EFFECT OF ALLOPURINOL ON INFLAMMATORY MARKERS IN CHRONIC KIDNEY DISEASE PATIENTS WITH ASYMPTOMATIC HYPERURICAEMIA

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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 on inflammatory markers in patients with chronic kidney disease (stage 3-5) with asymptomatic hyperuricaemia. 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 basally, 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. No significant change was found in case of mean ESR at 4th and 8th month in any group. But base line mean CRP was significantly reduced in treatment group and increased in control group at 4th and 8th month of follow up. 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. While comparing between two groups results showed means of serum uric acid and CRP were significantly decreased in treatment group compared to control group after 8th month. There was a positive correlation between Uric Acid with CRP level after 8 month of allopurinol treatment although this finding was not statistically significant. So, allopurinol may have a protective role in CKD by decreasing serum uric acid level and reduction of inflammatory response in patients with chronic kidney disease stage 3 - 5 with asymptomatic hyperuricaemia.

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Introduction

The prevalence of chronic kidney disease (CKD) is rapidly increasing worldwide. In the United States, recent data from the National Health and Nutrition Examination Survey (NHANES) estimate the prevalence of CKD to be 9.6% in non institutionalized adults, corresponding to approximately 19 million people. Population-based studies on the prevalence of kidney damage are limited in developing countries. There are only some few studies in Bangladesh showed an alarmingly high prevalence of CKD particularly CKD associated with insulin resistance in middle-income, urban Bangladeshis (Anand et al. 2014).In patients with renal disease, there is decreased uric acid (UA) urinary excretion, and whether this will give rise to hyperuricaemia depends on the gastrointestinal excretory compensation (Goicoechea et al., 2010). Chronic hyperuricaemia would stimulate the renin-angiotensin system and inhibit release of endothelial nitric oxide, contributing to renal vasoconstriction and increasing BP, at the same time, high levels of uric acid may have a pathogenetic role in interstitial inflammation

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and progression of renal disease (Feig et al., 2008; Johnson et al., 2003). 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., 2007and Sui et al., 2006), C-reactive protein (CRP) levels (Goicoechea et al., 2010 and Kanbay et al., 2007) and endothelial dysfunction (Mercuro G et al., 2004). However, there is increasing evidence that hyperuricaemia may not be completely benign and it is still unknown whether treatment of 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). A correlation of CRP, a marker of subclinical inflammation related to atherosclerosis, and serum UA levels has been described in a recent study by Ruggiero et al (2006). In their study they found a significant independent association has been found between uric acid and inflammatory markers, such as a white blood cell count, CRP, interleukins, and TNF levels. There are very few data regarding the effect of allopurinol treatment on the inflammatory markers in CKD stage 3, stage 4 and stage 5 patients. In a recent study by Goicoechea et al.(2010) showed that allopurinol treatment decreases CRP levels, slows the progression of renal disease, decreases the number of hospitalizations and reduces cardiovascular risk.

The current study had been designed to see the effect of allopurinol treatment on inflammatory markers 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 and inflammatory response and thus slowing the progression of renal function.

Hypothesis

Allopurinol may reduce the inflammatory response in patients with chronic kidney disease stage 3 - 5 with asymptomatic hyperuricaemia.

Objectives

General objectives:

To evaluate the effect of allopurinol on inflammatory markers such as CRP and ESR in patients with chronic kidney disease (stage 3-5) with asymptomatic hyperuricaemia.

Specific objectives:

1. To evaluate the effect of allopurinol in reduction of hyperuricaemia
2. To assess the association between decreased uric acid level and blood pressure
3. To identify the effect of allopurinol on other clinical parameters such as Haemoglobin and HbA1c.
4. 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 ;

3) Patients already on uric acid lowering drugs and 4) Patients having leukocytosis, raised ESR or CRP

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.
- To determine the effect of allopurinol on inflammatory markers ESR and CRP were measured at baseline and at 4 and 8 months of treatment.
- Serum uric acid was measured similarly to see the effect of allopurinol on asymptomatic hyperuricaemic patients.
- 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.

In present study mean age was 49 (±9) years in treatment group and 45 (±11) years in control group. (table i). Male were predominant in both group. In the study 68(56.67%) were male and 52(43.3%) were female. (Fig 1)

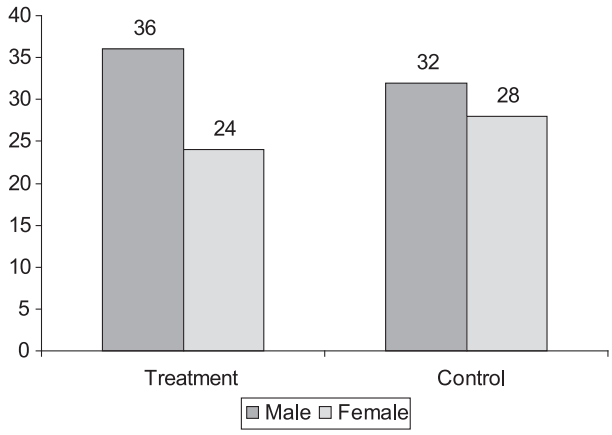

Fig.-1: *Sex distribution of the study population*

Figure 1 shows that by sex male were predominant in both groups. 68 (56.67%) were male and 52 (43.3%) were female.

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 2)

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 II).

Table I

Age distribution of the study population

	Group		p
	Treatment Mean ±SD n=60	Control Mean ±SD n=60	value
Age in years	49 (±9)	45 (±11)	0.06

Table I shows that mean age is 49 (±9) years in treatment group and 45 (±11) years in control group. There is no significant difference in age between two groups.

Table II

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 II 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 (Table III).

Table III

CKD stage of the study population

CKD stage	Group		Total	P
	Treatment	Control		value
Stage 3	06(10%)	10(16.67%)	16(13%)	
Stage 4	36(60%)	33(55.0%)	69(57%)	0.56
Stage 5	18(30%)	17(28.33%)	35(30%)	
Total	60	60		

Table III shows CKD stages of the patients. At CKD stage 3 , 06(10%) were in treatment group and 10(16.67%) were in control group, At stage 4, 36(60%) were in treatment group and 33(55%) were in control group, At 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: IV)

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 v). 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 VII)

Effect of allopurinol on UA level and inflammatory markers in CKD patients with hyperuricaemia:

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 between baseline mean ESR with 4th month and 8th month mean ESR. But mean CRP significantly reduced from baseline at 4th month and 8th month (p<0.001) (table VI). **In case of control group,** significant difference was found in case of mean serum uric acid at 4th month and 8th month (p<0.001) follow up. No significant difference was found

Table IV

Base line characteristics of the study population

	Study group		
	Treatmentn=60	Controln=60	p value
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 uric acid(mg/dl)	8.15 (±1.17)	7.49(±0.85)	0.22
Hb(gm/dl)	9.04 (±0.68)	9.21(±0.59)	0.15
HbA1c(%)	5.33 (±1.36)	5.55 (±1.31)	0.36
ESR(mm/hr)	19.68 (±6.70)	17.63(±4.98)	0.06
CRP(mg/L)	3.98(±0.85)	3.74(±1.10)	0.18
antihypertensive user(other than RAAS blocker)	45(75.0%)	44(73.3%)	1.0

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

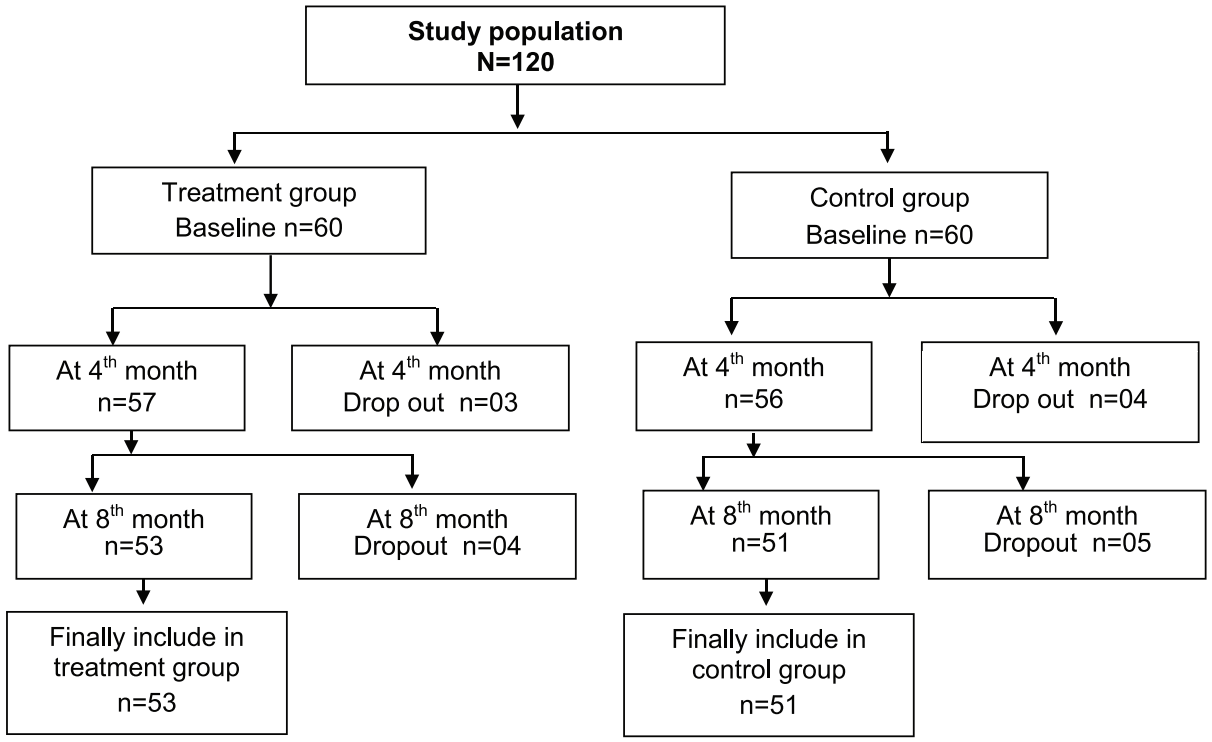

Figure 2 : *Flow chart of the patient distribution of the study population*

between baseline mean ESR and means ESR of 4th month and 8th month. But significantly increased mean CRP was seen from baseline with 4th month and 8th month mean CRP ($p<0.001$) (table VIII)

Comparison between two groups shows significant difference between means of serum uric acid and Hb at 8th month between treatment group and control group ($p<0.05$). (table IX)

CKD stage wise comparison shows significant difference in case of CRP and serum uric acid at 8th month between treatment group and control group in all the stages of CKD ($p<0.05$). (table X,XI,XII)

Treatment group:

Table VI

Effect of Allopurinol on clinical parameters in treatment group

	Baseline Mean (±SD)	At 4th month Mean (±SD)	p value	Baseline Mean (±SD)	At 8th 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 V 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 VI

Effect of allopurinol on UA level and Inflammatory markers in treatment group:

	Baseline Mean (±SD)	At 4th month Mean (±SD)	p value	Baseline Mean (±SD)	At 8th 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
ESR	18.85 (±5.57)	18.78(±5.34)	0.82	18.22(±4.76)	17.67(±4.31)	0.25
CRP	4.0 (±0.86)	3.27(±0.92)	<0.001	4.0 (±0.86)	2.83 (±0.85)	<0.001

(S.uric acid and CRP values are showing in mg/dl and ESR was measured in mm at 1st hour) ; Paired Samples t Test was done

Table VI shows effect of allopurinol on UA level and inflammatory markers 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 between baseline mean ESR with 4th month and 8th month mean ESR. But mean CRP significantly reduced from baseline at 4th month and 8th month (p<0.001).

Control group

Table VII

Clinical parameters in control group:

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

UA levels and renal function and progression of CKD in control group:

	Baseline Mean (±SD)	At 4th month Mean (±SD)	p value	Baseline Mean (±SD)	At 8th month Mean (±SD)	p value
S. Uric acid	7.46(±0.87)	7.77(±0.82)	<0.001	7.53(±0.84)	8.26(±1.06)	<0.001
ESR	17.67(±4.96)	18.21(±4.30)	0.22	17.54(±4.64)	18.23(±3.93)	0.25
CRP	3.76 (±1.14)	4.00(±1.07)	0.003	3.73(±1.16)	4.34(±1.06)	<0.001

(S.uric acid and CRP values are showing in mg/dl and ESR was measured in mm at 1st hour) ; Paired Samples t Test was done

Table VIII shows UA level and inflammatory markers in control group , significant difference was found in case of mean serum uric acid at 4th month and 8th month (p<0.001) follow up. No significant difference was found between baseline mean ESR and means ESR of 4th month and 8th month. But significantly increased mean CRP was seen from baseline with 4th month and 8th month mean CRP (p<0.001).

Table IX

Comparison between two groups at the end of 8th month

At 8th month	Study group		
	Treatment(mean±SD)	Control(mean±SD)	p value
SBP(mm of Hg)	139.50 (±10.37)	133.70(±10.59)	0.56
DBP(mm of Hg)	84.58 (±4.78)	82.75(±4.71)	0.07
S. uric acid (mg/dl)	6.0(±0.85)	8.26(±1.06)	<0.001
Hb(g/dl)	9.11(±0.61)	8.67(±0.70)	<0.001
HbA1C(%)	5.35 (±1.37)	5.58 (±1.44)	0.39
ESR(mm/hr)	17.67(±4.31)	18.23(±3.93)	0.49
CRP(mg/L)	2.83(±0.85)	4.34(±1.06)	<0.001

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

Table X

Stage wise Comparison between two group at the end of 8th month

At 8th month	CKD Stage 3				p value
	Treatment(mean±SD)		Control(mean±SD)		
SBP(mm of Hg)	130.33	(±12.36)	120.33	(±0.81)	0.07
DBP (mm of Hg)	83.33	(±4.08)	78.83	(±2.04)	0.06
Hb (g/dl)	8.72	(±0.31)	8.28	(±0.34)	0.04
HbA1c(%)	6.13	(±1.95)	4.83	(±0.78)	1.61
ESR(mm/hr)	18.83	(±3.31)	21.66	(±5.42)	0.30
CRP(mg/l)	3.12	(±0.86)	5.21	(±0.54)	0.000
UricAcid(mg/dl)	5.28	(±0.61)	8.51	(±2.00)	0.004

Table X shows significant difference between means of Hb, CRP and serum uric acid at 8th month between treatment group and control group in CKD stage 3 (p<0.05).

Table XI

Stage wise Comparison between two groups at the end of 8th month

At 8th month	CKD Stage -4				p value
	Treatment (mean±SD)		Control (mean±SD)		
SBP(mm of Hg)	139.35	(±9.26)	134.93	(±9.02)	0.06
DBP (mm of Hg)	84.07	(±4.50)	82.21	(±3.21)	0.06
Hb (g/dl)	9.33	(±0.42)	8.72	(±0.68)	0.000
HbA1c(%)	5.19	(±1.30)	5.76	(±1.48)	0.08
ESR(mm/hr)	17.45	(±4.36)	17.84	(±2.94)	0.66
CRP(mg/l)	2.83	(±0.84)	4.17	(±1.17)	0.000
UricAcid(mg/dl)	6.19	(±0.85)	8.19	(±0.90)	0.000

Table XI shows significant difference between means of Hb, CRP and serum uric acid at 8th month between treatment group and control group in CKD stage 4 (p<0.05).

Table XII

Stage wise Comparison between two groups at the end of 8th month

	CKD Stage 5				
At 8th month	Treatment(mean±SD)		Control(mean±SD)		**p value**
SBP(mm of Hg)	148.28	(±8.59)	136.84	(12.35)	0.06
DBP (mm of Hg)	88.57	(±5.56)	85.76	(±6.77)	0.36
Hb (g/dl)	8.20	(±0.76)	8.74	(±0.84)	0.17
HbA1c(%)	5.60	(±1.11)	5.56	(±1.58)	0.96
ESR(mm/hr)	18.00	(±5.16)	17.61	(±4.82)	0.87
CRP(mg/l)	2.58	(±0.95)	4.38	(±0.72)	0.000
UricAcid(mg/dl)	5.51	(±0.44)	8.33	(±0.93)	0.000

Table XII shows significant difference between means of CRP and serum uric acid at 8th month between treatment group and control group in patients with CKD stage 5 (p<0.05).

p value0.06
R value 0.25,
Pearson Correlation 0.25

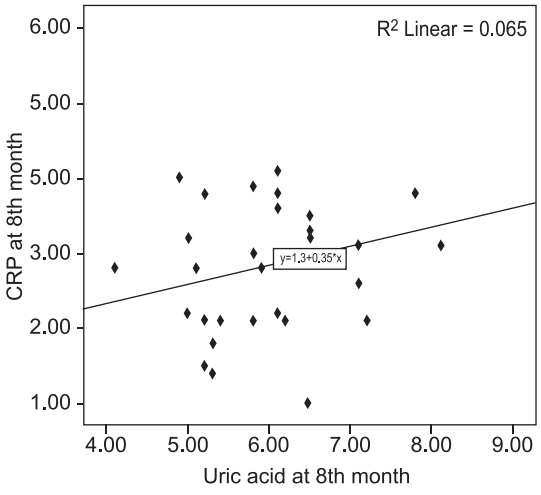

Figure 3 : Correlation between Uric Acid at 8th month with CRP at 8th month in treatment group

Figure 3 showing positive Pearson correlation (r=0.25; p=0.06) between Uric Acid at 8th month with CRP level at 8th month in treatment group but not statistically significant.

P value 0.974

R value 0.005

Pearson Correlation 0.005

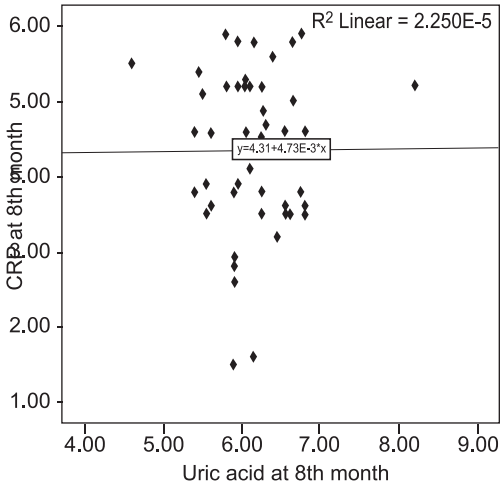

Figure 4 : Correlation between Uric Acid at 8th month with CRP at 8th month in control group

Figure showing positive Pearson correlation (r=0.97; p=0.005) between Uric Acid at 8th month with CRP level 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 as per inclusion and exclusion criteria. There were no significant difference in baseline characteristics between treatment group and control group (p>0.05).

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. Compared with study of Goicoechea M et al. (2010) , mean age were 71.4 (±9.5) years in control group and 72.1(±7.9) years were in treatment group. De Cosmo et al. (2015) study shows the mean age was 64.61 years, 56.0% of patients were male.

Most studies reported that the majority of patients were male, with males being a minority in only three studies (Siu et al., 2006; Atzori et al., 2012; and Lee et al., 2008) For studies that included a control group, (Goicoechea et al., 2010; Shi et al.,2012; Siu et al.,2006; Tassaneeyakul et al.,2009) the proportion of males was well balanced in both arms in only two (Goicoechea et al.,2010; Stamp et al.,2012). The majority of studies had a greater proportion of males in the control group (Siu et al., 2006; Atzori et al., 2012; Lee et al.,2008) than the allopurinol group (Shi et al.,2012).

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. Ahmed et al. (2012) found similar etiological distribution in a study on patients of chronic kidney disease.

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.

In present study, no significant change was found in case of both systolic and diastolic blood pressure in treatment group at 4^{th} and 8^{th} 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 case of Hb and HbA1c, no significant differences were found in treatment group at 4th month and 8^{th} month follow up ($p>0.05$) from the baseline. In control group no significant difference was found between baseline Hb (9.26±0.53) and 4^{th} month (9.20±0.51) but significant difference was found between baseline Hb (9.26±0.54) and 8^{th} month Hb (8.67±0.70) ($p <0.05$). Mean Hb was significantly decreased at the end of 8^{th} month. No significant difference was seen from the baseline in case of HbA1c both at 4^{th} and 8th month follow up in this group.

To determine the effect of allopurinol on inflammatory markers ESR and CRP were analyzed after 4^{th} and 8^{th} month with their baseline in treatment group. In case of ESR no significant difference was found in treatment group between baseline with 4^{th} month and 8^{th} month follow up ($p>0.05$). Similar result was found in control group. Mean CRP was significantly decreased in treatment group from the baseline (4.0±0.86) both at 4^{th} (3.27±0.92) and 8^{th} month of follow up (2.83±0.85) ($p<0.001$). On the other hand in control group CRP was significantly raised from the baseline (3.76±1.14) at 4^{th} month (4.0±1.07) and also from the baseline (3.73±1.16) at 8^{th} month follow up (4.34±1.06) ($p<0.001$).

In present study, effect of allopurinol on UA level was tried to determine. In treatment group, significant difference was found in case of serum uric acid between baseline (8.14±1.16) and at 4^{th} month follow up (7.01±0.76) and between baseline (8.14±1.17) and at 8^{th} month follow up (6.00±0.85) ($p<0.001$). Serum uric acid was significantly decreased after 8^{th} month of treatment.

In control group, significant difference was found in case of serum uric acid between baseline and at 4th month and also between baseline and at 8th month of follow up (p<0.001). Serum uric acid was significantly increased after 8th month of follow up.

Goicoechea et al. demonstrated almost similar result in their study. Similarly, in the J-HEALTH study (Ito et al.2012), which included 7629 subjects, a change in the eGFR was (negatively) correlated with a change in the serum uric acid level and associated with less cardiovascular events.

In comparison between two groups at 4th month of follow up no significant differences were found in case of ESR, Hb and HbA1c. But serum uric acid and CRP were significantly decreased at 4th month in treatment group compared to control group. 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 ESR and HbA1c in between two groups at 8th month of follow up. But serum uric acid and CRP were 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 ±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 study of Goicoechea et al. (2010) ,CRP median levels decreased significantly after 12 months of allopurinol treatment (from 4.4 mg/L to 3.0 mg/L) (*P* = 0.04 in comparison to baseline values), whereas the control group remained unchanged in the follow-up period (from 3.4 to 3.2 mg/L).

CKD stage wise comparison between two groups at the end of 8th month follow up shows, no significant change considering Hb in stage 5 but significant decrease of Hb was seen in control group at CKD stage 3 and stage 4. No significant changes were found in case of ESR and HbA1c at any stage of CKD at the end of 8th month between two groups. No significant changes were also found in case of SBP and DBP at any stages of CKD. Serum uric acid and CRP were significantly decreased in treatment group at all the stages of CKD at the end of 8th month. Siu et al. (2006) reported that allopurinol therapy slowed renal disease progression in hyperuricaemic subjects with modest (stage 3) CKD at 1 year compared with randomized controls.

A positive correlation between Uric Acid at 8th month with CRP level at 8th month in treatment group was found in the present study (*Correlation coefficient 0.25 and R= 0.25*) but this was not statistically significant (p=0.06) Positive correlation also found between Uric Acid at 8th month with CRP level at 8th month in control group (*Correlation coefficient 0.005 and R= 0.005*) but it was statistically insignificant (p= 0.97).

A correlation of CRP, a marker of subclinical inflammation related to atherosclerosis, and serum UA levels has been described in the study of Ruggiero et al., 2006. In their study they also found a significant independent association between UA and inflammatory markers, such as CRP (Khosla et al., 2005). In this present study result shows that allopurinol decreases uric acid and thus CRP levels at the end of 8th month after compared with the control group.

Multiple studies have demonstrated that uric acid is a potential causative agent of worsening renal function. Over the course of a large volume of literature review, Christin Giordano et al. (2015) have demonstrated that uric acid does indeed affect endothelial function and can contribute to worsening renal disease. Although there is lack of evidence of treating asymptomatic hyperuricaemia , allopurinol may play a role in reducing uric acid and inflammatory marker like CRP and thus retard the further deterioration of renal function.

Conclusion

Allopurinol may have a role in reduction of inflammatory marker CRP. So, allopurinol may have a protective role on renal function by decreasing serum uric acid level and reduction of inflammatory response 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 of our study may be limited by the concomitant use of statins, antiplatelet, and renin-angiotensin-aldosterone system (RAAS) blocker drugs.

Recommendadtions

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

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