

EFFECT OF ALLOPURINOL IN CHRONIC KIDNEY DISEASE PROGRESSION IN ASYMPTOMATIC HYPERURICAEMIC SUBJECTS

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Abstract

This was a hospital based prospective, interventional study which included CKD stage 3- 5 patients with higher level of uric acid (male>7mg/dl, female>6mg/dl). The objective of the study was to evaluate the effect of allopurinol in chronic kidney disease (stage 3-5) progression in asymptomatic hyperuricaemic patients. One hundred and twenty patients were distributed in two groups. Sixty patients were placed in treatment group and sixty in control group. Purposive sampling technique was followed. In the study mean age was 49 (±9) years in treatment group and 45 (±11) years in control groups. Male were predominant in both groups. There were no significant difference in baseline characteristics between treatment group and control group (p>0.05). Sixty patients of treatment group were administered a dose of 100 mg/d of allopurinol. Follow up assessment was done at baseline, at 4 months and at 8 month after starting treatment. No significant differences were seen between baseline SBP, DBP, Hb and HbA1c with 4th month and 8th month follow up in both treatment group and control group, but mean Hb was significantly decreased in control group from the baseline after 8 month. Serum uric acid was decreased in treatment group while it was significantly raised from the base line at 4th month and 8th month in control group. In treatment group serum creatinine was decreased and eGFR was raised from the baseline after 8 month. On the other hand, in control group serum creatinine was significantly raised and eGFR was significantly decreased from the baseline at 8th month. While comparing between two groups results showed means of serum uric acid was significantly decreased in treatment group compared to control group after 8th month. There was a negative correlation between Uric Acid with eGFR after 8 month of allopurinol treatment although this finding was not statistically significant. So, allopurinol may have a protective role in CKD progression by decreasing serum uric acid level in patients with chronic kidney disease stage 3 - 5 with asymptomatic hyperuricaemia.

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Introduction

The prevalence of elevated serum UA in patients with chronic kidney disease (CKD) is higher (Edwards, 2008). Elevated serum UA has been related to increased risk for the development of hypertension and cardiovascular disease (Gagliardi et al., 2009). Asymptomatic hyperuricaemia is commonly viewed as an entity that should not be treated (Duffy et al., 1981; Kanellis et al., 2004). Some short-term trials suggest a benefit from

lowering uric acid on BP (Feig DI, Soletsky B et al., 2008 and Kanbay M et al., 2007), estimated GFR (eGFR) (Goicoechea et al., 2010, Kanbay et al., 2007 and Sui et al., 2006), C-reactive protein (CRP) levels (Goicoechea et al., 2010 and Kanbay et al., 2007) and endothelial dysfunction (Mercurio G et al., 2004). However, there is increasing evidence that hyperuricaemia may not be completely benign and it is still unknown whether treatment of

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asymptomatic hyperuricaemia in low-risk patients would provide benefit to patients in terms of renal function, endothelial dysfunction, and blood pressure (Kanbay M et al., 2011). Allopurinol decreases serum uric acid level by inhibiting the enzyme xanthine oxidase. For animal models of established renal diseases, correction of the hyperuricaemic state can significantly improve BP control, decreasing proteinuria and slowing the progression of renal disease (Johnson et al., 2003). There are few data on patients with CKD that confirm these findings. In different small randomized controlled trials, allopurinol treatment resulted in the improvement of oxidative stress, endothelial function (Farquharson et al., 2002; George et al., 2006) and progression of CKD (Siu et al., 2006). Some other recent studies suggest that lowering levels of uric acid may slow progression of renal disease, especially in patients with hyperuricaemia. Kanbay et al. (2007) reported that treatment of asymptomatic hyperuricaemia improved renal function. Likewise, Siu et al. (2006) reported that the treatment of asymptomatic hyperuricaemia delayed disease progression. However, most of these studies were short term or were not randomized, and only a few prospective randomized trials have been performed. Several prospective studies are necessary to find the effect of uric acid level reduction over progression of CKD in asymptomatic hyperuricaemic patients. The current study had been designed to see the effect of allopurinol treatment on renal function in patients with CKD stage 3-5 with asymptomatic hyperuricaemia.

Rationale

It is clear that treatment of chronic kidney disease and its advanced stage end stage renal disease is expensive and beyond the reach of average Bangladeshis. The resources and skill for taking care of the large CKD load, both in terms of personal and health care infrastructure do not exist currently in our country and would need to be created To tackle the problem of limited access to renal replacement therapy, an important method would be to try and reduce the incidence of end

stage renal disease and the need of renal replacement therapy by preventive measures. Elevated serum uric acid increase the risk of developing chronic renal dysfunction (Ling Li et al., 2014). As hyperuricaemia is associated with CKD and may often remain asymptomatic, if hyperuricaemic patients could be identified and treated properly even asymptomatic it might be possible to halt the progression of CKD and reduce the extra load of ESRD patients which will be highly economical for a economically constrained country like Bangladesh. Considering the above-mentioned facts and the fact this study was performed to determine the effect of allopurinol in reduction of hyperuricaemia in slowing down the progression of renal function.

Hypothesis

Allopurinol may retard the progression of renal function in patients with chronic kidney disease stage 3 - 5 with asymptomatic hyperuricaemia.

Objectives

General objectives:

To evaluate the effect of allopurinol in chronic kidney disease (stage 3-5) progression in asymptomatic hyperuricaemic patients.

Specific objectives:

1. To evaluate the effect of allopurinol in reduction of hyperuricaemia
2. To determine whether reduction of hyperuricaemia retard the deterioration of renal function by measurement of eGFR.
3. To assess the association between decreased uric acid level and blood pressure
4. To identify the effect of allopurinol on other clinical parameters such as Haemoglobin and HbA1c.
5. To record the partial demographic profile of the study subjects.

Methodology

This prospective interventional study was carried out at Department of Nephrology, Dhaka Medical College Hospital, Dhaka in between the period of January 2015 to December 2015.

Patients with CKD stage 3 - 5 with higher level of uric acid (female > 6 mg/dl, male > 7 mg/dl) without sign symptoms of hyperuricaemia were the target population of the study. Purposive sampling technique followed samples were selected as per inclusion and exclusion criteria.

Inclusion criteria were : 1) Patients with age 18 years and above ; 2) Patients with CKD stage 3, stage 4 and stage 5 and 3) Patients with higher level of uric acid (for female >6mg/dl and for male >7mg/dl) but having no sign symptoms of hyperuricaemia.

Exclusion criteria were: 1) Patients with serum uric acid level > 10 mg/dl or sign symptoms of hyperuricaemia ; 2) Known hypersensitive patients to allopurinol and 3) Patients already on uric acid lowering drugs

Methods of Data Collection:

One hundred and twenty patients were enrolled in this study selected from out patients and in patients of department of Nephrology, Dhaka Medical College Hospital, who fulfilled the inclusion and exclusion criteria set for this study. All the patients were briefed in details about the purpose and nature of the study. The patients of control group were also explained properly regarding the nature of their participation in the study. All the patients of the study gave written consent to be enrolled in the study.

One hundred and twenty patients were distributed in two groups. Sixty patients were placed in treatment group and sixty in control group. Purposive sampling technique was followed. However similar pattern of distribution has been attempted by alternative placement of the subjects in treatment and control group by considering i) stages of CKD ii) confounding factors –hypertension and diabetes and iii) treatment history of hypertension and diabetes with similar groups of drugs. Similarly normotensive and non-diabetic patients were placed alternatively in both groups. The dosage of antihypertensive drugs, lipid-lowering agents, antiproteinuric drugs and antiplatelet drugs were continued and adjusted according to the individual patient's clinical condition.

Sixty patients of treatment group were administered a dose of 100 mg/d of allopurinol (Goicoechea et al.,2010). Every patient went through detailed history taking and physical examination. A questionnaire was used to collect demographic data, clinical presentation and findings.

Follow-Up Assessment

- The time of follow-up were 8 months.
- Systolic BP (SBP), diastolic BP (DBP) were recorded and Haemoglobin (Hb) was measured at baseline, at 4, and 8 months after starting treatment to analyze the clinical parameters.
- HbA1c was measured similarly to see the glycaemic status of the patients.
- Serum uric acid was measured similarly to see the effect of allopurinol on asymptomatic hyperuricaemic patients.
- To determine the effect of allopurinol on renal function and progression of CKD, serum creatinine was measured and eGFR was calculated by using MDRD formula at baseline, at 4 and 8 months after starting treatment.
- Clinical and biochemical findings were compared between control group and with that of the treatment group.

Adverse Events

Any adverse events considered to be related to the use of allopurinol were recorded during the follow-up assessment. For serious adverse events, allopurinol therapy was discontinued.

Statistical analysis:

Data was processed and analyzed using SPSS (Statistical Package for Social Sciences) software, version 23.0 for Windows XP. Test statistics were used to analyze the data are Chi-square Test and Student's "t" test. Data processed on categorical scale was presented as frequency and percentage and was analyzed by Chi-square or X^2 test. While the data presented on continuous scale it was presented as mean standard deviation and analyzed with the help of student's 't' test. The level of significance was 0.05. P value <0.05 was

considered significant. The summarized data was then presented in the table and chart.

Ethical Consideration:

Prior to the commencement of this study, the thesis protocol was approved by the ethical committee of DMCH, Dhaka. The aims and objectives of the study along with its procedure, risks and benefits of this study were explained to the respondent in easily understandable local language and then informed written consent were taken from each. It was assured that all information and records would be kept confidential and the procedure would be helpful for the researcher. The participant was given the right to withdraw from the study anytime without any explanation. All participant was assured that any complication arise during the procedure would be managed by the researcher.

Results

This was a hospital based prospective interventional study conducted on 120 patients with chronic kidney disease (CKD) stage 3, stage 4 and stage 5 in the department of Nephrology of Dhaka Medical College and Hospital (DMCH) Dhaka. The results were presented by graphs and tables.

Initially 60 patients were included in treatment group and 60 patients were included in control group. After 4th month follow up 3 patients were dropout in treatment group and 4 patients were dropout in control group. After 8th month follow up in total 07 patients were dropout in treatment group and 09 patients were drop out in control group. Finally 53 patients were included in treatment group and 51 patients were included in control group. (Fig 1)

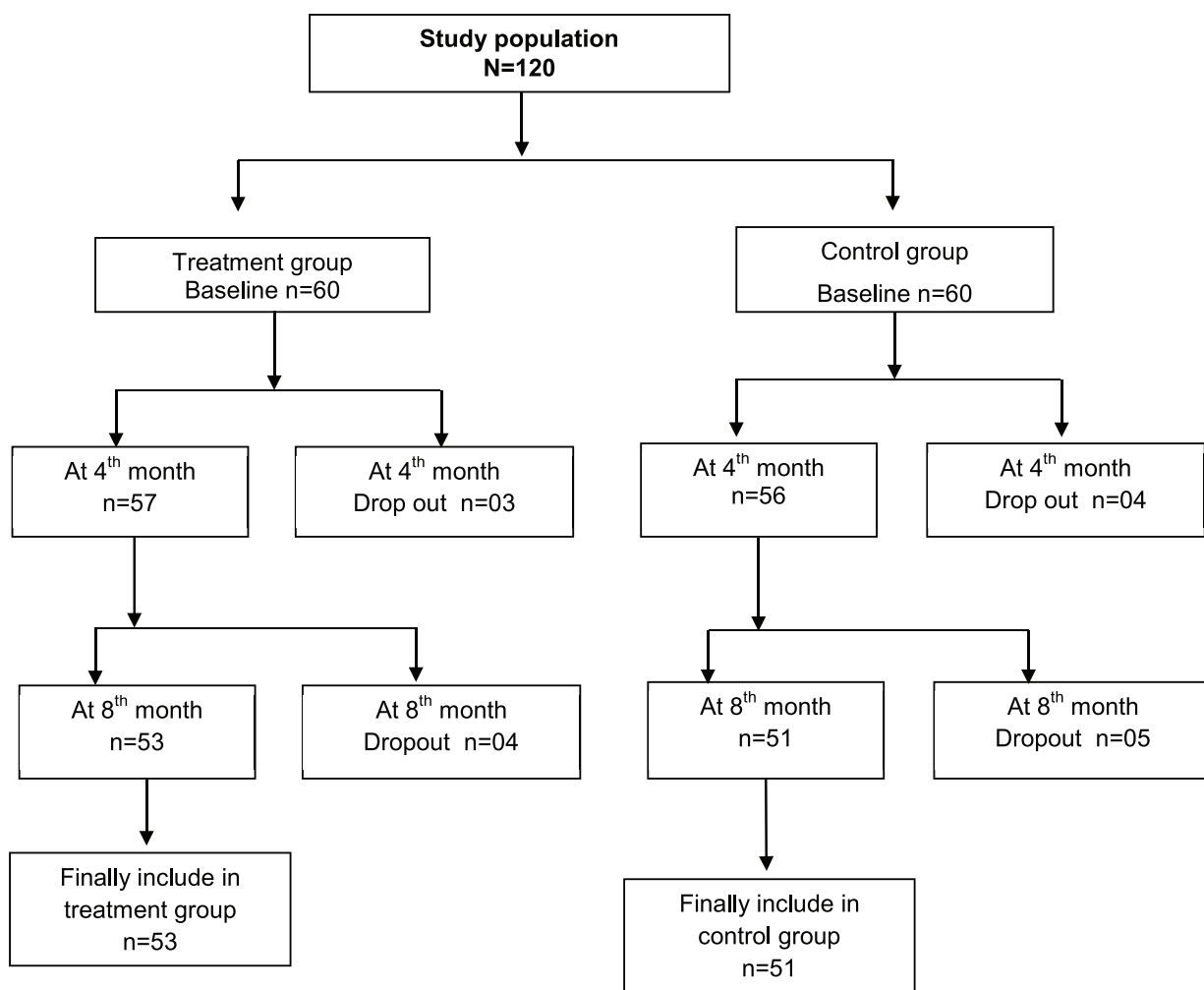


Figure 1 : Flow chart of the patient distribution of the study population Treatment group:

In present study mean age was 49 (± 9) years in treatment group and 45 (± 11) years in control group. Male were predominant in both group. In the study 68(56.67%) were male and 52(43.3%) were female.

This study showed common etiology of CKD in treatment group and control group where GN, DM, HTN, ADPKD and others were 29(48.33%) vs 24(40%), 24(40%) vs 23(38.33%), 13(21.67%) vs 12(20%), 01(1.67%) vs 1(1.67%) and 08(13.3%) vs 04(6.67%) respectively (Table I).

Table -I
Etiology of CKD of study population

Etiology	Group		Total
	Treatment	Control	
GN	29(48.33%)	24(40.0%)	53
DM	24(40.0%)	23(38.33%)	47
HTN	13(21.67%)	12(20.0%)	25
ADPKD	01(1.67%)	01(1.67%)	02
Others	08(13.3%)	04(6.67%)	12

Table I shows common etiology of CKD in treatment group and Control group were GN,

DM, HTN, ADPKD and Others were 29(48.33%) vs 24(40.0%), 24(40.0%) vs 23(38.33%), 13(21.67%) vs 12(20.0%), 01(1.67%) vs 01(1.67%), 08(13.3%) vs 04(6.67%) respectively.

In this study, in CKD stage 3, 06(10%) patients were in treatment group and 10(16.67%) were in control group; in stage 4, 36(60%) were in treatment group and 33(55%) were in control group; in stage 5, 18(30%) were in treatment group and 17(28.33%) were in control group.

Result shows no significant difference in baseline characteristics between treatment group and control groups ($p > 0.05$). (Table-II)

Effect of Allopurinol on clinical parameters

No significant difference between baseline means of SBP, DBP, Hb and HbA1c with 4th month and 8th month follow up in treatment group ($p > 0.05$). (table III). On the other hand in control group, no significant difference between baseline means of SBP, DBP and HbA1c with 4th month and 8th month follow up. But significant difference was found from baseline mean Hb level in control group ($p < 0.05$) at 8th month follow up. (table V)

Table II
Base line characteristics of the study population

	Study group		p value
	Treatment n=60	Control n=60	
SBP(mm of Hg)	138.13(± 14.22)	135.63(± 12.81)	0.31
DBP (mm of Hg)	83.78 (± 5.65)	83.03 (± 6.18)	0.49
Serum creatinine(mg/dl)	4.05(± 1.97)	3.66(± 1.41)	0.22
Serum uric acid(mg/dl)	8.15 (± 1.17)	7.49(± 0.85)	0.22
eGFR(ml/min/1.73m ²)	17.05(± 6.85)	18.78(± 7.95)	0.20
Hb(gm/dl)	9.04 (± 0.68)	9.21(± 0.59)	0.15
HbA1c(%)	5.33 (± 1.36)	5.55 (± 1.31)	0.36
antihypertensive user (other than RAAS blocker)	45(75.0%)	44(73.3%)	1.0

Table - II shows no significant difference in baseline characteristics between treatment group and control groups ($p > 0.05$).

Effect of allopurinol on UA levels and renal function and in progression of CKD:

In treatment group, significant difference was found between baseline mean serum uric acid with 4th month and 8th month (p<0.001). No significant difference was seen between baseline mean serum creatinine and mean eGFR with 4th month follow up but it was significant with baseline means of serum creatinine and eGFR with 8th month follow up (p<0.001).(table iv). In case of control group, significant difference was found in case of mean serum uric acid and mean serum

creatinine between baseline and at 4th month and 8th month (p<0.001) follow up. No significant difference was found between baseline mean eGFR with 4th month follow up but it was significant between baseline mean eGFR with 8th month follow up (p<0.001). (Table VI).

Comparison between two groups shows significant difference between means of serum uric acid and Hb at 8th month between treatment group and control group (p<0.05). Serum creatinine was reduced and eGFR was increased in treatment group compared to control group but these results were not statistically significant . (p> 0.05) (table VII).

Table III
Effect of Allopurinol on clinical parameters in treatment group

	Baseline Mean (±SD)	At 4 th month Mean (±SD)	p value	Baseline Mean (±SD)	At 8 th month Mean (±SD)	p value
SBP	138.14(±14.24)	139.71 (±11.35)	0.23	137.90(±14.60)	139.50(±10.37)	0.29
DBP	83.89 (±5.44)	84.56(±5.30)	0.17	84.09(±5.56)	84.58(±4.78)	0.34
Hb	9.11 (±0.60)	9.07 (±0.56)	0.53	9.16(±0.56)	9.11 (±0.61)	0.20
HbA1c	5.34 (±1.39)	5.32 (±1.32)	0.61	5.39 (±1.43)	5.35 (±1.37)	0.36

(Values are showing in mm of Hg for SBP and DBP and in gm/dl for Hb and in % for HbA1c) Paired Samples t Test was done

Table III shows effect of allopurinol on clinical parameters in treatment group. No significant difference between baseline means of SBP, DBP, Hb and HbA1c with 4th month and 8th month follow up in treatment group (p>0.05).

Table IV
Effect of allopurinol on UA levels and renal function and in progression of CKD in treatment group:

	Baseline Mean (±SD)	At 4 th month Mean (±SD)	p value	Baseline Mean (±SD)	At 8 th month Mean (±SD)	p value
S. Uric acid	8.14 (±1.16)	7.01 (±0.76)	<0.001	8.14(±1.17)	6.00 (±0.85)	<0.001
S. Creatinine	3.77(±1.53)	3.72(±1.49)	0.07	3.58(±1.39)	3.32(±1.18)	<0.001
eGFR	17.68(±6.42)	17.78(±6.32)	0.08	18.41(±6.04)	19.83(±6.08)	<0.001

(S.uric acid and S.creatinine values are showing in mg/dl and eGFR values are in ml/min/1.73m² . Paired Samples t Test was done

Table IV shows effect of allopurinol on UA levels and renal function estimated by MDRD-4 in treatment group. Significant difference was found between baseline mean serum uric acid with 4th month and 8th month (p<0.001). No significant difference was seen between baseline mean serum creatinine and mean eGFR with 4th month follow up but it was significant with baseline means of serum creatinine and eGFR with 8th month follow up (p<0.001).

Control group**Table V**
Clinical parameters in control group:

	Baseline Mean (\pm SD)	At 4 th month Mean (\pm SD)	p value	Baseline Mean (\pm SD)	At 8 th month Mean (\pm SD)	p value
SBP	134.78(\pm 12.06)	134.64(\pm 10.97)	0.77	135.05(\pm 11.52)	133.70(\pm 10.59)	0.06
DBP	82.53(\pm 5.48)	82.55(\pm 4.56)	0.95	83.11(\pm 5.26)	82.72(\pm 4.71)	0.32
Hb	9.26(\pm 0.53)	9.20(\pm 0.51)	0.07	9.26(\pm 0.54)	8.67(\pm 0.70)	<0.001
HbA1c	5.56(\pm 1.35)	5.60(\pm 1.39)	0.39	5.47(\pm 1.32)	5.58(\pm 1.44)	0.08

(Values are showing in mm of Hg for SBP and DBP and in gm/dl for Hb and in % for HbA1c) Paired Samples t Test was done

Table V shows clinical parameters in control group; no significant difference between baseline means of SBP, DBP and HbA1c with 4th month and 8th month follow up. But significant difference was found from baseline mean Hb level in control group ($p < 0.05$) at 8th month follow up.

Control group:**Table VI**
UA levels and renal function and progression of CKD in control group:

	Baseline Mean (\pm SD)	At 4 th month Mean (\pm SD)	p value	Baseline Mean (\pm SD)	At 8 th month Mean (\pm SD)	p value
S. Uric acid	7.46(\pm 0.87)	7.77(\pm 0.82)	<0.001	7.53(\pm 0.84)	8.26(\pm 1.06)	<0.001
S. Creatinine	3.51(\pm 1.27)	3.57(\pm 1.34)	0.005	3.40(\pm 1.23)	3.73(\pm 1.39)	<0.001
eGFR	19.44(\pm 7.75)	19.25(\pm 7.88)	0.09	20.23(\pm 7.58)	18.39(\pm 6.86)	<0.001

(S.uric acid and S.creatinine values are showing in mg/dl and eGFR values are in ml/min/1.73m² and ACR values are in mg/g) Paired Samples t Test was done

Table VI shows UA levels and renal function estimated by MDRD-4 in control group, significant difference was found in case of mean serum uric acid and mean serum creatinine between baseline and at 4th month and 8th month ($p < 0.001$) follow up. No significant difference was found between baseline mean eGFR with 4th month follow up but it was significant between baseline mean eGFR with 8th month follow up ($p < 0.001$).

Table VII
Comparison between two groups at the end of 8th month

At 8 th month	Study group		p value
	Treatment (mean \pm SD) n=53	Control (mean \pm SD) n=51	
SBP(mm of Hg)	139.50 (\pm 10.37)	133.70(\pm 10.59)	0.56
DBP(mm of Hg)	84.58 (\pm 4.78)	82.75(\pm 4.71)	0.07
S. creatinine(mg/dl)	3.32(\pm 1.18)	3.73(\pm 1.39)	0.10
S. uric acid (mg/dl)	6.0(\pm 0.85)	8.26(\pm 1.06)	0.000
eGFR(ml/min/ 1.73m ²)	19.83(\pm 6.08)	18.39(\pm 6.86)	0.26
Hb(g/dl)	9.11(\pm 0.61)	8.67(\pm 0.70)	0.000
HbA1C(%)	5.35 (\pm 1.37)	5.58 (\pm 1.44)	0.39

Table VII shows significant difference between means of serum uric acid and Hb at 8th month between treatment group and control group ($p < 0.05$).

P value 0.87
 R value 0.021
 Pearson Correlation -0.021

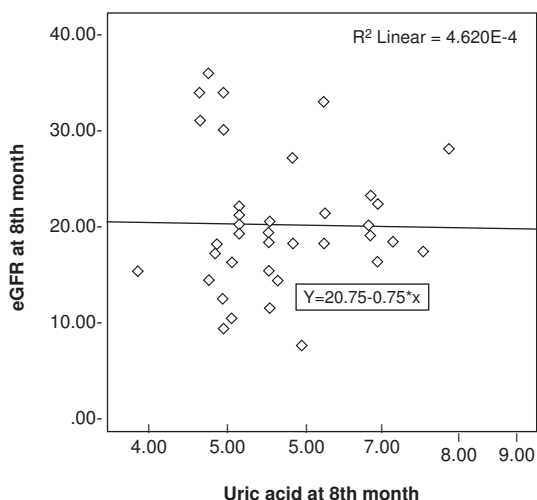


Fig.-2 : Correlation between Uric Acid at 8th month with eGFR at 8th month in treatment group

Figure 2 showing negative Pearson correlation (r=0.021; p=0.87) between Uric Acid at 8th month with eGFR at 8th month in treatment group but not statistically significant.

P value 0.18
 R value 0.187
 Pearson Correlation -0.187

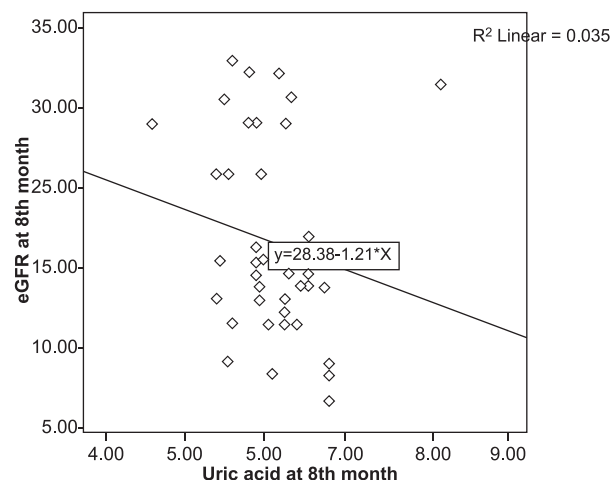


Fig.-3: Correlation between Uric Acid at 8th month with eGFR at 8th month in control group

Figure 3 showing negative Pearson correlation (r=0.18; p=0.18) between Uric Acid at 8th month with eGFR at 8th month in control group but not statistically significant.

Discussion

This prospective study was conducted at department of Nephrology in DMCH, Dhaka where patients were selected by purposive sampling method in control and treatment group. There were no significant difference in baseline characteristics between treatment group and control group (p>0.05).

In present study, no significant change was found in case of both systolic and diastolic blood pressure in treatment group at 4th and 8th month follow up (p>0.05). In case of control group similar results were observed. There was no significant change was observed in between treatment group and control group at the end of the study (p>0.05). A study reported statistical difference between groups in any of the presented clinical markers at baseline was reported in diastolic blood pressure by Kao et al.(2011) .In this trial, diastolic blood pressure was higher in the control group (p=0.036). However, in Siu et al.(2006) an even larger difference in diastolic blood pressure between treatment groups was reported, but this was not reported to be significant (p=0.25).

In present study, effect of allopurinol on UA level and renal function was tried to determine. To see the deterioration of renal function eGFR was analyzed at 4th and 8th month with baseline. In treatment group, significant difference was found in case of serum uric acid between baseline (8.14±1.16) and at 4th month follow up (7.01±0.76) and between baseline (8.14±1.17) and at 8th month follow up (6.00±0.85) (p<0.001). Serum uric acid was significantly decreased after 8th month of treatment. No significant difference was found in case of baseline serum creatinine and eGFR at 4th month follow up but significant differences with baseline serum creatinine and eGFR were observed at 8th month (p<0.001). Mean serum creatinine was significantly decreased and mean eGFR was raised significantly at the end of the study in treatment group.

In control group, significant difference was found in case of serum uric acid between baseline and at 4th month and between baseline and at 8th month of follow up ($p < 0.001$). Serum uric acid was significantly increased after 8th month of follow up. Baseline serum creatinine was significantly raised at 4th and 8th month follow up ($p < 0.001$). In case of eGFR no significant difference was found between baseline eGFR (19.44 ± 7.75) and at 4th month follow up (19.25 ± 7.88) but baseline eGFR (20.23 ± 7.58) was significantly decreased at 8th month follow up (18.39 ± 6.86) ($p < 0.001$).

Goicoechea et al. demonstrated almost similar result in their study. They found that in the allopurinol group, there was no significant change in eGFR (MDRD-4) after 24 months (from 40.8 ± 11.2 to 42.2 ± 13.2 ml/min per 1.73 m²), whereas in the control group, there was worsening by the end of the study (from 39.5 ± 12.4 to 35.9 ± 12.3 ml/min) ($P = 0.000$ between groups). In the control group, eGFR decreased 3.3 ± 1.2 ml/min per 1.73 m², and in allopurinol group, eGFR increased 1.3 ± 1.3 ml/min per 1.73 m² after 24 months ($P = 0.018$). Siu et al. (2006) reported patients who had stable and worsening of renal function, defined, respectively, as an increase in serum creatinine level at the end of study by 40% compared with baseline, but not yet requiring dialysis. It was reported that significantly more patients in the control group showed deterioration in kidney function at the end of the study (stable disease, 84% vs. 54%; worsening disease: 12% vs. 42%, for allopurinol and control respectively; $p = 0.015$). Pooled data from Goicoechea et al. (2010) and Siu et al. (2006) show a borderline significant improvement at 12 months [mean difference -0.17 mmol/l (95% CI -0.33 to 0.00 mmol/l)].

In comparison between two groups at 8th month of follow up serum creatinine was decreased and eGFR was increased in treatment group compared to control group but these changes were not statistically significant ($p > 0.05$). Hb was found significantly decreased in control group than treatment group after 8th month of follow up. No significant differences were found in case of HbA1c in between two groups at 8th

month of follow up. But serum uric acid was significantly decreased at 8th month in treatment group compared to control group. Goicoechea et al. (2010) study showed after 24 months of allopurinol treatment, serum UA levels were significantly decreased in subjects treated with allopurinol, from 7.8 ± 2.1 mg/dl to 6.0 ± 1.2 mg/dl ($P = 0.000$), whereas serum UA levels for subjects in the control group remain unchanged throughout the study period (7.3 ± 1.6 mg/dl at baseline and 7.5 ± 1.7 mg/dl at 24 months) ($P = 0.016$ between groups and time period). The change in UA levels at 24 months was $+0.3 \pm 0.27$ mg/dl in the control group in comparison to -1.6 ± 0.27 mg/dl in the allopurinol group ($P = 0.000$).

In the present study at the end of 8th month in treatment group, estimated glomerular filtration rate (eGFR) and the serum uric acid (UA) had a negative correlation (P value = 0.87, R value = 0.021, Pearson Correlation = -0.021) but it was not statistically significant. (Fig 2). In control group at the end of 8th month this study also found a negative correlation between estimated glomerular filtration rate (eGFR) and the serum uric acid (UA) (Correlation coefficient -0.18 and R = 0.18) but the result was statistically insignificant (p value = 0.18) (Fig 3)

When plotted the dose of previously administered allopurinol and UA, *Ishikawa et al. (2014)* found a statistically significant negative correlation between them ($p = 0.0020$). *Ishikawa et al. (2014)* study focused on the relationship between UA and baseline eGFR, there was a weak negative correlation but this was statistically insignificant. Goicoechea et al. (2010) have evaluated the correlation between UA levels and eGFR in the whole data and within each experimental group. There is a significant inverse correlation between UA levels and eGFR in all cases. The change in UA levels at 24 months has been plotted against the change in eGFR and they found a significant inverse correlation between changes ($r = 0.375$; $P = 0.001$).

Multiple studies have demonstrated that uric acid is a potential causative agent of worsening renal function. However, despite the work done thus far in hyperuricaemia and its effects on

hypertension and potential effects on mortality, the 2012 Kidney Disease Improving Global Outcomes practice guidelines for the evaluation and management of chronic kidney disease state that there is insufficient evidence to recommend the use of medications such as allopurinol to delay the progression of CKD (KDIGO,2012).

Conclusion

Allopurinol in a dose of 100mg/day in asymptomatic hyperuricaemic patients with CKD stage 3-5 may improve GFR. So, allopurinol may have a protective role in CKD progression by decreasing serum uric acid level in patients with chronic kidney disease stage 3 - 5 with asymptomatic hyperuricaemia.

Limitations

- Sample size was small.
- Follow up time was short.
- Important confounders that may cause hyperuricaemia (e.g. chronic lymphatic leukaemia, lymphoma, polycythaemia rubra vera, lead toxicity, congenital abnormality etc.) were not properly excluded with relevant investigations.
- The results may be limited by the concomitant use of statins, antiplatelet, and renin-angiotensin-aldosterone system (RAAS) blocker drugs. Although there were no baseline differences in the use of these drugs between the groups, but these treatments might have been modified during the study period.

Recommendations

Allopurinol may play a protective role in progression of renal disease in patients with asymptomatic hyperuricaemia. Further research on this topic with a larger sample collected by random sampling and long time follow up is recommended.

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