fisher’s exact test was used for analysis of quantitative data.

Results
Demographic and laboratory characteristics of treatment and control groups are shown in Table 1. One hundred thirty-two patients with stage 3 CKD were incorporated to the investigation. Mean age was 54.57 ± 13.68 years in allopurinol-receiving group and 56.38 ± 12.8 years in control group (P=0.429). Treatment group consisted of 19 females (28.4%), 48 males (71.6%); control group consisted of 22 females (33.8%) and 43 males (66.2%) (P=0.496). Mean duration of follow up was 12.03 ± 1.56 months in treatment group and 12.08 ± 1.50 months in control group (P=0.651).

Twenty-five patients (37.3%) in treatment group and 27 patients (41.5%) in control group were receiving thiazide group diuretics (P=0.726). No difference was detected between the patients who were receiving or not receiving allopurinol treatment with respect to age, gender, duration of follow up, ratios of vitamin D and diuretic administration, coronary artery disease, diabetes mellitus, hypertension (P>0.05).

Both in the groups treated or not-treated with allopurinol; baseline eGFR, 3rd month eGFR, 6th month eGFR, 9th month eGFR and 12th month eGFR were calculated. A reduction was not detected in eGFR value beginning from 3rd month compared to baseline value in allopurinol-receiving group. eGFR value increased 1.02±8.9 mL/min/1.73 m² on month 12 compared to baseline value however, the difference was not statistically significant (P=0.352). In control group, eGFR decreased beginning from month 3 compared to baseline value. eGFR value decreased 2.59±7.9 mL/min/1.73 m² on month 12 compared to baseline value and the difference was statistically significant (P=0.012) (Table 2).

There was not a significant difference between baseline uric acid levels of the patients receiving allopurinol or not (P>0.05). Serum uric acid values on months 3, 6, 9 were significantly higher in control group compared to the ones receiving allopurinol (P<0.05). Serum uric acid values significantly decreased on months 3, 6, 9 and 12 compared to baseline values in allopurinol-receiving group (P<0.05). A reduction of 2.09±1.12 mg/dL was detected at the end of month 12 compared to baseline values and the difference was statistically significant (P<0.001) (Table 3).

Discussion
Elevated serum uric acid level was found to be associated...
with increased hypertension and cardiovascular disease risk (9-11). Hyperuricemia was detected to have a patho-
genetic role in renal disease progression. Serum uric acid level was shown to be a predictor for renal progression in patients with IgA nephropathy (12,13). Elevated uric acid level was shown to be correlated with renal failure development also in type 2 diabetic patients with normal renal function (14). Allopurinol decreases serum uric acid level by inhibiting xanthine oxidase enzyme. In experimental animal models, hyperuricemia-induced functional and structural injury regressed with allopurinol treatment (15,16).

In animal models, hyperuricemia was shown to increase vascopathy through impairing blood pressure control, increasing proteinuria, glomerulosclerosis and tubulointerstitial fibrosis (7). It was reported that reduced serum uric acid levels improved renal functions and slowed down renal disease progression. Although the mechanism of allopurinol’s slowing down renal progression is not known, many factors are considered to be effective. Afferent arterioles are known to increase proliferation in vascular smooth muscle cells, lead to hardening of vessel wall and impair auto-regulatory protective mechanisms. Arterial pressure directly reflects to glomerulus and this leads to glomerular hypertension, glomerular hypertrophy and sclerosis (15). Allopurinol indirectly decreases hydrostatic pressure by reducing serum uric acid level and helps to prevent renal injury.

Uric acid has recently begun to be defined as a mediator for renal disease and its progression. Hyperuricemia leads to elevated blood pressure, kidney afferent arteriopathy, strengthened glomerular hydrostatic pressure and renal scar formation. Studies have indicated that renal dysfunction was slowed down by reducing systolic blood pressure through reducing serum uric acid levels (8). We analyzed stage 3 CKD patients who were followed up at our predialysis clinic, who had hyperuricemia and used allopurinol. We obtained similar data with literature when we compared hyperuricemic control group who were not receiving allopurinol and one year GFR changes. An increase of 1.02±8.89 mL/min/1.73 m² was detected in GFR values compared to baseline values at the end of 12.3±1.56 months of follow up period (P<0.352). In control group, GFR values were seen to decrease 2.59±7.9 mL/min/1.73 m² at the end of follow up period (P=0.012). We may state that allopurinol treatment has a positive effect on renal function as a significant decrease was detected in GFR in non-treated group.

Fifty-four hyperuricemic patients with mild to moderate CKD were included in a small randomized-controlled study conducted by Siu et al (8). Treatment group was started 100-200 mg daily allopurinol based on baseline renal functions (200 mg daily allopurinol if creatinine is equal to or below 1.7 mg/dL and 100 mg daily allopurinol if creatinine is above 1.7 mg/dL). Basal serum creatinine levels were similar in both groups and 1.64±0.63 mg/dL in treatment group, 1.86±0.69 mg/dL in control group. A significant difference was not detected in creatinine level at the end of 12 months in allopurinol group (1.99±0.92 mg/dL). Serum creatinine levels were seen to impair in control group at the end of the study (2.89±0.97 mg/dL). We obtained similar data with literature when we compared hyperuricemic control group who were not receiving allopurinol and one year GFR changes. An increase of 1.02±8.89 mL/min/1.73 m² was detected in GFR values compared to baseline values at the end of 12.3±1.56 months of follow up period (P<0.352). In control group, GFR values were seen to decrease 2.59±7.9 mL/min/1.73 m² at the end of follow up period (P=0.012). We may state that allopurinol treatment has a positive effect on renal function as a significant decrease was detected in GFR in non-treated group.

Fifty-four hyperuricemic patients with mild to moderate CKD were included in a small randomized-controlled study conducted by Siu et al (8). Treatment group was started 100-200 mg daily allopurinol based on baseline renal functions (200 mg daily allopurinol if creatinine is equal to or below 1.7 mg/dL and 100 mg daily allopurinol if creatinine is above 1.7 mg/dL). Basal serum creatinine levels were similar in both groups and 1.64±0.63 mg/dL in treatment group, 1.86±0.69 mg/dL in control group. A significant difference was not detected in creatinine level at the end of 12 months in allopurinol group (1.99±0.92 mg/dL). Serum creatinine levels were seen to impair in control group at the end of the study (2.89±0.97 mg/dL). A total of 113 patients with GFR<60 ml/min were included in the prospective randomized study of Goicoechea et al (17). Fifty-seven patients were administered allopurinol

### Table 2. eGFR change in allopurinol and control group

<table>
<thead>
<tr>
<th>eGFR (mL/min/1.73 m²)</th>
<th>Allopurinol group</th>
<th>Control group</th>
<th>P*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline</td>
<td>39.97±8.12</td>
<td>40.07±8.36</td>
<td>0.945</td>
</tr>
<tr>
<td>3rd month</td>
<td>40.18±8.78</td>
<td>38.43±9.11</td>
<td>0.264</td>
</tr>
<tr>
<td>6th month</td>
<td>40.03±10.11</td>
<td>37.88±9.20</td>
<td>0.205</td>
</tr>
<tr>
<td>9th month</td>
<td>40.38±10.00</td>
<td>37.43±10.50</td>
<td>0.101</td>
</tr>
<tr>
<td>12th month</td>
<td>40.98±10.47</td>
<td>37.60±10.42</td>
<td>0.067</td>
</tr>
<tr>
<td>Baseline/3rd month change</td>
<td>0.21±6.31</td>
<td>-1.64±6.35</td>
<td>0.096</td>
</tr>
<tr>
<td>Baseline/6th month change</td>
<td>0.06±8.10</td>
<td>-2.19±7.41</td>
<td>0.099</td>
</tr>
<tr>
<td>Baseline/9th month change</td>
<td>0.41±8.10</td>
<td>-2.64±7.48</td>
<td>0.027</td>
</tr>
<tr>
<td>Baseline/12th month change</td>
<td>1.2±8.89</td>
<td>-2.59±7.90</td>
<td>0.016</td>
</tr>
</tbody>
</table>

*P<0.05.

### Table 3. The effect of allopurinol treatment on uric acid level

<table>
<thead>
<tr>
<th></th>
<th>Allopurinol group</th>
<th>Control group</th>
<th>P*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline</td>
<td>8.04±0.72</td>
<td>8.15±0.97</td>
<td>0.429</td>
</tr>
<tr>
<td>3rd month</td>
<td>6.44±1.02</td>
<td>7.62±1.43</td>
<td>0.000</td>
</tr>
<tr>
<td>6th month</td>
<td>6.08±1.07</td>
<td>7.99±1.23</td>
<td>0.000</td>
</tr>
<tr>
<td>9th month</td>
<td>5.94±1.05</td>
<td>7.74±0.95</td>
<td>0.000</td>
</tr>
<tr>
<td>12th month</td>
<td>5.94±1.13</td>
<td>7.82±1.22</td>
<td>0.000</td>
</tr>
<tr>
<td>Baseline/3rd month change</td>
<td>-1.59±1.00</td>
<td>-0.53±1.26</td>
<td>0.000</td>
</tr>
<tr>
<td>Baseline/6th month change</td>
<td>-1.95±1.11</td>
<td>-0.17±1.20</td>
<td>0.000</td>
</tr>
<tr>
<td>Baseline/9th month change</td>
<td>-2.10±1.18</td>
<td>-0.42±1.12</td>
<td>0.000</td>
</tr>
<tr>
<td>Baseline/12th month change</td>
<td>-2.09±1.12</td>
<td>-0.35±1.28</td>
<td>0.000</td>
</tr>
</tbody>
</table>

*P<0.05.
100 mg daily, remaining 56 patients continued their routine treatment. Clinical, biochemical and inflammatory indices were assessed at the beginning and on months 6, 12 and 24. Renal disease progression, cardiovascular events and hospitalization with any reasons were evaluated. Serum uric acid and CRP values were seen to decrease significantly in allopurinol-treated group. In our study, serum uric acid levels were seen to decrease 2.09 ± 1.12 mL/min/1.73 m² at the end of 12 months compared to baseline values. Serum uric acid levels on months 3, 6, and 9 were significantly higher in the group not receiving allopurinol compared to allopurinol-receiving group.

The study of Kanbay et al (18) showed that endothelial dysfunction, blood pressure, GFR and inflammatory markers may improve with reducing uric acid using allopurinol in patients with asymptomatic hyperuricemia. Asymptomatic hyperuricemic patients without gout and 30 normouricemic control patients were included in 4 months of prospective study. Thirty hyperuricemic patients were given allopurinol 300 mg daily, 37 hyperuricemic patients were compared with 30 normouricemic patients. Basal and month 4 eGFR, blood pressure, protein/creatinine ratio in spot urine and hsCRP measurements were done. Age, gender, baseline lipid profile, eGFR, hemoglobin, glucose and proteinuria levels were found similar in three groups. CRP levels were high in hyperuricemic patients compared to normouricemic patients, as expected. Allopurinol treatment led to a decrease in serum uric acid value and systolic blood pressure and an increase in eGFR value.

In the prospective cohort study of Bellomo et al (19) conducted with 900 healthy normotensive adults (153 females, 747 males), eGFR levels were seen to decrease with increasing uric acid level. At the end of mean 59 months of follow up, GFR was shown to regress to 88±14 mL/min/1.73 m² from 97±16 mL/min/1.73 m². High serum uric acid levels were seen to be associated with GFR reduction both in females and males. Serum uric acid levels were shown to be a risk factor for the reduction in renal functions also in healthy normotensive individuals. In another retrospective cohort study conducted with 183 chronic renal disease patients, allopurinol receiving group (100 mg daily) and untreated group were compared. Blood pressure was detected to be lower on months 6, 1 and 2 years compared to baseline in allopurinol-receiving group. An inverse correlation was detected between serum uric acid level and months 6, 1 and 2 year eGFR. It was concluded that allopurinol treatment reduced uric acid and led to better blood pressure control and reduced renal disease progression in hyperuricemic chronic renal disease patients (20). Using data of modification of diet in renal disease (MDRD), uric acid was shown to be associated with all causes of mortality and cardiovascular mortality in diabetic stage 3-4 chronic renal disease patients (21). In a study conducted with a new xanthine oxidase inhibitor —febuxostat— uric acid and creatinine levels were tested before and after treatment in 60 chronic renal disease patients of whom 67% had an eGFR <30 mL/min/1.73 m². Uric acid levels effectively decreased with febuxostat treatment and a progressive reduction of eGFR values decreased (22).

Conclusion
In conclusion, we showed that we could slow down renal disease progression with allopurinol treatment in hyperuricemic stage 3 CKD patients. However our study has some limitations like having small number of patients and non-randomized trial. Larger, multi-center, prospective studies are required in order to better understand the positive effects of allopurinol in hyperuricemic patients.

Limitations of the study
This study was conducted on a small group of patients. We suggest larger studies on this subject.

Authors’ contribution
AO: study design, data collection and statistical analysis; AI: study design and manuscript reviewing.

Conflicts of interest
The results presented in this paper have not been published previously in whole or part, except in abstract format. We certify that there is no conflict of interest with any financial organization regarding the material discussed in the manuscript.

Ethical considerations
Ethical issues (including plagiarism, data fabrication, double publication) have been completely observed by the authors.

Funding/Support
This study was supported by a grant from Antalya Training and Research Hospital. It was the thesis of Aygul Ozdemir, MD.

References
7. Johnson RJ, Kang DH, Feig D, Kvilighn S, Kanellis J,


