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# Efficacy of Oral Febuxostat drug for Slowing the Glomerular Filtrate Rate Decline in Patients With Chronic Kidney Disease and Asymptomatic Hyperuricemia: A 6-Month, Single-Blind, Randomized, Placebo-Controlled Trial

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## ABSTRACT

**Introduction:** Hyperuricemia is considered as putative risk factor for progression of renal disease and febuxostat is used as an additional therapy for the control of lowering eGFR in CKD 3 and 4 patients.

**Objective:** To determine the effect of febuxostat on eGFR among patients with chronic renal failure and increased uric acid levels.

**Materials and Methods:** A single-Blind, RCT was conducted at Mayo Hospital, Lahore from 1st February, 2019 to 31st January, 2020. 330 Patients who full filled the inclusion criteria were enrolled. After the approval from Ethical Committee, written informed consent was taken and they were randomly divided into 2 groups. Group A patients received febuxostat 40 mg daily and group B received placebo with conventional therapy. Patients were evaluated for mean eGFR at the start, 3 and 6 months of treatment in both groups. Data was entered and analysed in SPSS ver: 21. Mean and standard deviation were calculated for numerical variables. Independent test was used to compare the means between the groups at baseline, 3 and 6 months with  $p < .05$  as statistical significant.

**Results:** In this study, efficacy was determined in terms of retardation in eGFR decline. At baseline and at 3rd month, no significant difference was found in eGFR in both groups however at 6th month mean eGFR was higher in Group A as compared to group B.

**Conclusion:** The study concluded that febuxostat is more efficacious in slowing of declining e-GFR in patients with CKD stage 3 and 4.

**Key Words:** Febuxostat, CKD, Hyperuricemia, renal failure Grade 3 – 4, renal insufficiency, GFR, Placebo

## INTRODUCTION

According to available research data, it is estimated that 13% of adult population is currently suffering from Chronic Kidney Disease (CKD), a value which is expected to increase in

future.<sup>1</sup> The main causative factor for this disease is Diabetic nephropathy. Pakistan Economic Survey 2005-06 declares, a total of 21 million people suffering from CKD stage 3 or 4.<sup>2,3</sup> Definition of Chronic renal failure by National Kidney Foundation is decrease in glomerular filtration rate (GFR)

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to  $<60$  mL/min/1.73m<sup>2</sup> in the presence of renal insult for the span of minimum three months.<sup>4</sup>

Increase in the rate of chronic kidney disease (CKD) is multifactorial, progressing in South Asian countries like Pakistan. In these countries people do not have access to Primary health care services, ignorance about healthcare facilities, primarily due to lack of awareness, inadequate funding on the part of government, also socioeconomic factors are responsible for the disease burden. Moreover, there has been an increase in the prevalence of risk factors for CKD in which increased sugar level and elevated blood pressure levels making the major contribution. Other conditions that may contribute are dry weather, glomerulonephritis, kidney stones and infections of genitourinary system.<sup>5</sup>

It has been proposed that adverse outcomes in CKD occur due to Hyperuricemia, more specifically in those patients who have renal failure due to chronically increased sugar levels and they are more prone to develop complications like macro vascular heart disease.<sup>6</sup> According to cross-sectional studies linked with high uric acid levels in the body, it is found that high levels can cause a decrease in glomerular filtration rate (GFR).<sup>7,8</sup> Febuxostat, used to decrease uric acid levels, is a strong inhibitor of Xanthine oxidase inhibiting both the reduced and oxidized forms of the enzyme as compared to allopurinol that works by inhibiting the enzymes in oxidized form only.<sup>9</sup> Febuxostat, has recently been accepted for marketing, and hence is taken as an alternate drug for patients of hyperuricemia along with chronic kidney disease (CKD). There is no need to adjust the dose of febuxostat in renal failure due to its hepatic metabolism.<sup>10,11</sup>

A study conducted in 2015 reported that average eGFR in the treatment group showed a minimal increase from  $31.5 \pm 13.6$  SD at baseline to  $33.7 \pm 16.6$  mL/min/1.73 m<sup>2</sup> at the interval of six months. In the placebo group, mean eGFR decreased from  $32.6 \pm 11.6$  to  $28.2 \pm 11.5$  mL/min/1.73 m<sup>2</sup> in the same time frame, and this was decreased significantly shown by the p value of 0.003. The pre-treatment and post treatment mean eGFR values in febuxostat group was  $2.2 \pm 0.3$  while it was  $4.4 \pm 0.1$  in the placebo group.<sup>12</sup> Another study conducted on Japanese population in December 2015 showed that febuxostat group showed relatively less decrease of GFR compared to the control group for the entire duration of study, moreover after 8 weeks the measured eGFR was less decreased as equated with baseline in the febuxostat group, yet the differences in eGFR between the febuxostat group and the control group was not significant throughout the entire study and changes in eGFR and serum creatinine after 12 weeks were not significantly different between the study groups.<sup>13</sup>

Owing to its novelty, there is limited literature on the use of febuxostat as an alternative or conjunctive therapy for reduction of eGFR in CKD 3 and 4 patients. Result of this study

will show the baseline data about the use of this drug as an alternative/additive therapy in CKD as no study has been conducted on this topic in Pakistan till date.

### Objective:

To determine the effect of febuxostat on eGFR among patients with chronic renal failure along with increased uric acid levels.

## MATERIALS AND METHODS

A Randomized controlled study was conducted at Medical and Nephrology outpatient of Mayo Hospital, Lahore from 1<sup>st</sup> February, 2019 to 31<sup>st</sup> January, 2020. Sample size of 330 patients (165 patients in each group) was estimated by using 5% level of significance, 90% power of test with expected %age Febuxostat as 38% and placebo group as 54 %. Subjects with grade 3 and 4 chronic renal failure were divided into 2 group's randomly using random number table (computer generated method). Patients of both gender, age 15 to 75 years, uric acid level 6-9 in female and 6-10 in males and CKD stage 3 and 4 based on eGFR calculated by Cockcroft and Gault formula were included in the study. Patients with ALT and AST level double the normal range, history of taking any urate lowering drugs in last 4 weeks, uncontrolled diabetes mellitus  $HbA_{1c} \geq 8.5\%$ , systolic blood pressure  $\geq 160$  mmHg or diastolic blood pressure  $\geq 100$  mmHg, history of acute renal disease, dialysis, acute/chronic infections and renal transplantation and pregnancy were excluded. After approval from institutional ethical research committee (No. 386/RC/KEMU, Dated.17/01/2019), informed written consent was obtained from all the patients. Group A patients received conventional therapy plus febuxostat 40 mg daily after breakfast and the group B received conventional therapy alone plus placebo. Demographic profile like name, age and gender was recorded, plus baseline investigations included. Patients were evaluated for the mean eGFR at the start of treatment for the both groups. Later on mean change in the eGFR was measured after 3 months and 6 months of treatment in both groups. Mean change in eGFR was calculated by subtracting post treatment eGFR from baseline values. All the information was recorded on a pre-designed proforma. (Annexure-I). The data was analysed by consultant physician and nephrologist with 10 year post fellowship experience using the SPSS 20. Continuous variables like age, pre and post treatment eGFR was expressed in the form of means  $\pm$ SD. Categorical variables like sex was expressed in the form of frequencies & percentage. Mean difference between conventional therapy for CKD stage 3 and 4 and conventional therapy plus febuxostat for CKD stage 3 and 4 was determined Data was entered and analysed in SPSS version 21. Mean and standard deviation were calculated for numerical variables. Independent test was used to compare

the means between the groups at baseline, 3 months and 6 months with  $p < .05$  as statistical significant.

## RESULTS

A Total of 330 patients were included in study. Mean age of patients in Group-A was  $43.67 \pm 17.61$  and in Group – B was  $44.45 \pm 17.29$  years. In Group A 63.64% were male and 36.4% were females and among Group B 57.6% were male and 42.4% were female (Table No.1). Renal function test and other parameters were evaluated as mean and standard deviation. Anova test was used to compare the mean difference at baseline, 3 months and 6 months.

Mean urea level at baseline in Group-A and in Group-B was  $113.32 \pm 31.44$  and  $111.69 \pm 29.38$ . At 3<sup>rd</sup> month and 6<sup>th</sup> month mean urea level was in Group-A and in Group-B was  $109.78 \pm 25.23$ ,  $105.65 \pm 25.52$ ,  $110.07 \pm 34.19$  and  $112.64 \pm 36.36$  respectively, and was non-significant. ( $p = 0.688$ ). Mean creatinine level at baseline in Group-A and in Group-B was  $2.00 \pm 0.81$  and  $2.03 \pm 0.84$ . At 3<sup>rd</sup> and 6<sup>th</sup> month mean creatinine level in Group-A and in Group-B was  $1.98 \pm 0.80$ ,  $2.00 \pm 0.78$ ,  $2.41 \pm 1.06$  and  $2.41 \pm 1.07$  respectively and was non-significant ( $p = 0.935$ ). Mean HbA1c level at baseline in both treatment groups was  $6.39 \pm 1.15$  and  $6.55 \pm 1.06$ . At 3<sup>rd</sup> month it was  $7.10 \pm 0.78$  in Group-A and  $6.98 \pm 0.77$  in Group-B and at 6<sup>th</sup> month it was  $6.55 \pm 1.19$  in Group-A and  $6.36 \pm 1.09$  in Group-B. ( $p = 0.868$ ). Mean uric level at baseline in Group-A and in Group-B was  $9.69 \pm 1.72$  and  $8.53 \pm 1.11$ , at 3<sup>rd</sup> month post treatment it was  $6.61 \pm 1.14$  and  $7.34 \pm 1.10$  and at 6<sup>th</sup> month mean uric acid level in

Group-A and in Group-B was  $5.98 \pm 0.82$  and  $7.03 \pm 0.81$  respectively ( $p = 0.756$ ).

Mean eGFR at base line in Group-A and in Group-B was  $36.99 \pm 12.20$  and  $35.60 \pm 11.39$ , at 3<sup>rd</sup> month post treatment it was  $37.93 \pm 12.43$  and  $37.66 \pm 12.40$  and at 6<sup>th</sup> month mean eGFR in Group-A and in Group-B was  $38.06 \pm 13.41$  and  $35.46 \pm 13.22$  respectively ( $p = 0.057$ ). Although mean eGFR was higher in Group-A but it was not statically significant. (Table no: 2)

## DISCUSSION

Literature evidence showed a certain relationship between hyperuricemia and deterioration in kidney functionality.<sup>14-16</sup> however still there is an on-going discussion that needs further specifically designed studies which can give conclusive results about the efficiency and usage of agents used for reducing urate levels to treat asymptomatic hyperuricemic patients with CKD. This is due to the reporting of some risks associated with inappropriate treatment of asymptomatic hyperuricemia.<sup>17,18</sup>

Febuxostat, novel xanthine oxidase inhibitor is safe for patients with chronic kidney disease due to its hepatic elimination. It is good alternative to allopurinol for patients who have intolerance for allopurinol.<sup>19</sup> Multiple studies<sup>20-22</sup> stated about Renal protective effects of febuxostat, and it has been reported to enhance kidney functions for patients with Chronic Kidney Disease stage 3.<sup>12</sup> This study evaluated the effect and efficacy of febuxostat for patients with hyperuricemia and chronic kidney disease. No significant difference noticed at

**Table 1: Demographic profile of subjects:**

Variables n=330	Group-A n=165 (Febuxostat)	Group-B n=165 (Control)
Age	Mean 43.67 + 17.61	Mean 44.45 + 17.29
15 - 45	65 (40.4%)	55 (33.4%)
46 - 75	100 (60.6%)	110 (66.6%)
Gender		
Male	105(63.64%)	95 (57.6%)
Female	60(36.4%)	70 (42.4%)

**Table 2: Descriptive statistics for Renal Function Test .**

N =165	Baseline Mean + SD		3 Months Mean + SD		6 Months Mean + SD		p value
	Group-A	Group-B	Group-A	Group-B	Group-A	Group-B	
(Urea)	$113.32 + 31.44$	$111.69 + 29.38$	$109.78 + 25.23$	$105.65 25.52$	$110.07 + 34.19$	$112.64 + 36.36$	$p = 0.688$
Creatinine	$2.00 + 0.81$	$2.03 + 0.84$	$1.98 + 0.80$	$2.00 + 0.78$	$2.41 + 1.06$	$2.41 + 1.07$	$p = 0.935$
HbA1c Level	$6.39 + 1.15$	$6.55 + 1.06$	$7.10 + 0.78$	$6.98 + 0.77$	$6.55 + 1.19$	$6.36 + 1.09$	$p = 0.868$
Uric Acid	$9.69 + 1.72$	$8.53 + 1.11$	$6.61 + 1.14$	$7.34 + 1.10$	$5.98 + .82$	$7.03 + .81$	$p = 0.756$
eGFR	$36.99 + 12.20$	$35.60 + 11.39$	$37.93 + 12.43$	$37.66 + 12.40$	$38.06 + 13.41$	$35.46 + 13.22$	$p = 0.057$

the end of 3<sup>rd</sup> month in eGFR of both groups. However, after 6 months, group A had higher eGFR than group B, but again there was no significant statistical difference was noticed ( $38.06 \pm 13.41$  ad  $35.46 \pm 13.22$ , p-value=0.075).

Sircar et al. on effectiveness of febuxostat on delaying renal failure in patients with increased urate levels, stated that eGFR was increased (38% of patients) in the febuxostat group in comparison to 54 % of patients in the non-treated group (p-value, 0.004) and increase in eGFR after 6 months of treatment with febuxostat as compared to significant decline for placebo.<sup>12</sup> The results of our study are comparable with Sircar et al. as after 6 months, there was an increase for febuxostat group and for the placebo group eGFR was low when compared to the baseline or 3<sup>rd</sup> month of treatment.

Although Kenichi Tanaka's study opposed the findings of Sircar et al. study, this study reports that there was a significant reduction of uric acid in patients with CKD stage 3 after 8 weeks, but there were no significant differences between eGFRs of both groups. And, there were no significant changes in serum creatinine after 12 weeks in both groups.<sup>22</sup>

In 2019, Jang Wok compared the Reno protective effects of allopurinol and febuxostat for hyperuricemic patients with CKD. In that study, febuxostat group had significantly higher mean eGFR and significantly lower mean serum SUA levels ( $5.7 \pm 1.0$  vs.  $7.1 \pm 1.2$  vs.  $8.0 \pm 0.8$  mg/dL, p-value < 0.001) consistently for 4 years when compared to placebo and allopurinol group.<sup>23</sup>

A Study by Sakai et al.<sup>24</sup> reported that there was gradual and slow recovery of eGFR for patients with CKD and hyperuricemia after being treated with febuxostat when they resisted to allopurinol, whereas Tsuruta et al.<sup>25</sup> showed that deviation in estimated GFR was significant when febuxostat was replaced instead of allopurinol. Since eGFR and albuminuria are important markers of kidney function assessment, there might be a chance that febuxostat is more Renoprotective as compared to allopurinol.

In a meta-analysis by Xiang Xia Zeng reported for the positive effect of febuxostat in improving serum eGFR for CKD patients. It also indicated that there might be amelioration of kidney function in early chronic kidney disease.<sup>26</sup> Another finding that should be pointed out that high uric acid levels need treatment to prevent progression of chronic renal failure. There is substantiation that decreasing urate levels provide an advantage in renal failure patients. Some authors like Ramirez and Bargman<sup>27</sup> put emphasis on the usage of xanthine oxidase inhibitors in asymptomatic hyperuricemic patients with chronic renal failure, but Stefamidis<sup>28</sup> have opposite opinion that no treatment should be offered in these patients.

It might be the case that hyperuricemia may cause the activation of renin angiotensin system. It acts directly and

indirectly, Direct action is by the reduction of neuronal nitric oxide synthesis in the juxtaglomerular apparatus whereas indirect action is by the decrease in kidney perfusion leading to afferent arteriolar vascular smooth cell proliferation, or it might be due to expression of cyclooxygenase 2 in the macula densa and arterioles. A decrease in nitric oxide synthase and increase in juxtaglomerular renin secretion has been described; this injury is attenuated by L-arginine and enalapril which suggest that damage occurs by a crystal-independent mechanism.<sup>29-30.</sup>

## CONCLUSION

Results of this study showed no significant difference in eGFR at baseline & 3<sup>rd</sup> month in both groups, However mean eGFR was greater in treatment group (Group A) as compared to placebo after 6<sup>th</sup> month. So febuxostat can be effectively used to decrease the decline of estimated GFR in patients with CKD stage 3 and 4.

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## Conflict of interest

None

## Authors Contribution

**Dr. Abdul Malik Mujahid.**

Principal contributor, conceptualization and design of research work, final approval

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Co contributor, data analysis, plagiarism correction, literature search

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Writing of manuscript, collection of data, drafting

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Literature search, statistical analysis, result analysis, review of manuscript

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