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Research Article

COMPARISON BETWEEN RENOPROTECTIVE EFFECTS OF FEBUXOSTAT AND ALLOPURINOL IN CHRONIC KIDNEY DISEASE PATIENTS WITH HYPERURICEMIA

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ABSTRACT

Objective: The objective of the study was to compare the renoprotective effects of febuxostat versus allopurinol in chronic kidney disease patients with hyperuricemia.

Methods: One hundred and ten patients were divided randomly into two equal groups: group F (febuxostat) and group A (allopurinol). Group F patients received tablet febuxostat 40 mg OD for 4 months and group A patients received tablet allopurinol 100 mg TDS for 4 months. Following parameters such as estimated glomerular filtration (eGFR) assessment, serum creatinine, serum uric acid (SUA), total serum protein, urine creatinine, urine protein, blood urea, and number of dialysis were carried out and repeated at the end of 1st–4th month to check for the effect of the test drugs on the status of kidney function.

Observations: Febuxostat caused more rise in eGFR than allopurinol. Meanwhile, the number of patients with eGFR ≤15/mL/min/1.73 m^2 showed no difference between the groups. No patient showed >10% decrease in the eGFR values. Febuxostat showed more decline in SUA levels than allopurinol, although the number of patients reaching the target SUA levels was the same in both groups. Febuxostat led to a more reduction in serum creatinine levels than allopurinol. Urine creatinine and urine albumin levels decline were associated more with febuxostat. No remarkable difference in comparison of both the groups in terms of total serum protein and serum globulin, although a significant rise was seen with febuxostat in serum albumin levels. Both drugs had a similar sequel in declining blood urea nitrogen levels. No discernible difference in the number of dialysis sessions needed by patients in the previous month was seen in the study groups.

Conclusion: The present study concluded that febuxostat appears to be a better alternative to allopurinol for chronic kidney disease patients with hyperuricemia. Febuxostat has a superior renoprotective effect than allopurinol.

Keywords: Chronic kidney disease, Hyperuricemia, Febuxostat, Allopurinol, Renoprotective.

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INTRODUCTION

Chronic kidney disease (CKD) has a significant impact on the patient population and the health-care system. Owing to its multi-factorial etiology, it is extremely challenging to identify and address just all the contributing factors. Hyperuricemia is one of the most unappreciated and independent risk factors of CKD. It is elevated serum uric acid (SUA) levels in the blood. Uric acid is the end product of purine metabolism in humans. According to recent studies, hyperuricemia independently predicts the development of CKD [1]. It is now confirmed that SUA level rises in parallel with the estimated glomerular filtration (eGFR) rate decline. Urate-lowering therapies include uricosuric drugs such as probenecid, benzbromarone, and lesinurad. These drugs act by preventing the reuptake of uric acid by the proximal convoluted tubule, primarily through inhibition of the human urate-1 transporter (URAT1) thus increasing the excretion of uric acid. In lieu of these drugs, xanthine oxidase inhibitors (XOIs) act by inhibiting the xanthine oxidase production which ultimately decreases the uric acid production. Uric acid-lowering drugs reduce oxidative stress and lower the inflammation caused by an accumulation of urate crystals [2]. Thus, curbing hyperuricemia with XOIs may assist in regression or even arrest the progression of CKD [3]. The most commonly used XOI is allopurinol, which is an analog of hypoxanthine and xanthine; it competes with these molecules in binding xanthine oxidase and inhibits the formation of uric acid. Another is febuxostat, which non-selectively inhibits oxidized and reduced forms of xanthine oxidase [2]. Hence, we conducted this study to compare the renoprotective effects of febuxostat and allopurinol in CKD patients with hyperuricemia.

METHODS

This was a prospective, randomized controlled, and open-label clinical study. Institutional ethics committee approval was taken before starting the study. Newly diagnosed 110 patients of CKD with hyperuricemia of either sex, 18 years and above were taken. All the patients of CKD were of stage G3a to G5 (according to kidney disease improving global outcomes) [4]. Patients who had a history of hypersensitivity to any of the study drugs or any contraindication to any of the studies, pregnant and breast-feeding females, patients on other urate-lowering therapy, and patients with acute kidney injury were excluded from the study. The eligible patients were randomly divided into two study groups, that is, group F (febuxostat) and group A (allopurinol) based on a computer-generated randomized scheme. Fifty-five patients in each group were allotted. Group F patients received tablet febuxostat 40 mg OD for 4 months and group A patients received tablet allopurinol 100 mg TDS for 4 months. After the baseline investigations and starting the drug treatment, the patients were followed up at the end of the 1st–4th months. At the time of follow-up, all the relevant investigations were again carried out to check for the effect of the test drugs on the status of kidney function by the efficacy parameters. The mean and standard deviation of the readings were calculated at baseline and follow-up intervals of 1–4 months. The scores were compared for intergroup and intragroup analysis for each of the following efficacy parameters.

RESULTS

Participants

A total of 200 patients were screened out of which 51 patients did not meet the inclusion and exclusion criteria, 24 patients declined

to participate, 15 patients were lost to follow-up, and 110 patients completed the study. The mean age of the patients in both groups was comparable 45.25±11.51 years in group F and 44.87±13.08 years in group A. The number of females was 18 and 30 in group F and group A, respectively. The number of males was 37 and 25 in group F and group A, respectively.

eGFR

At the end of the 3rd and 4th month of our study, the eGFR and mean change in eGFR from baseline was significantly greater in group F than in group A as shown in Table 1. The number of patients with an eGFR of ≤15ml/min/1.73 m^2 analysis revealed no statistically significant difference between the two study groups. During the study, the number of patients who experienced a >10% fall in eGFR (kidney event) from baseline was also assessed. We discovered that neither study group contained any such individuals.

Serum uric acid

SUA levels were significantly higher in group A than in group F at all follow-up intervals of our study. The mean change in SUA from baseline was significant only at the end of the 4th month in group F as shown in Table 2. When the number of patients reaching the target SUA level of <6 mg/dL was compared between groups F and A, no significant difference was observed during the study.

Serum creatinine

In our study, serum creatinine levels when compared between group F and group A showed a significant difference at the end of 4th month which was significantly higher in group A as shown in Fig. 1. No patient in both group showed doubling of serum creatinine levels (kidney event) from the baseline during the study.

Urine protein and creatinine assessment

The values of urine creatinine levels on intergroup analysis were significantly higher in group A only at the end of 4th month as compared to group F. In our study, mean urinary albumin levels on intergroup analysis at 4th month were significantly higher in group A. The mean urinary albumin creatinine ratio (ACR) values on intergroup comparison were significantly higher in group A at the end of 4th month as shown in Table 3.

Serum protein assessment

No significant difference was seen in serum protein levels at any time interval of the study. Mean serum albumin levels showed a significant difference only at the end of 4th month. No significant difference was seen in the mean serum globulin levels and mean albumin globulin ratio between the groups at any time interval of the study as shown in Table 4.

Blood urea

Blood urea assessment showed no significant difference at any time interval of the study between group F and group A as shown in Fig. 2.

Number of dialysis required in prior month

The number of dialysis required in the prior month by patients showed no significant difference in the values seen on intergroup analysis at any point of the study in any of the groups.

Table 1: eGFR assessment

(Mean±SD)	Mean eGFR of patients		Mean change in the eGFR from the baseline	
	Group F (mL/min/1.73 m^2)	Group A (mL/min/1.73 m^2)	Group F (mL/min/1.73 m^2)	Group A (mL/min/1.73 m^2)
Baseline	23.10±5.23	22.85±4.30	_____	_____
End of 1st Month	24.15±4.01	23.78±3.11	1.74±1.63	1.55±1.40
End of 2nd Month	25.26±5.34#	24.86±6.43#	2.86±2.66#	2.63±1.64#
End of 3rd Month	26.08±3.77#	25.54±7.78#	4.67±1.83##*	3.32±2.02##
End of 4th Month	30.15±6.23##*	27.04±4.22##	8.75±2.47##*	4.81±2.03##

*Indicates a significant difference between the groups (p≤0.05), #Indicates significant difference as compared to the baseline value (p≤0.05), ##Indicates highly significant difference as compared to the baseline value (p≤0.001), eGFR: Estimated glomerular filtration, SD: Standard deviation

Table 2: Serum uric acid assessment

(Mean±SD)	Mean SUA levels		Mean change in SUA from the baseline	
	Group F (mg/dL)	Group A (mg/dL)	Group F (mg/dL)	Group A (mg/dL)
Baseline	10.23±2.79	10.47±2.21	_____	_____
End of 1st Month	8.84±1.75#	9.34±1.81#*	0.51±0.75	0.74±1.3
End of 2nd Month	8.09±1.69#	8.83±1.70#*	0.93±0.89	0.81±1.01
End of 3rd Month	7.94±2.13##	8.53±1.63##*	2.10±0.82#*	1.99±1.06#
End of 4th Month	7.07±1.16##	7.61±1.24##*	3.1±1.2##*	2.30±1.05##

*Indicates significant difference between the groups (p≤0.05), #Indicates significant difference as compared to the baseline value (p≤0.05), ##Indicates highly significant difference as compared to the baseline value (p≤0.001). SUA: Serum uric acid, SD: Standard deviation

Table 3: Urine protein and creatinine assessment

(Mean±SD)	Urinary albumin levels		Urinary creatinine levels		Urinary ACR	
	Group F (mg/day)	Group A (mg/day)	Group F (mg/day)	Group A (mg/day)	Group F (µg/mg creatinine)	Group A (µg/mg creatinine)
Baseline	284.73±87.98	283.45±92	644.27±219.28	650.82±173.28	545.40±226.03	550.84±246.89
End of 1st Month	266.09±91.13	271.09±87.38	611.55±228.14	622.93±190	473.65±221.05##	490.04±242.82##
End of 2nd Month	255.55±8662##	262.64±8611##	587.82±229.50#	603.44±196.44#	441.13±200.57##	464.44±228.12##
End of 3rd Month	232.91±85.38##	246.73±87.01##	575.64±234.44##	592.56±193.23##	418.33±248.92##	443.24±216.71##
End of 4th Month	214.91±81.48##	238.73±85.53##*	543.18±247.65##	566.27±216.12##	367.33±173.67##	410.80±203.90##

*Indicates significant difference between the groups (p≤0.05), #Indicates significant difference as compared to the baseline value (p≤0.05), ##Indicates highly significant difference as compared to the baseline value (p≤0.001). ACR: Albumin creatinine ratio, SD: Standard deviation

Table 4: Serum protein assessment

(Mean±SD)	Total serum protein levels		Serum albumin levels		Serum globulin levels		Serum albumin globulin ratio	
	Group F (g/dL)	Group A (g/dL)	Group F (g/dL)	Group A (g/dL)	Group F (g/dL)	Group A (g/dL)	Group F	Group A
Baseline	5.95±1.10	5.92±1.32	2.79±0.54	2.64±0.61	3.17±0.80	3.28±0.94	0.69±0.79	0.73±0.33
End of 1st Month	6.04±1.08	6.08±1.27	2.87±0.49	2.74±0.58	3.20±0.76	3.35±0.92	0.73±0.69	0.74±0.33
End of 2nd Month	6.19±1.12	6.21±1.32	2.93±0.42	2.77±0.53	3.26±0.79	3.44±0.95	0.74±0.69	0.75±0.38
End of 3rd Month	6.26±1.08#	6.27±1.33#	3.01±0.51#	2.83±0.59	3.27±0.78	3.45±0.94	0.80±0.44#	0.78±0.36#
End of 4th Month	6.40±1.02##	6.41±1.30##	3.08±0.44###*	2.89±0.53##	3.31±0.74	3.50±0.95#	0.80±0.91#	0.78±0.32#

*Indicates significant difference between the groups (p≤0.05), #Indicates significant difference as compared to the baseline value (p≤0.05), ##Indicates highly significant difference as compared to the baseline value (p≤0.001). SD: Standard deviation

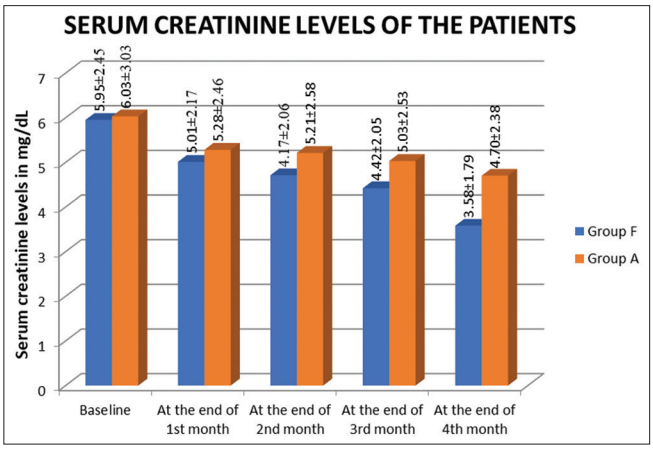

Fig. 1: Serum creatinine assessment

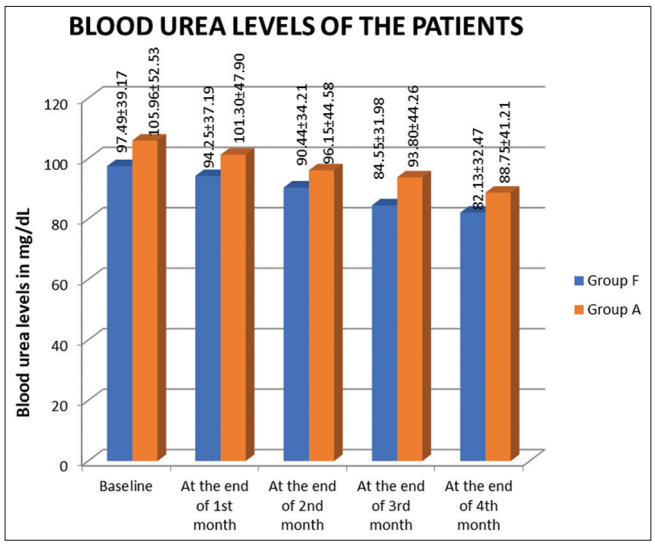

Fig. 2: Blood urea assessment

DISCUSSION

In both groups, eGFR levels increased progressively from the start to the end of the study period, according to our findings, but group F had higher mean eGFR levels than group A. In our study, we discovered that the mean change in eGFR readings from baseline increased significantly in both groups. Furthermore, the number of patients with eGFR 15/mL/min/1.73 m^2 revealed no statistically significant results at any point during the study. No patient showed more than a 10% decrease in the eGFR values from the baseline in both the groups at all the time intervals and the end of the study. This indicates that both drugs improve the patient's renal status, with febuxostat improving more than allopurinol. Similar results were obtained by Liu *et al*. in 2018 in which they found that in the febuxostat group, there was an increase in eGFR whereas worsening of eGFR was seen in the allopurinol group, by the end of 6 months [5]. Lee and Lee in 2018 also found similar results in patients who received febuxostat, they maintained significantly higher mean eGFR values than patients who received allopurinol and these values were consistent for over 4 years [6]. Contraindicating results to our study were observed by Kimura *et al*. in 2018 which stated that there was no significant difference in mean eGFR between febuxostat and placebo at the end of 108 weeks. However, there was one major limitation that was only stage 3 CKD patients were enrolled in this study [7]. A recent retrospective study by Park *et al*. in 2022 concluded that allopurinol has a superior effect in controlling the decline of eGFR value as compared to febuxostat [8]. Sircar *et al*. in 2015 found that >10% decline in eGFR value from the baseline values was not significant in the febuxostat group during a 6-month trial [9]. Sakai *et al*. in 2013 observed that during febuxostat treatment the increase of eGFR after 6 months was significant. However, number of patients having eGFR <15/ml/min/1.73 m^2 remained the same after 6 month [10].

We discovered a significant progressive reduction in SUA levels in both study groups at all study intervals. However, the decline was more significant in group F. We also observed that the difference in number of patients reaching the target SUA level of <6 mg/dL was non-significant when we compared both the study groups. Thus, our study concluded that febuxostat has superior urate-lowering action as compared to allopurinol in CKD patients. Our findings were corroborated by the study conducted by Peng *et al*. in 2020 which revealed that a decrease in SUA level was significantly more in febuxostat compared to allopurinol. They also observed that febuxostat was associated with a higher rate of patients maintaining SUA <6 mg/dL [11]. Liu *et al*. also concluded that the serum uric-lowering effect was significantly greater in the febuxostat group as compared to allopurinol and a significant difference was observed in a number of patients reaching target SUA level <6 mg/dL in the febuxostat group at 6-month follow-up [5]. Lee and Lee in 2019 also concluded that febuxostat seems to reduce SUA levels more effectively than allopurinol which seems to retards renal disease progression [6].

In our study, we observed that febuxostat led to a greater decline in serum creatinine levels than allopurinol. Interestingly, no patient showed a doubling of serum creatinine from the baseline (kidney event) in the study groups. Our results were corroborated by a study done by Kimura *et al*. in 2018 in which a significant reduction in serum creatinine levels was observed in febuxostat-treated patients. Although there were 2 incidences of kidney event (doubling of serum creatinine from the baseline) in febuxostat and placebo groups each [7]. Another study done by Sarvepalli *et al*. in 2018 observed that there was a significant decrease in mean serum creatinine levels from the baseline at the end of 6 months in the febuxostat group [12]. Thus, our findings corroborated with the findings of other studies in terms of lowering serum creatinine levels. However, none of these studies compared febuxostat and allopurinol.

In our study, urine creatinine levels showed a progressive decline although group F had significantly lower urine creatinine levels as

compared to group A. Similarly, a retrospective study conducted by Krishnamurthy *et al*. in 2017 concluded that the allopurinol-treated group had a lower final urine creatinine level than placebo [13]. A meta-analysis done by Zheng *et al*., in 2022, concluded that patients with CKD and hyperuricemia who received febuxostat had lower urine creatinine compared with placebo [14].

In our study, urinary albumin levels showed a highly significant decline in both study groups. However, the intergroup analysis showed a significant lower albuminuria in group F. Urinary ACR showed a statistically significant decrease in group F. Liu *et al*. in 2018 concluded that there is a significant reduction in urinary albumin levels in the febuxostat than allopurinol group. This finding is suggestive of the possibility of a more renoprotective effect of febuxostat than allopurinol. These findings were hence similar to our study [5]. Contradicting results were found by Badve *et al*. in 2020 in which they observed that there was no significant difference in urinary albumin creatinine ratio [15]. Lee and Lee in 2019 observed that differences in urinary albumin levels were insignificant between both the groups [6].

In serum protein assessment, total mean serum protein levels showed a significant rise as compared to the baseline in both groups, although no significant change was observed between both the study groups. The mean serum albumin levels showed more significant rise in group F. The mean serum globulin levels and albumin globulin ratio (AGR) showed no significant difference between both the study groups. To the best of our knowledge, after going through extensive literature thoroughly no study was found that compared febuxostat and allopurinol in CKD patients with hyperuricemia in terms of total serum protein, serum albumin, serum globulin, and serum albumin ratio. It has been recently established that lower serum albumin levels are strongly and independently associated with kidney function decline [16]. Apart from serum albumin, serum AGR has also emerged as a novel prognostic indicator of CKD [17]. Low levels of serum albumin and serum globulin directly correlate with decline in kidney function in CKD. Thus, rise in such levels would be indicative of renoprotective action, as is observed in our study.

Mean blood urea levels showed no statistically significant difference between group F and group A at any time interval of the study. A recent meta-analysis done by Zheng and Sun in 2022 concluded that the serum urea nitrogen of the febuxostat group was significantly lower than the placebo group [14]. A retrospective study done by Huda *et al.* in 2021 on the effect of allopurinol on blood urea nitrogen (BUN) in patients with CKD concluded that allopurinol effectively reduced the BUN levels during the study period of 1 year [18]. However, in the above studies, the efficacy parameter is BUN which differs from our study's efficacy parameter which is blood urea. BUN measures the amount of urea nitrogen in the blood whereas blood urea measures the amount of urea in the blood. The BUN values are roughly one-half of the blood urea [19].

In our study, we observed the number of dialysis required by a patient in the prior month. No significant change was observed in the number of dialysis required by patients in prior month in both the study groups. To the best of our knowledge, no studies have been reported in the literature which compared the number of dialysis required by patients in the prior month in febuxostat and allopurinol in CKD patients with hyperuricemia.

CONCLUSION

The present study concluded that the drug febuxostat increases the eGFR values more effectively than allopurinol which points to the fact that febuxostat has a more renoprotective effect than drug allopurinol. Febuxostat also exerts much superior urate-lowering action than the drug allopurinol. Febuxostat is more effective in lowering serum creatinine levels and urine creatinine levels than allopurinol. More reduction in urinary albumin levels and urinary albumin creatinine ratio is seen with the use of the drug febuxostat than the drug allopurinol. Both the drugs increase total serum protein levels and serum globulin levels to similar extent, whereas serum albumin levels are increased more with the febuxostat group. Furthermore, both of the drugs decrease blood urea levels to a similar extent. The number of dialysis required in prior month by the patient is not affected by any of the drugs significantly. Both of these drugs are similar in terms of side effects.

Therefore, febuxostat has a better renoprotective effect than allopurinol. However, additional studies are required to further verify the renoprotective effects of febuxostat in CKD patients with hyperuricemia.

AUTHORS' CONTRIBUTIONS

Dr. Saksham Matta- The writer, collected the data, conceived, and designed the analysis. Dr. Garima Bhutani, Dr. Tarun Arora, and Dr. Renu Garg- Contributed to structure and designing the analysis, editing the article, and data collection. Dr. Seema Rani and Dr. Rahul Saini- assisted in the interpretation of data.

CONFLICTS OF INTEREST

The authors have no conflicts of interest.

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Nil.

REFERENCES

1. Kuwabara M, Niwa K, Hisatome I, Nakagawa T, Roncal-Jimenez CA, Andres-Hernando A, *et al*. Asymptomatic hyperuricemia without comorbidities predicts cardiometabolic diseases: Five-year Japanese Cohort Study. Hypertension 2017;69:1036-44. doi: 10.1161/HYPERTENSIONAHA.116.08998, PMID 28396536
2. Lee Y, Hwang J, Desai SH, Li X, Jenkins C, Kopp JB, *et al*. Efficacy of xanthine oxidase inhibitors in lowering serum uric acid in chronic kidney disease: A systematic review and meta-analysis. J Clin Med 2022;11:2468-72. doi: 10.3390/jcm11092468, PMID 35566594
3. Kielstein JT, Pontremoli R, Burnier M. Management of hyperuricemia in patients with chronic kidney disease: A focus on renal protection. Curr Hypertens Rep 2020;22:102. doi: 10.1007/s11906-020-01116-3, PMID 33128170
4. Chen TK, Knicely DH, Grams ME. Chronic kidney disease diagnosis and management: A review. JAMA Intern Med 2019;322:1294-304. doi: 10.1001/jama.2019.14745, PMID 31573641
5. Liu X, Wang H, Ma R, Shao L, Zhang W, Jiang W, *et al*. The urate-lowering efficacy and safety of febuxostat versus allopurinol in Chinese patients with asymptomatic hyperuricemia and with chronic kidney disease stages 3–5. Clin Exp Nephrol 2019;23:362-70. doi: 10.1007/s10157-018-1652-5, PMID 30291473
6. Lee JW, Lee KH. Comparison of renoprotective effects of febuxostat and allopurinol in hyperuricemic patients with chronic kidney disease. Int Urol Nephrol 2019;51:467-73. doi: 10.1007/s11255-018-2051-2, PMID 30604229
7. Kimura K, Hosoya T, Uchida S, Inaba M, Makino H, Maruyama S, *et al*. Febuxostat therapy for patients with stage 3 CKD and asymptomatic hyper uricemia: A randomized trial. Am J Kidney Dis 2018;72:798-810. doi: 10.1053/j.ajkd.2018.06.028, PMID 30177485
8. Park S, Lee JP, Kim DK, Kim YS, Lim CS. Superior effect of allopurinol compared to febuxostat on the retardation of chronic kidney disease progression. PLoS One 2022;17:e0264627. doi: 10.1371/journal.pone.0264627, PMID 35226683
9. Sircar D, Chatterjee S, Waikhom R, Golay V, Raychaudhury A, Chatterjee S, *et al*. Efficacy of febuxostat for slowing the GFR decline in patients with CKD and asymptomatic hyperuricemia: A 6-month, double blind, randomized, placebo-controlled trial. Am J Kidney Dis 2015;66:945-50. doi: 10.1053/j.ajkd.2015.05.017, PMID 26233732
10. Sakai Y, Otsuka T, Ohno D, Murasawa T, Sato N, Tsuruoka S. Febuxostat for treating allopurinol-resistant hyperuricemia in patients with chronic kidney disease. Ren Fail 2014;36:225-31. doi: 10.3109/0886022X.2013.844622, PMID 24152124
11. Peng YL, Tain YL, Lee CT, Yang YH, Huang YB, Wen YH, *et al*. Comparison of uric acid reduction and renal outcomes of febuxostat vs allopurinol in patients with chronic kidney disease. Sci Rep

2020;10:10734. doi: 10.1038/s41598-020-67026-1, PMID 32612180

12. Sarvepalli PS, Fatima M, Quadri AK, Taher AR, Habeeb A, Amreen F, *et al*. Study of therapeutic efficacy of febuxostat in chronic kidney disease Stage IIIA to stage VD. Saudi J Kidney Dis Transpl 2018;29:1050-6. doi: 10.4103/1319-2442.243953, PMID 30381500
13. Krishnamurthy A, Lazaro D, Stefanov DG, Blumenthal D, Gerber D, Patel S. The effect of allopurinol on renal function. J Clin Rheumatol 2017;23:1-5. doi: 10.1097/RHU.0000000000000480, PMID 28002149
14. Zheng Y, Sun J. Febuxostat improves uric acid levels and renal function in patients with chronic kidney disease and hyperuricemia: A meta-analysis. Appl Bionics Biomech 2022;2022:9704862.
15. Badve SV, Pascoe EM, Tiku A, Boudville N, Brown FG, Cass A, *et al*. Effects of allopurinol on the progression of chronic kidney disease. N Engl J Med 2020;382:2504-13. doi: 10.1056/NEJMoa1915833, PMID 32579811
16. Lang J, Katz R, Ix JH, Gutierrez OM, Peralta CA, Parikh CR, *et al*. Association of serum albumin levels with kidney function decline and incident chronic kidney disease in elders. Nephrol Dial Transplant 2018;33:986-92. doi: 10.1093/ndt/gfx229, PMID 28992097
17. Wu PP, Hsieh YP, Kor CT, Chiu PF. Association between albumin-globulin ratio and mortality in patients with chronic kidney disease. J Clin Med 2019;8:1990-1. doi: 10.3390/jcm8111991, PMID 31731708
18. Huda M, Pralampita PW, Agustina D, Abrori C, Wahyudi SS. The effect of allopurinol on blood urea nitrogen and creatinine serum levels in patients with chronic kidney disease. J Agromedicine 2021;7:8-15. doi: 10.19184/ams.v7i1.10928
19. Hosten AO, Walker KH, Hall WD. BUN and creatinine. In: National Center for Biotechnology Information. United States National Library of Medicine; 2022. Available from: https://pubmed.ncbi.nlm.nih.gov/21250147 [Last accessed on 2022 Nov 01].