

The effect of allopurinol on lowering blood pressure in hemodialysis patients with hyperuricemia

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Background: Hyperuricemia has been associated with the development of high blood pressure (BP). We studied the effects of allopurinol therapy in hyperuricemic hemodialysis (HD) patients with high BP. **Materials and Methods:** This single-blind, randomized cross-over clinical study involved 55 HD patients with serum uric acid level > 6.5 (men) and > 5.5 mg/dL (women). They were randomly divided in two groups, each of which went through two phases. Group-1 in phase-1 received 100 mg/day orally of allopurinol for three months; while Group-2 was given whatever medication they received prior to the study. After two months of washing period, the groups were crossed-over. The BP levels were measured before and after HD during the eight months study period. **Results:** Fifty-three patients completed the study (33 men and 20 women, with mean age of 55.8 years). Uric acid levels decreased significantly during the 12 weeks of allopurinol therapy (7.71 ± 1.53 to 5.2 ± 1.2 $P < 0.005$). Overall, after the 12 weeks of allopurinol therapy, systolic and diastolic BP also significantly decreased in allopurinol group, 15.8% (139 to 117, $P < 0.0005$) and 8.6% (81 to 74, $P < .0005$), respectively. There were not significant changes in body mass index, blood urea nitrogen, creatinine, albumin, cholesterol, triglyceride, hemoglobin, liver enzymes and serum electrolytes level after treatment. Patients treated with allopurinol had a significant increase in the quality of dialysis (KT/V) ($P: 0.043$). **Conclusions:** In HD patients, allopurinol treatment reduced BP. The results indicate a new potential therapeutic approach for controlling BP in HD patients.

Key words: Allopurinol, end stage renal disease, high blood pressure, uric acid

INTRODUCTION

Hypertension is a very common disease affecting 25-30% of people in the world.^[1] Despite a large number of safe and effective anti-hypertensive medications and useful lifestyle changes, BP control is achieved in less than 40% of patients.^[2] Increased serum uric acid level has been associated with increased risk for development of hypertension (HTN)^[3-7] and cardiovascular (CV) disorders.

Animal experiments suggest that hyperuricemia can induce high BP through activation of the renin-angiotensin system, reduction in endothelial nitric oxide

levels, superoxide generation, elevated levels of systemic inflammatory mediators, induction of endothelial dysfunction and vascular smooth muscle proliferation.^[8-16]

By inhibiting the enzyme xanthine oxidase, allopurinol can decrease serum uric acid levels. Its effect is achieved by changing plasma renin activity and nitric oxide syntheses, which improves endothelial dysfunction and prevents vasculopathy.^[17-20]

Studies in humans have also shown correlation between uric acid levels with both endothelial dysfunction and elevated plasma renin activity.^[21,22]

Uric acid has also been suggested as an important risk factor in the development of primary HTN in humans.^[23,24] Hyperuricemia is strongly associated with increased mortality.^[25-27]

In two cohort studies of chronic kidney disease stage-5, there were a J-shaped correlation between uric acid level and all causes of mortality.^[28,29]

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However, there is no data available linking uric acid levels and BP levels in patients with ESRD. The present study aimed to investigate the effect of allopurinol on lowering blood pressure in hemodialysis patients with hyperuricemia.

MATERIALS AND METHODS

This single blind, randomized crossover clinical trial study was conducted between October 2009 and August 2010. One hundred and forty two dialysis patients aged 18-88 years old were enrolled in the study. They had been dialyzed in two HD centers (Vali-e-Asr and Beheshti hospitals) in the Iranian provincial capital of Zanzan.

Inclusion criteria were high level of serum uric acid (greater than 6.5 mg/dl for men; and 5.5 mg/dL for women) and existence of HTN. The definition of hyperuricemia was based on analyses from the Atherosclerosis Risk in Communities (ARIC).^[30]

Hypertension was defined as systolic BP of 140 mm Hg or higher, diastolic BP 90 mm Hg or higher; or combined factors of diagnosed with high BP and using antihypertensive medication.

Exclusion criteria were malignant HTN due to Erythropoietin therapy diagnosed with cancer, alcohol consumption, noncompliance with taking prescribed medication and those patients with a known history of hypersensitivity to allopurinol or being already on allopurinol. Each participating patient gave written informed consent before enrollment in the study.

Fifty-five patients meet the inclusion criteria, hence, their BP were measured before and after each session of HD for the eight months duration of the study. To prevent any observer bias at the time of measuring BP, the nurse in charge was prevented from knowing which patients were under treatment of allopurinol.

BP was measured by a calibrated mercury sphygmomanometer in the dialysis ward, after the patients were at the sitting and relaxed position for 10 min. The mean of all weekly measurements for systolic and diastolic BP, before and after HD, was used for analysis.

During the study, the antihypertensive therapies, as well as lipid-lowering drugs such as (ACE inhibitor, β blocker, Ca channel blocker and inhibiting HMG-CoA reductase) were kept constant.

In patients, who were taking antihypertensive medication, the class and dosage of medication were extracted from their records.

Patients were randomly divided into two groups, each of which went through two phases. In the first phase of the study, Group-1 received 100 mg/day of allopurinol, Hakim Pharmaceutical Company of Iran, for three months; while Group-2 was given whatever medication they received prior to enrollment into the study. After three months, patients passed two months of washout period. Then in the second phase of the study, the two groups were crossed over and Group-2 was administered allopurinol for three months, similar to Group-1 in the first phase. This was while; Group-1 was given whatever medication they received prior to enrollment into the study [Figure 1].

To assess the relation between serum uric acid and other paraclinical and demographic factors, the following variables were checked: Age, gender, diabetes (no, yes), serum cholesterol (Chol), high-density lipoprotein (HDL) and low-density lipoprotein (LDL) cholesterol, hemoglobin (Hgb), serum albumin (Alb), Na, K, AST, ALT, Ca and P levels, body mass index (kg/m²) and quality of dialysis which measured by KT/V. Data and laboratory values were collected when patients got to their dry weight 6 months after the start of chronic maintenance dialysis. Each month laboratory values were checked.

To evaluate the efficacy of dialysis, KT/V was calculated. The HD protocol for all patients was 4 hours, three times per week, using polysulphane membranes from Meditechs and Soha Companies and an average blood flow rate of 300 to 350 mL/min and with bicarbonate basis dialysate. The mean duration of dialysis was 36.21 \pm 35.6 months (with maximum of 192 and minimum of one month).

Subjects were observed for any adverse events related to the use of allopurinol (including Stevens-Johnson syndrome and an increase in transaminase level), but none were found. This trial was approved by committee of ethics of research of Zanzan University of Medical Sciences (Ethics No; 19/3-3/976).

Trial Registration Number: IRCT138902043325N2

Statistical analysis

The data analysis was conducted base on intent-to-treat. All statistical analysis was performed by using the SPSS software version 16.0 (SPSS Inc., Chicago, IL, USA).

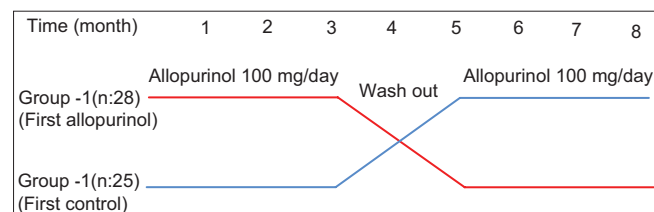


Figure 1: Flow-chart of the study: Single-blind, two-period randomized cross-over study

Means of quantitative variables were compared by using student T-test between the two groups. In the case of discontinuous variables, Chi-square test was applied. Response to Allopurinol in the study groups, before and after intervention, was assessed with a paired samples T-test analysis. Paired samples T-test and independent sample T-test were used to assess carry-over effect. The repeated measures analysis of variance model was used to assess the effect of allopurinol on change of BP over time (time effect), the difference of this effect between the two groups (time*treatment interaction) and treatment effect. In the cases, which specificity test was significant, *P* value was corrected with Greenhouse-Geisser test (G-G³). All *P* values were two-tailed and a *P* value <.05 was considered as significant.

RESULTS

One hundred and forty two HD patients were enrolled in the study, 55 of whom met the inclusion criteria. In the first phase of the study, Group-1 (28 patients) received 100 mg/day of allopurinol for three months; while Group-2 (27 patients) was given whatever medication they received prior to enrollment into the study [Figure 1].

During phase-1, two patients in Group-1 dropped out of the study due to kidney transplantation. In the second phase, one patient in Group-1 and two patients in Group-2 died due to cardiovascular events. Thus, 53 patients (33 men and 20 women, with the mean age of 55.8 years) were included in the primary analysis [Figure 2]. This is while; twenty-seven patients in Group-1 and 23 in Group-2 completed the eight-month follow-up period of observation. Table 1 presents demographic and baseline clinical characteristics of the study population while Table 2 present baseline laboratory parameters. There was no significant difference between the two groups in different variables at each phase of the study.

In the first assessment to determine the patients' eligibility for the study, we found that the prevalence of elevated serum uric acid levels was 38.7% (55/142). 80.4% of hyperuricemic patients had HTN and 95.3% of HTN patients had elevated uric acid levels.

There was no association between age and hyperuricemia in development of HTN.

In addition, Table 1 shows the percentage of patients, who were taking antihypertensive medication: This distribution did not differ between the two groups.

Comparison of baseline BP at the beginning of the two phases of the study showed there was no carry-over effect in this crossed clinical trial [Table 3].

Pooled data analysis

After 12 weeks of allopurinol therapy, uric acid levels was reduced significantly from 7.71 ± 1.53 (5.6-11.5) to 5.2 ± 1.2 (2.6-9.1) (*t*: 9.24, *P* value < 0.005). Patients treated with allopurinol also had a significant decrease in systolic and diastolic BP.

Pooled data analysis of BP in control and allopurinol groups at baseline showed there was no significant changes in systolic and diastolic BP before and after dialysis in the control group, but BP significantly decreased in the allopurinol group over time (F: 14.707, *P* < 0.0005 corrected with G-G³) [Figure 3]. Overall, after 12 weeks of treatment with allopurinol, systolic BP before and after dialysis decreased from 139 and 128 to 117 (F: 14.707, *P* < 0.0005 corrected with G-G³) and 110 (F: 8.460, *P* < 0.0005 corrected with G-G³), respectively. Also, overall after 12 weeks of treatment with allopurinol diastolic BP before and after dialysis decreased from 81 and 78 to 74 (F: 5.851, *P* < 0.0005) and 69 (F: 8.241, *P* < 0.0005 corrected with G-G³), respectively, [Table 4].

The effect of time was not the same for the two groups (time* treatment). As it is shown in Figure 3, trend of BP in allopurinol group is significantly decrescendo, but it is crescendo in the control group. There were no significant

Table 1: Baseline characteristics of patient population

Characteristic	Value
Sex, No (%)	
Male	33 (62.3)
Female	20 (37.7)
Age (years), mean±SD (min-max)	55.89±15.79 (20-88)
Weight before dialysis (kg), mean±SD (min-max)	63.11±13.29 (33-92)
Weight after dialysis (kg), mean±SD (min-max)	61.00±12.82 (32.5-88)
Intra dialytic weight gain (kg), mean±SD (min-max)	2.11±0.95 (0.25-4)
Height (cm), mean±SD (min-max)	160.93±9.38 (123-178)
BMI (kg/m ²), mean±SD (min-max)	23.53±4.2 (16.4-37.9)
Duration of dialysis (months), mean±SD (min-max)	36.21±35.6 (1-192)
KT/V, mean±SD (min-max)	0.98±0.25 (0.41-1.96)
BP, mean±SD (min-max)	
Systolic BP before dialysis	137.35±27.46 (90-200)
Diastolic BP before dialysis	79.62±13 (50-110)
Systolic BP after dialysis	125.84±23.15 (80-180)
Diastolic BP after dialysis	75.84±10.81 (50-100)
Anti HTN drug, No (%)	
ACE inhibitor	6 (11.3)
β blocker	3 (5.7)
Ca channel blocker	1 (1.9)
ACE inhibitor+β blocker	4 (7.5)
ACE inhibitor+Ca channel blocker	6 (11.3)
β blocker+Ca channel blocker	1 (1.9)
ACE inhibitor+β blocker+Ca channel blocker	13 (24.5)

BMI=Body mass index (measured as weight in kilograms divided by height in meters squared); HTN=Hypertension; BP=Blood pressure; DM=Diabetes Mellitus; KT/V is a number used to quantify HD, K - dialyzer clearance of urea, t - dialysis time - volume; Values are expressed as Mean ± SD for continuous variables with normal distribution and as median rank (25th, 75th percentiles) for continuous variables without normal distribution

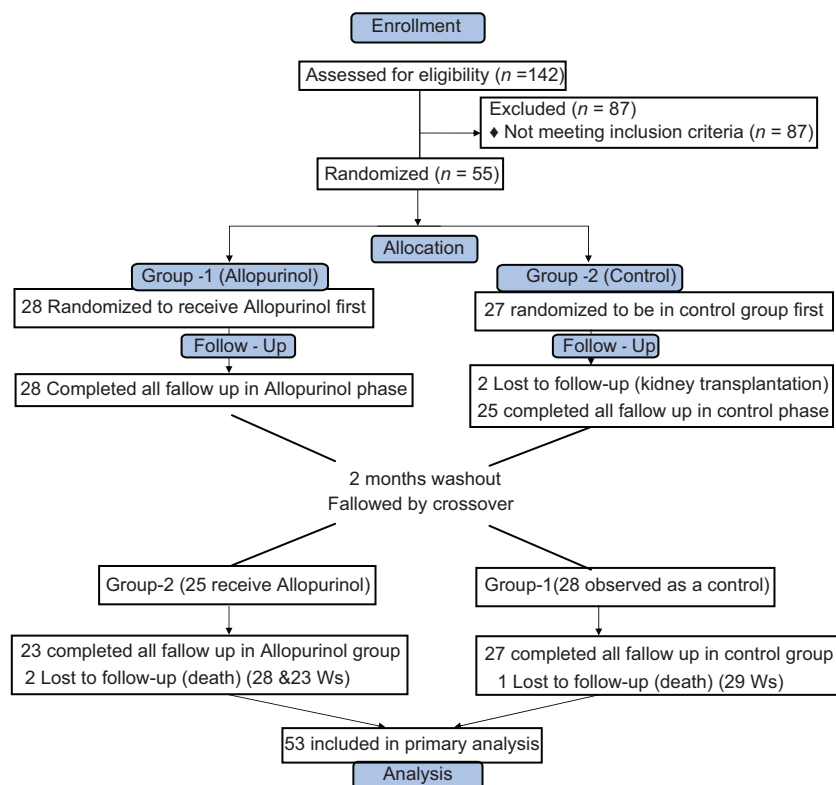


Figure 2: Study design

Table 2: Baseline laboratory features of patients

Laboratory characteristic	Value, mean±SD (min-max)
Serum uric acid (mg/dl)	7.71±1.53 (5.6-11.5)
BUN (mg/dl)	112.13±87.93 (17-424)
Cr (mg/dl)	8.51±3.16 (3.5-15)
Alb (g/dl)	4.05±0.46 (3.3-5)
Chol (mg/dl)	171.62±49.69 (102-288)
TG (mg/dl)	146.84±98.80 (58-574)
ALT (mg/dl)	25.72±22.37 (7-137)
AST (mg/dl)	22.83±15.95 (5-74)
ALP (IU/L)	310.02±204.39 (65-955)
Hgb (g/dl)	10.6±2.15 (5.7-14.7)
Na (mg/dl)	140.88±4.70 (132-148)
K (mg/dl)	5.44±0.99 (3.3-8)
Ca (mg/dl)	9.67±0.74 (6.5-10.8)
P (mg/dl)	5.38±1.53 (2.6-12)

BUN=Blood Urea Nitrogen; Cr=Creatinine; Alb=Albumin; Chol=Cholesterol; TG=Triglyceride; ALT=Alanine aminotransferase; AST=Aspartate transaminase; ALP=Alkaline phosphatase; Hgb=Hemoglobin

changes in intradialytic weight gain, nPNA, BUN, Cr, Alb, Chol, TG, Hgb, liver enzymes and serum electrolytes after treatment period. Patients treated with allopurinol also had a significant increase in kt/v (t: 2.1, P value: 0.043). There was a significant treatment effect with allopurinol in BP of the intervention group [Table 4].

Parallel analysis for each phase

Parallel analysis was also conducted separately for each phase of the study. In first Phase, before and after dialysis, systolic BP were 134.6 and 122.1, which after

treatment with allopurinol decreased to 119.8 ($P < 0.0005$) and 111.4 ($P < 0.0005$). Before and after dialysis, diastolic BP were 78.5 and 75.7, which dropped to 74.6 ($P < 0.0005$) and 70.7 ($P < 0.0005$) after treatment. In second Phase, before and after dialysis, systolic BP were 145.6 and 136, which decreased to 113.9 ($P < 0.0005$) and 109.5 ($P < 0.0005$) after treatment with allopurinol. Before and after dialysis, diastolic BP was 85.6 and 81.3, which dropped to 73.6 ($P < 0.0005$) and 68.6 ($P < 0.0005$) after treatment. This trend was not the same between the two groups. In phase-1 of the allopurinol group, systolic BP before and after dialysis decreased from 134 and 122 to 119 (F: 4.553, $P < 0.0005$) and 111 (F: 2.481, $P = 0.025$), respectively. However, in the control group, systolic BP increased from 138 and 130 to 153 (F: 2.858, $P = 0.001$) and 133 (F: 1.160, $P = 0.333$), respectively. Treatment effect in phase-1 and phase-2 statistically were statistically significant.

DISCUSSION

In our study, we investigated the effect of hyperuricemia on blood pressure of HD patients. Hypertension is caused by multifactorial etiology. Family or genetic background, diet, sodium intake, physical activity and stress level are among the many factors considered as contributing to the development of high BP. Hypertension is also associated with CV diseases such as

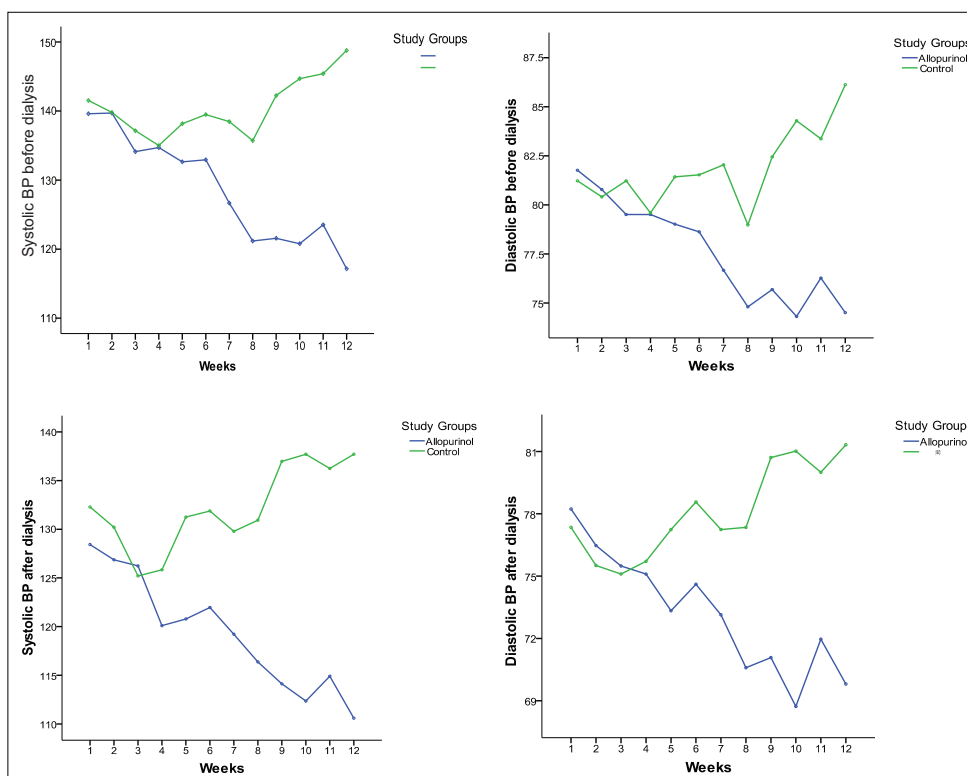


Figure 3: Change of blood pressure in two study groups over time

Table 3: Comparison between baseline blood pressure at the beginning of two phases (testing for carry-over effect)

Group	At the beginning of phase 1	At the beginning of phase 2	t, P value
Study group			
Sys BP before dialysis	135.18±27.5	142.40±32.2	1.39, 0.175
Dias BP before dialysis	78.88±11.54	82.22±11.87	1.66, 0.107
Sys BP after dialysis	122.5±22.11	133.7±28.3	2.36, 0.026 (95%CI:1.4-20.7)
Dias BP after dialysis	75.92±10.47	78.51±12.31	1.15, 0.257
Weight before dialysis	68.77±14.09	67.96±14.83	0.19, 0.84
Weight after dialysis	66.39±13.11	65.72±14.59	0.17, 0.86
Control group			
Sys BP before dialysis	140.83±28.5	145.41±27.6	1.13, 0.268
Dias BP before dialysis	80.83±15.01	85.41±11.78	1.96, 0.061
Sys BP after dialysis	129.58±24.75	135.8±26.5	1.87, 0.074
Dias BP after dialysis	75.83±11.76	81.25±11.90	4.51, 0.005(95%CI:2.9-7.9)
Weight before dialysis	57.92±10.14	57.2±10.23	0.25, 0.80
Weight after dialysis	55.56±10.23	55.76±9.95	0.07, 0.94

Values are expressed as Mean±SD

coronary heart disease, peripheral vascular disease, stroke and renal disease.^[31-33]

Uric acid is considered as a strong predictor of hypertension and BP progression.^[3-7,34,35]

There is no universally accepted definition for hyperuricemia. In one study, patients who had a serum uric acid >5.5 mg/dL had an 89% positive predictive value for essential HTN, whereas a serum uric acid level of less than <5.0 mg/dL had a 96% negative predictive value for essential HTN.^[36]

In our study, we investigated the effect of hyperuricemia on blood pressure of HD patients. We defined hyperuricemia as serum uric acid of >6.5 mg/dL in men and >5.5 mg/dL in women.

Epidemiologic studies support possible role of uric acid on development of hypertension and cardiovascular events

Hyperuricemia has been reported in 25% of untreated HTN patients,^[37] in 50% of those taking diuretics and in 75% of subjects with malignant hypertension.^[38] It has been reported that 50-70% of hyperuricemic patients had HTN.^[39] In our study, we found 80.4% of hyperuricemic patients had HTN

Table 4: Is there effect of time the same for both groups (time * treatment interaction) and is there any treatment effect (between 2 group)? (Pooled analysis for treatment effect)

Time (week)		1	2	3	4	5	6	7	8	9	10	11	12	F, P value time*treatment	F, P value between 2 groups
Sys BP before dialysis	Allopurinol	139.6	139.7	134.1	134.7	132.6	132.9	126.6	121.1	121.5	120.7	123.5	117.1	13.28,<.0005 corrected with G-G ^c	8.62, .004
	Control	141.5	139.8	137.1	135.0	138.1	139.4	138.4	135.7	142.2	144.6	145.4	148.7		
Dias BP before dialysis	Allopurinol	81.7	80.7	79.5	79.5	79.0	78.6	76.6	74.8	75.6	74.3	76.2	74.5	7.04,<.0005 corrected with G-G ^c	6.36, .013
	Control	81.2	80.4	81.2	79.5	81.4	81.5	82.0	78.9	82.4	84.2	83.3	86.1		
Sys BP after dialysis	Allopurinol	128.4	126.8	126.2	120.1	120.7	121.9	119.2	116.3	114.1	112.3	114.9	110.5	10.79,<.0005 corrected with G-G ^c	11.26, .001
	Control	132.2	130.2	125.2	125.8	131.2	131.8	129.7	130.9	136.9	137.7	136.2	137.7		
Dias BP after dialysis	Allopurinol	78.2	76.4	75.4	75.1	73.3	74.6	73.1	70.5	71.0	68.7	71.9	69.8	11.02,<.0005 corrected with G-G ^c	8.14, .005
	Control	77.3	75.5	75.1	75.7	77.2	78.5	77.2	77.3	80.7	81.0	80.0	81.3		
Weight before dialysis	Allopurinol	62.84	62.85	62.47	62.41	62.54	63.23	62.37	64.65	63.03	63.25	62.8	61.04	0.971, 0.471 corrected with G-G ^c	0.037, .85
	Control	63.33	62.14	63.36	63.31	63.11	62.98	63.25	63.12	63.23	62.91	63.39	63.02		
Weight after dialysis	Allopurinol	60.97	60.86	60.55	60.60	60.54	61.44	60.51	68.87	60.66	61.29	60.80	60.86	0.933, 0.342 corrected with G-G ^c	0.025, .87
	Control	60.92	61.29	61.30	61.33	61.12	60.75	61.18	61.09	61.00	60.89	61.28	60.83		

Table 5: Effect nPNA on the uric acid levels

Time (week)		1	5	9	12	F, P value time*treatment	F, P value between 2 groups
nPNA before dialysis	Allopurinol	1.31	1.26	1.31	1.29	1.489, 0.235 corrected with G-G ^c	3.97, .054
	Control	1.40	1.38	1.40	1.39		
nPNA after dialysis	Allopurinol	1.22	1.20	1.28	1.23	1.986, 0.149 corrected with G-G ^c	18.69, .001
	Control	1.39	1.40	1.44	1.41		

nPNA=normalized protein nitrogen appearance

and 95.3% of HTN patients had elevated uric acid levels.

The relation between uric acid level and HTN decreases with higher patient age and duration of HTN,^[40] suggesting that uric acid may be more of a significant factor in younger patients with early-onset of HTN. In a recent Framingham Heart Study, serum uric acid level was found to be an independent predictor of HTN incidence and BP progression over as few as four years in young and middle age adults who had never been diagnosed with HTN.^[41]

In our study, there was no association between age and hyperuricemia in development of HTN. Feig and Johnson^[42] have demonstrated a significant correlation between elevated uric acid levels and BP in children and adolescents. The Moscow Children's Hypertension Study found hyperuricemia in 9.5% of children with normal BP, 49% of children with borderline HTN and 73% of children with moderate and severe HTN.^[43] A Hungarian Children's Health Study followed 17,624 children for 13 years and found that significant risk factors for the development of HTN were elevated heart rate, early sexual maturity and hyperuricemia.^[44]

Other studies have shown a linear relationship between serum uric acid and systolic BP in both white and black individuals.^[45,46] However one study, involving patients in whom hypertension had developed after the age of 60, has shown that uric acid did not predict the development of HTN.^[46]

In addition, high uric acid levels have been associated with organ damage in hypertensive patients.^[47,48] There are also studies related to an association between serum uric acid and subsequent CV events, left ventricular hypertrophy and risk for cardiac death in the general population.^[49-52]

In our study, we did not investigate the association between uric acid level and CV events and mortality, since survival analysis needs larger sample size and more follow-up.

Dose allopurinol has an effect on high BP

Allopurinol treatment can reduce BP in hyperuricemic adolescents with newly diagnosed hypertension.^[53-55] Mehmet Kanbay and colleagues investigated the effect of allopurinol on blood pressure, creatinine clearance and proteinuria in patients with normal renal functions. They found that hyperuricemia increases blood pressure and decreases GFR.^[53]

In our study, we also found that treatment of hyperuricemia with allopurinol reduced serum uric acid levels and controlled BP.

Finally, since daily protein intake of the patients may influence the uric acid levels, normalized protein nitrogen appearance (nPNA), which reflects the daily protein intake in HD patients were considered to be calculated. We found that before and after HD there was not any statistical significant difference in terms of nPNA between these two groups, Table 5.

SUMMARY

Several clinical and laboratory studies have shown that uric acid level might be an important factor in the development of hypertension in humans. Our study has found that reducing hyperuricemia decreases BP, while decreasing KT/V in HD patients. Uric acid is a pro-inflammatory factor,^[55] so reducing uric acid to normal level may have anti-inflammatory effect. This may be the reason for improvement of KT/V in our study population. Hence, management of hyperuricemia may prevent HTN and consequently reduce CV events.

To our knowledge, this is the first study in the literature that shows the benefits of allopurinol therapy on BP in hyperuricemic patients who are under HD treatment.

For further confirmation of the findings, we suggest studies with larger sample size. We also recommend studies to be conducted to access the effect of early treatment with allopurinol on patients with normal BP, as an important part of a prevention regime for any kind of vascular events in ESRD patients.

Limitation of this study

One of the main limitations of this study was avoidance of placebo.

Also, it is important to note that the results of our study may be confined by the concurrent use of antihypertensive drugs by patients. However, we agree that our sample size was too small to allow us to make concrete conclusion.

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