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Effect of febuxostat on oxidative stress in hemodialysis patients with endothelial dysfunction: a randomized, placebo-controlled, double-blinded study

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Abstract

Purpose Oxidative stress, which is most likely a key mediator in the development of cardiovascular disease, is implicated in the progression and deterioration of chronic kidney disease. Patients on hemodialysis exhibit the excessive generation of oxidative stressors, which may also be responsible for the endothelial dysfunction prevalent in these patients. Febuxostat, an inhibitor of xanthine oxidase enzyme, is emerging as a novel drug in the amelioration of oxidative stress status. However, studies regarding its effect among hemodialysis patients are still lacking.

Methods This prospective, block-randomized, double-blinded, placebo-controlled study was carried out to assess the effect of oral 40 mg febuxostat on oxidative stress in hemodialysis patients. In total, fifty-seven eligible patients were randomly assigned to either a drug group or a placebo group for the 2-month study period. Serum malondialdehyde (MDA) and serum superoxide dismutase (SOD) were assessed at baseline and at the end of the study. A correlation analysis between previously reported serum asymmetric dimethylarginine (ADMA), serum MDA and serum SOD was performed.

Results Febuxostat significantly decreased the serum MDA and significantly increased the serum SOD, while no significant results were observed in the placebo group. A highly positive correlation between the MDA levels and ADMA levels at baseline was noticed in both groups, while there was a highly negative correlation between the SOD levels and ADMA levels at baseline in both groups. A positive correlation between the change in ADMA levels and MDA levels from baseline was observed only in the drug group.

Conclusion Febuxostat appears to have a direct ameliorating effect on oxidative stress in hemodialysis patients with endothelial dysfunction.

Keywords Oxidative stress · Hemodialysis · Febuxostat · Endothelial dysfunction · Clinical trial

Introduction

The incidence of cardiovascular disease (CVD) in end-stage renal disease (ESRD) patients is approximately 10- to 20-fold higher than that in the general population, and it is considered the leading cause of death in these categories of patients, rather than the progression to ESRD [1].

Patients on hemodialysis have substantially higher cardiovascular risk factors and a higher mortality rate, even higher than expected from their Framingham risk scores [2]. The observed increased mortality and morbidity has been linked with both endothelial dysfunction and oxidative stress (OS) in this category of patients [1].

Oxidative stress simply represents the imbalance between the excessive formation and/or insufficient removal of reactive oxygen species (ROS) [3]. Endothelial dysfunction, which is

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emerging as a key element in CVD prognosis, is mainly the result of either reduced nitric oxide (NO) bioavailability or inhibition of endothelial nitric oxide synthase (eNOS) enzyme activity [4].

An increasing body of evidence suggests the fundamental role of OS in aggravating endothelial dysfunction. It is believed that OS accounts for a significant part of the overproduction of ROS and the degradation of NO [5]. ROS are believed to inactivate both NO production and the renin–angiotensin system, which in turn promotes endothelial dysfunction and tubular injuries, as well [6, 7].

In contrast, several lines of research may attribute a beneficial effect of xanthine oxidase inhibitors (XOIs) on endothelial dysfunction to the reduction of OS [8, 9], rather than to urate reduction [10, 11]. Interestingly, XOIs may exert a beneficial action on endothelial dysfunction, even in patients with normal baseline urate levels [12]. This area of research is still being debated, and the precise mechanism is unclear.

We previously reported the beneficial direct effect of Febuxostat, a novel non-purine specific XOI, on endothelial dysfunction in hyperuricemic hemodialysis patients [13]. Due to the technical challenges of using the flow-mediated dilatation (FMD) technique for assessing endothelial dysfunction [14–17], asymmetric dimethyl arginine (ADMA), an independent determinant of endothelial dysfunction, was used [18, 19]. Depending on a multiple regression model used by previous studies, ADMA can also be an independent determinant of FMD in CKD patients [18].

Both OS and the increase in ADMA levels can reflect endothelial dysfunction in CKD patients [20]. Malondialdehyde (MDA), an OS marker, has been reported to be an independent determinant of plasma ADMA levels. In addition, both superoxide dismutase (SOD), another OS marker, and ADMA were reported to be independent determinants of FMD [18].

In previous experimental animal models, febuxostat succeeded in attenuating the OS status by reducing MDA and enhancing SOD levels [21, 22], with a decrease in the ADMA levels, as a marker of endothelial dysfunction [21].

As the causal relationship between XOI, febuxostat and OS in hemodialysis patients has not yet been firmly established, this study aims to assess whether there is a direct preferential role of febuxostat on OS biomarkers and to correlate it with the improvement in ADMA levels observed previously in these category of patients.

Materials and methods

Study design

This is a block-randomized, placebo-controlled, double-blinded study that was carried out in the hemodialysis units of Ain Shams University Hospital, Cairo, Egypt. The study was conducted in accordance with good clinical practice guidelines and the ethical principles in the Declaration of Helsinki. This clinical trial followed the CONSORT guidelines and ICMJE recommendations. The protocol was approved by the institutional review board and has been registered on ClinicalTrials.gov: NCT02866214. Written informed consent was provided to the patients prior to their participation in the study. An intention-to-treat analysis was performed.

Patient eligibility

Inclusion criteria Male or female patients on maintenance hemodialysis, aged 18–70 years old with a serum uric acid level of 7.0 mg/dL or more, and in stable clinical condition (no hospitalization in the previous 3 months).

Exclusion criteria Patients on current urate-lowering therapy such as allopurinol, probenecid, bucolome or febuxostat, patients on current treatments that induce hyperuricemia such as pyrazinamide or ethambutol, patients on current treatments that are metabolized by the xanthine oxidase enzyme such as mercaptopurine and azathioprine, patients with a history of hypersensitivity to febuxostat, and participants in another clinical trial within the past 4 weeks or being judged to be unsuitable as a subject by the attending physician.

Treatment intervention

A total of 57 eligible hemodialysis patients were randomized into two groups.

Drug group Twenty-eight patients (age: 47 ± 12.25 years, 16 males:12 females) received 40 mg of febuxostat film-coated tablets by Eva Pharma Company, Cairo, Egypt), taken post-hemodialysis session, thrice weekly.

Placebo group Twenty-nine patients (age: 47 ± 13.83 years, 17 males:12 females) received starch-based placebo tablets that were also manufactured by Eva Pharma (Cairo, Egypt) using the same regimen.

Patients in the two study groups were followed up for 2 months. Each patient's routine medications were taken with either a febuxostat tablet or placebo tablet without any change occurring in the study period. The treatment was ensured by drug administration at the hemodialysis unit just after the session, supplied by the designated nurse. Adherence was ensured by returning the empty strips to the principal investigator on a weekly basis.

Enrolment and allocation

A total 120 patients were assessed for eligibility, 63 patients were excluded (55 patients did not meet the inclusion criteria, and eight patients declined to participate in the study). Fifty-seven patients were randomized, with 28 patients randomized to the drug group, and 29 patients randomized to the placebo group. Seven patients were lost to follow-up (three patients were in the drug group: one patient was transferred to another hospital, two patients dropped out due to non-compliance; and four patients in the placebo group: two patients were transferred to another hospital, and two patients dropped out due to non-compliance) (Fig. 1) [13].

Laboratory measurements

Blood samples

Blood samples were drawn just before the start of the hemodialysis session. Sera were then separated and kept frozen at − 80 °C at the Central Labs of Ain Shams University Hospital. Both serum malondialdehyde (MDA) and serum superoxide dismutase (SOD) levels were measured using the enzyme linked immunosorbent assay (ELISA) technique with a commercial kit "MyBioSource™", San Diego, USA. All ELISA procedures were performed according to the manufacturer's instructions using the Hyprep® automated ELISA system.

Statistical analysis

Data management and statistical analysis were performed using the statistical package for social science (SPSS, Chicago, IL, USA) version 22. Statistical comparisons with respect to numerical data were performed using unpaired Student's *t* test, paired Student's *t* test and analysis of covariance, with baseline values as covariates. Correlation using Pearson's correlation test was performed to correlate both the change of the MDA levels and SOD levels from baseline, with the previously reported change in ADMA levels. All *P* values were two-sided, and *P* values < 0.05 were considered significant, while *P* values < 0.001 were considered highly significant.

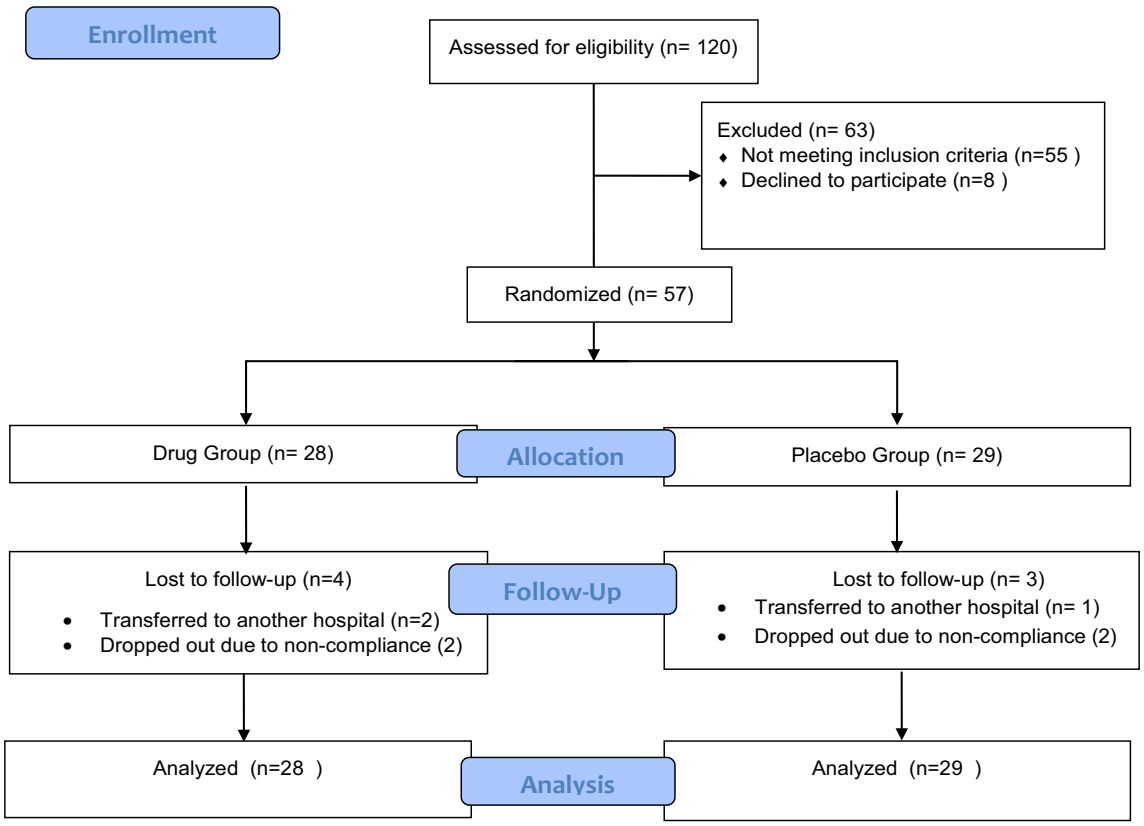

Fig. 1 Flow diagram representing the enrollment, the allocation, the follow-up and the analysis processes

Results

Baseline clinical data and demographics

Demographics and clinical characteristics were assessed, and there was no significant difference between the two study groups (Table 1) [13].

Baseline laboratory measurements have also shown no significant difference between the two study groups (Table 2) [13].

Effect of febuxostat on uric acid, MDA and SOD

Treatment with febuxostat for 2 months succeeded in decreasing serum uric acid from 7.5 ± 0.8 to 5.1 ± 1.2 mg/dL (P value < 0.001). It significantly decreased serum MDA from 28.67 ± 3.13 to 26.29 ± 2.20 nmol/mL (P value < 0.001) and significantly increased serum SOD from 5.55 ± 1.06 to 6.6 ± 0.7 U/mL (P value < 0.001). The placebo group failed to show a significant difference in uric acid, MDA, ADMA or SOD (Table 3).

Correlation analysis

At baseline, there was a highly positive correlation between ADMA levels and MDA levels ($r = +0.827$, P value < 0.001, $r = +0.866$, P value < 0.001) in both the drug group and placebo group, while a highly negative correlation between ADMA and SOD (drug group: $r = -0.604$, P value < 0.001, placebo group: $r = -0.750$, P value < 0.001) was found.

A correlation analysis for the change from baseline between ADMA and both MDA and SOD showed a statistically significant positive correlation between ADMA and MDA in the drug group, with a non-significant positive correlation in the placebo group. A negative but non-significant correlation was observed between ADMA levels and SOD levels in the drug group, and a positive non-significant correlation was observed in the placebo group (Table 4).

Table 1 Patients demographics and clinical characteristics [13]

Baseline evaluation	Drug group ($n = 28$)	Placebo group ($n = 29$)	P value
A. Demographic data			
Age (years); mean ± SD	47 ± 12.25	47 ± 13.83	0.992
Sex			
Male; n (%)	16 (57%)	17 (58%)	0.910
Female; n (%)	12 (43%)	12 (42%)	
Dry weight; mean ± SD	77 ± 15	74 ± 15	0.469
Hemodialysis duration (years)			
Median (range)	5 (3–17)	6 (3–14)	0.339
B. Clinical characteristics			
Etiology: n (%)			
Hypertension	9 (32%)	7 (24%)	0.761
Systemic lupus erythematosus	4 (14%)	5 (17%)	
Chronic glomerulonephritis	3 (11%)	3 (10%)	
Diabetes mellitus and hypertension	3 (11%)	3 (10%)	
Diabetes mellitus	3 (11%)	3 (10%)	
Reflux nephropathy	2 (7%)	0 (0%)	
Chronic pyelonephritis	0 (0%)	1 (3.4%)	
Unknown	3 (14%)	7 (24%)	
Antihypertensive medications: n (%)			
B-blocker (atenolol)	4 (14.3%)	2 (6.9%)	0.767
Angiotensin converting enzyme inhibitor (captopril)	1 (3.6%)	1 (3.4%)	
Calcium channel blockers (nifedipine)	1 (3.6%)	1 (3.4%)	
Diuretics (furosemide)	1 (3.6%)	0 (0.0%)	
Methyldopa	2 (7.1%)	1 (3.4%)	
None	19 (67.9%)	24 (82.8%)	

n number of patients

Table 2 Baseline laboratory measurements [13]

Baseline evaluation	Drug group ($n=28$)	Placebo group ($n=29$)	P value
Systolic BP[a] (mmHg)	131.4 ± 29.7	121.1 ± 25.4	0.162
Diastolic BP (mmHg)	84.6 ± 17.1	79.7 ± 16.8	0.272
Urea (mg/dL)	90.9 ± 23.8	85.1 ± 28.8	0.411
Ca[b] (mg/dL)	8.3 ± 1.0	8.3 ± 1.2	0.890
PO_4^c (mg/dL)	4.5 ± 1.6	4.3 ± 1.6	0.574
Albumin (g/dL)	3.8 ± 0.3	3.6 ± 0.3	0.142
Hemoglobin (g/dL)	10.5 ± 1.3	10 ± 1.8	0.243
Iron (µg/dL)	82.3 ± 47.5	76 ± 37.5	0.590
TIBC[d] (mcg/dL)	253.5 ± 53.1	230.3 ± 82.2	0.212
TSAT[e] (%)	40.9 ± 23.5	45.6 ± 21.2	0.318
ALT[f] (IU/L)	16.5 ± 4.8	16.5 ± 3.7	0.964
AST[g] (IU/L)	15.7 ± 3.1	16.1 ± 3.7	0.363
WBCs[h] (10^9/L)	6.68 ± 1.21	6.95 ± 1.17	0.557
Platelets (10^9/L)	233.4 ± 12.9	233.1 ± 12.7	0.851
Uric acid (mg/dL)	7.5 ± 0.8	7.5 ± 0.7	0.928
ADMA[i] (µmol/L)	1.027 ± 0.116	1.007 ± 0.103	0.500
HsCRP[j] (mg/L)	12.5 ± 1.65	12.3 ± 1.66	0.715
MDA[k] (nmol/mL)	28.67 ± 3.13	27.6 ± 2.67	0.18
SOD[l] (U/mL)	5.55 ± 1.06	5.61 ± 0.97	0.82

Data expressed as mean ± SD

n number of patients

[a]Systolic blood pressure, [b]calcium, [c]phosphate, [d]total iron binding, [e]transferrin saturation capacity, [f]alanine aminotransferase (alt), [g]aspartate aminotransferase, [h]white blood cells, [i]asymmetric dimethylarginine, [j]high-sensitivity C-reactive protein, [k]malondialdehyde, [l]superoxide dismutase

Discussion

Both OS and endothelial dysfunction are two inter-related conditions that are mostly seen in patients with CVD [23]. To the best of our knowledge, this is the first controlled study to correlate the direct effect of febuxostat on OS to the endothelial dysfunction status in patients on hemodialysis.

In the literature, a crossed-linked relationship between increased OS and increased ADMA levels was observed [24]. This, in turn, is closely associated with the development of endothelial dysfunction, a reliable determinant of future cardiovascular events [25, 26]. According to Sydow et al. and Münzel et al., OS is a contributing factor not only in the increased production of ADMA, but also in inhibiting its degradation [24].

Although it has been hypothesized that uric acid provides antioxidant characteristics [27] as a significant part of the serum total antioxidant status [28], there are contrasting studies and data that suggest its deleterious pro-oxidative effects [29, 30]. This comes with its potential mechanism by which it causes endothelial dysfunction via NO depletion under conditions of oxidative stress [29].

Xanthine oxidase (XO) enzyme, which is involved in uric acid production, is also a major contributor to OS because it is a significant source of ROS in the vasculature [31]. Experimental studies suggest a direct role of XOIs in ameliorating OS, independent of the urate level [32, 33]. This is also supported by this study and other clinical studies that show their beneficial effect on OS regardless of the level of uric acid [34, 35].

We previously addressed the beneficial role of febuxostat, a novel non-purine XOI, on alleviating both serum uric acid levels and serum ADMA levels in hemodialysis patients [13]. Whether the beneficial role of xanthine oxidase inhibitors in ameliorating endothelial dysfunction is related to their ability to decrease serum uric acid, decrease the production of ROS, or both, this area of investigation is still interesting.

The preliminary results of this study showed a baseline elevation of MDA levels, the marker of free radical activity, and a baseline drop of SOD levels, as well as antioxidant enzyme activity, among the two study groups.

This increase in baseline MDA was also shown by previous studies [36–41], and the drop in the SOD baseline was noted in several studies, as well [1, 41, 42]. It is becoming a well-established truth that ESRD is a state of elevated OS [43].

In this study, we documented an improvement of OS by febuxostat based on the reduction in MDA levels and the

Table 3 End of study results

Parameter before and after 2 months	Drug group ($n=28$)	Placebo group ($n=29$)
MDA[a] (nmol/mL)		
Baseline	28.67 ± 3.13	27.6 ± 2.67
Endpoint	26.29 ± 2.20	27.73 ± 2.69
P value	< 0.001**	0.33
SOD[b] (U/mL)		
Baseline	5.55 ± 1.06	5.61 ± 0.97
Endpoint	6.6 ± 0.70	5.61 ± 0.97
P value	< 0.001**	0.95
ADMA[c] (μmol/L)		
Baseline	1.027 ± 0.116	1.007 ± 0.103
Endpoint	0.944 ± 0.104	1.009 ± 0.101
P value	< 0.001**	0.39

Parameters after 2 months	Drug group ($n=28$)	Placebo group ($n=29$)	*P* value
MDA endpoint (nmol/mL)	26.29 ± 2.20	27.73 ± 2.69	< 0.001**[†]
% change	− 7.83 ± 6.34	0.45 ± 2.2	< 0.001**[!]
SOD endpoint (U/mL)	6.6 ± 0.70	5.61 ± 0.97	< 0.001**[†]
% change	21.49 ± 18.86	1.89 ± 21.72	< 0.001**[!]
ADMA endpoint (μmol/L)	0.944 ± 0.104	1.009 ± 0.101	< 0.001**[†]
% change	− 7.9 ± 4.26	0.2 ± 1.04	< 0.001**[!]

Data expressed as mean ± SD

n number of patients

*$P \leq 0.05$ is considered significant; **$P \leq 0.001$ is considered highly significant

[†]Data are analyzed using ANCOVA with baseline values as covariates

[!]Data are analyzed using unpaired *t* test

[a]Malondialdehyde

[b]Superoxide dismutase

[c]Asymmetric dimethylarginine

Table 4 Correlations for the changes from baseline

Variable	Drug group ($n=28$) Change in ADMA[a]		Placebo group ($n=29$) Change in ADMA[a]	
	R	*P* value	*R*	*P* value
Change in MDA[b]	+ 0.49	< 0.001**	+ 0.011	0.95
Change in SOD[c]	− 0.24	0.22	+ 0.016	0.93

n number of patients

*$P \leq 0.05$ is considered significant; **$P \leq 0.001$ is considered highly significant

[a]Asymmetric dimethylarginine (μmol/L)

[b]Malondialdehyde (nmol/mL)

[c]Superoxide dismutase (U/mL)

elevation in SOD levels in the drug group compared to the placebo group.

Febuxostat had a similar result with MDA when it was administered to chronic tophaceous patients [44]. Although febuxostat had promising effects on both the MDA and SOD levels in recent studies on animals [45–48], its direct effect on patients on hemodialysis has not been fully studied.

The inter-relation between the febuxostat effect on ADMA and OS was addressed once by Li et al. in his experimental administration of febuxostat to New Zealand white rabbits with induced atrial fibrillation [21]. These results highlight a way for us to investigate its effect on hemodialysis patients, taking into consideration the favorable effects on ADMA levels and inflammation we noticed before.

This study showed a highly positive correlation between ADMA and MDA levels in both groups at baseline. This finding was also observed by Zhang et al. in renal transplantation patients when he assessed the association between ADMA and MDA levels before and after transplantation [49]. The study results were also in agreement with Yilmaz et al., who found a positive correlation between ADMA levels and MDA levels and a negative correlation between ADMA levels and SOD levels in CKD patients. This finding

suggests that both endothelial dysfunction and OS status are highly interrelated.

In addition, this is the first study to correlate the change in ADMA levels from baseline with the change of both MDA and SOD levels under the effect of an XOI. A statistically significant positive correlation was observed between the change in ADMA and MDA levels in the drug group, while a negative but non-significant correlation was noticed between the change in ADMA and SOD levels in the drug group.

Febuxostat seemed to be well-tolerated in clinical trials. Fortunately, this study showed no adverse or side effects of the drug. However, some concerns were raised regarding febuxostat and a non-significant elevation in liver enzymes, as reported by Jansen et al. in 2010 [50]. In contrast, other studies have shown no significant change [13, 51]. Non-significant nausea and arthralgia were also found to be associated with febuxostat in previous clinical trials. It was not until recently in 2018 that febuxostat has shown to have cardiovascular issues. Although it has similar rates of major cardiovascular adverse events as observed in allopurinol, it should be noted that higher all-cause mortality was observed with febuxostat than with allopurinol [52].

Conclusion

This randomized placebo-controlled study emphasizes the promising effects of febuxostat, which is a xanthine oxidase inhibitor, on OS that is consistent with the improvement in endothelial dysfunction that has been shown previously. However, larger multicentre studies with longer durations and higher dosing regimens are warranted to validate these outcomes.

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Compliance with ethical standards

Conflict of interest The authors declare that they have no conflicts of interest. All the authors have contributed significantly to the publication. All the authors are aware of the submission and agree with it.

Ethical approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee (Ethical committee of Faculty of Pharmacy, A.S.U.) and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards.

Informed consent Informed consent was obtained from all individual participants included in the study.

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