Evaluation of the effect of febuxostat on endothelial dysfunction in hemodialysis patients

A thesis submitted for the fulfillment of Master's degree in Pharmaceutical Sciences (Clinical Pharmacy)

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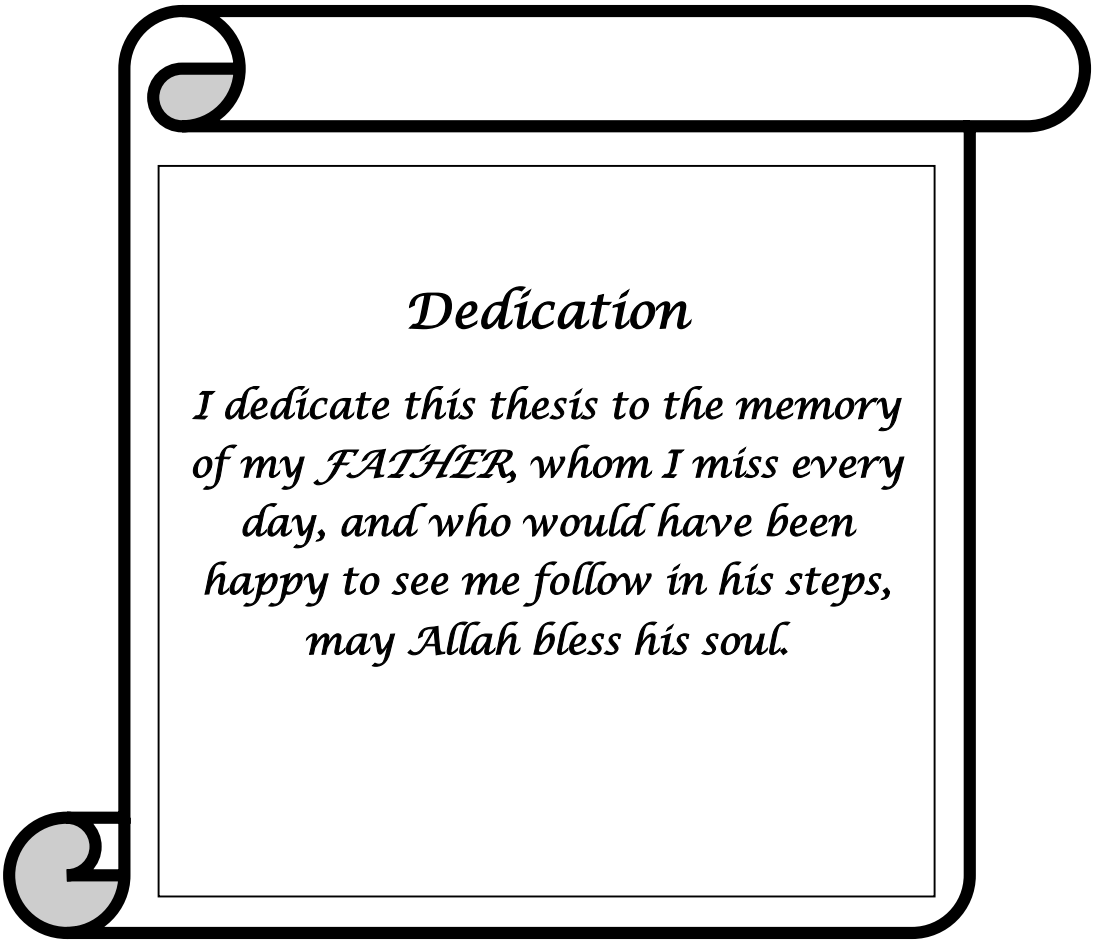

Dedication

I dedicate this thesis to the memory of my FATHER, whom I miss every day, and who would have been happy to see me follow in his steps, may Allah bless his soul.

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List of abbreviations

ACCP	**American College of Clinical Pharmacy**
ADE	**Adverse drug events**
ADMA	**Asymmetric Dimethylarginine**
AKI	**Acute Kidney Injury**
ANCOVA	**Analysis of Covariance**
ARIC	**Atherosclerosis Risk in Communities**
CBC	**Complete Blood Count**
CKD	**Chronic Kidney Disease**
CRP	**C-Reactive Protein**
CVD	**Cardiovascular Disease**
DDAH	**Dimethylargnine Dimethyl Aminohydrolase**
ELISA	**Enzyme Linked Immunosorbent Assay**
ESRD	**End Stage Renal Disease**
FMD	**Flow mediated dilatation**
GFR	**Glomerular filtration rate**
HsCRP	**High Sensitivity C-reactive Protein**
KDIGO	**Kidney Disease Improving Global Outcome**
MDRD	**Modification of Diet for Renal Disease**
MRI	**Magnetic resonance imaging**
NADPH	**Nicotinamide Adenine Dinucleotide Phosphate**
NOS	**Nitric-oxide synthase**
PAT	**Pulse amplitude tonometry**
PBS	**Phosphate Buffered Saline**
PCA	**Pulse contour analysis**
pmp	**Patient per million**
PWA	**Pulse wave analysis**
ROS	**Reactive oxygen species**

RRT	**Renal Replacement Therapy**
SPSS	**Statistical package for social science**
TBS	**Tris Buffered Saline**
TMB	**Tetramethylbenzidine**
TRP	**Treatment related problems**
UA	**Uric acid**
XD	**Xanthine Dehydrogenase**
XO	**Xanthine oxidase**

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Abstract

Abstract

Background:

Endothelial dysfunction is an important risk factor for developing cardiovascular diseases in End Stage Renal Disease (ESRD) patients. Febuxostat; being a novel xanthine oxidase inhibitor, is apparently having a beneficial role in improving endothelial dysfunction, however, data among hemodialysis patients is still limited.

Methods:

A prospective, placebo controlled, block randomized double blinded study was carried out to evaluate the effect of oral febuxostat on endothelial dysfunction in hemodialysis patients. Fifty-seven eligible hemodialysis patients were randomly assigned to either drug group (40 mg thrice weekly) or placebo group. Serum Asymmetric dimethylarginine (ADMA), serum uric acid (UA) and serum high sensitivity C-reactive protein (HsCRP) were measured at baseline and at the end of a two months study. Serum Alanine Aminotransferase (ALT), serum Aspartate Aminotransferase (AST) and occurrence of pancytopenia were tested as safety parameters at baseline and at the end of study.

Results:

Serum UA significantly decreased from 7.5 ± 0.8 mg/dL to 5.1 ± 1.2 mg/dL in Febuxostat group while it didn't change significantly in placebo group. Treatment with Febuxostat resulted in a significant decrease in serum ADMA level from (1.027 ± 0.116 µmol/L to 0.944 ± 0.104 µmol/L) and serum HsCRP level from (12.5 ± 1.65 mg/L to 12.1 ± 1.70 mg/L). Testing of serum ALT, serum AST and pancytopenia revealed no significant difference in both groups.

Conclusion:

Febuxostat appears to improve hyperuricemia, endothelial dysfunction and ameliorate inflammation in hemodialysis patients with no safety concerns.

Key words:

Hemodialysis, Febuxostat, Endothelial dysfunction, Asymmetric dimethylarginine, Hyperuricemia, Inflammation.

Review of Literature

Renal Failure

Renal failure can be classified into acute kidney injury and chronic kidney disease. While disease progression is fast in acute kidney injury, gradual deterioration (in the range of years) of the kidneys occurs in Chronic Kidney Disease (CKD) **(Chawla et al., 2014).**

Total loss of kidney functions can occur from both chronic and acute kidney disease. It then consequences to total or partial dependence on renal replacement therapy, either dialysis with its two types; hemodialysis and peritoneal dialysis, or kidney transplantation **(Tammen et al., 2014).**

Acute Kidney Injury (AKI):

It is a syndrome that characterized by the rapid loss of the kidney's excretory function. It is typically diagnosed by the accumulation of end products of nitrogen metabolism (urea and creatinine) or decreased urine output, or both **(Bellomo et al., 2012)**. The most popular definition for AKI is the elevation of creatinine of ≥ 0.3 mg/dl within 48 hours, or ≥ 50% above baseline within 7 days **(Khwaja, 2012).**

Chronic Kidney Disease (CKD):

It's a life-threatening condition with progressive and irreversible loss of kidney function ***(*Gansevoort et al., 2013).** It's defined by the international guidelines as decreased kidney function shown by glomerular filtration rate (GFR) of less than 60 mL/min per 1·73 m^2, or markers of kidney damage, or both, of at least 3 months duration, regardless of the underlying cause **(Webster et al., 2016).**

I. Criteria for the definition of CKD by Kidney Disease Improving Global Outcome (KDIGO): (Andrassy, 2013; Kasiske & Wheeler, 2013)

One or more markers of kidney damage:

- Albuminuria (Albumin excretion rate more than/equal 30mg/24 hours; albumin to create ratio more than/equal 3mg/mmol)
- Urine sediments abnormalities
- Histology abnormalities.

- Tubular disorders and electrolyte abnormalities.
- Imaging structural detected abnormalities.
- Kidney Transplantation History.
- Decreased GFR < 60ml/min/1.73m^2.

II. Staging of chronic kidney disease: *(Kasiske & Wheeler, 2013)*

Staging of CKD in Kidney Disease Improving Global Outcome (KDIGO) is based on either GFR or Albuminuria:

Table 1: CKD classification based on GFR and Albuminuria

GFR categories		
Category	**GFR**	**Description**
G1	90	Normal or increased
G2	60-89	Mildly decreased
G3a	45-59	Mildly to moderately decreased
G3b	30-44	Moderately to severely decreased
G4	15-29	Severely decreased
G5	<15	Renal Failure
Albuminuria categories		
Category	**A/C ratio**	**Description**
A1	<30	Normal to mildly increased
A2	30-300	Moderately increased
A3	>300	Highly increased

Abbreviations: GFR: Glomerular Filtration Rate, A/C ratio: Albumin to Creatinine ratio.

CKD Classification and Staging

- **Green:** Low risk (LR)
- **Yellow:** Moderate risk (MR)
- **Orange:** High risk (HR)
- **Red:** Very high risk (VHR)

Kidney function stage GFR (ml/min/1.73m²) Description and range				Kidney damage stage Urine albumin/creatinine ratio Description and range		
				A1	A2	A3
				Normal to mild increase <30mg/g	Moderate increase 30-300 mg/g	Severe increase >300mg/g
	G1	Normal or high	≥90	LR	MR	HR
	G2	Mild decrease	60-89	LR	MR	HR
	G3a	Mild to moderate decrease	45-59	MR	HR	VHR
	G3b	Moderate to severe decrease	30-44	HR	VHR	VHR
	G4	Severe decrease	15-29	VHR	VHR	VHR
	G5	Kidney failure	<15	VHR	VHR	VHR

Figure 1: Guide to frequency of monitoring by GFR and albuminuria categories.

III. Epidemiology of CKD:

Chronic kidney disease is a worldwide problem which overburdens healthcare systems and governments. It eventually leads to millions of deaths and years lived with disabilities and poor quality of life. It's found that 3,200,000 patients reach End Stage Renal Disease (ESRD) without even starting Renal Replacement Therapy (RRT) each year, while only 440,000 patients do initiate RRT **(Anand et al., 2013).** CKD is one of the three causes of death with the greatest increase from 1990 to 2010 among the top 20 killers **(Lozano et al., 2013).**

Worldwide, the prevalence of ESRD differs greatly. According the United States Renal Data System, the highest prevalence was found in Taiwan, with 2447 patients per million (pmp), and the lowest prevalence was in Philippines, at 110 pmp **(Afifi, 2008).**

The incidence of CKD is at least three to four times more frequent in Africa than in developed countries, but the prevalence of ESRD is relatively lower, which reflects the lack of medical care facilities and health-care systems **(Naicker, 2009).**

In Egypt, there are no recent data about the prevalence of ESRD; however, the last statistics that was performed showed an increase from 225 pmp in 1996 to 483 pmp in 2004 **(El Minshawy, 2011; Ghonemy et al., 2016).** The estimated annual incidence of ESRD is around 74 per million and the total prevalence of patients on dialysis is 264 per million **(El-Arbagy et al., 2016).**

According to an epidemiological study of ESRD in El-Menia Governorate 2011, the prevalence was 308 pmp. Patients' mean age was 46 ± 13 years with 65% males 65% and 35% females. The etiology of the CKD in the study showed 20% due to hypertension, 12% due to obstructive abnormalities, 11% due to chronic glomerulonephritis, 8% due to diabetic nephropathy, 5% chronic pyelonephritis 3% due to bilharziasis , 9% due to other causes while 20% with unknown cause **(El Minshawy, 2011).**

Menoufia governorate presented with an ESRD prevalence rate of 330 pmp in 2011. Patients' mean age was 52.45 ± 14.12 years with 52.4% males and 47.6 females. Hypertension was the prevalent cause of ESRD in this study with 31.1% and diabetic nephropathy with 15.9%, while the unknown causes represented 20.5% of the cases **(Zahran, 2011).**

The prevalence rate of ESRD in Assiut governorate in 2014 was 366 pmp. Patients' mean age was 44.5 ± 12.3 years, with 65.7% males and 34.3 females. The etiology of ESRD was unknown in 25% of cases, whereas hypertension was responsible in 21.4% of cases, obstructive uropathy in 11% of cases, chronic glomerulonephritis in 8% of cases, analgesic nephropathy in 3% of cases, chronic pyelonephritis in 8.9% of cases, diabetic nephropathy in 14.9% of cases, toxemia of pregnancy in 2% of cases, and polycystic kidney disease in 0.7% of cases **(El-Arbagy et al., 2016)**.

Latest in Kafr El-Sheikh governorate, 282.6 pmp was the prevalence of ESRD in 2015. Patients' mean age was 51.34 ± 13.5 years with 60.7% males patients while 39.3% females. The main known causes of the ESRD in those patients was hypertension with 34%, diabetic nephropathy 14% while 25.3% of patients with unknown cause **(Ahmed et al., 2015).**

In an ESRD retrospective 5-years epidemiological study at Ain Shams University Hospital, incidence rate of dialysis raised from 257 to 381 patients/year in a period from 2005 to 2009. Patients' mean age was raised from 51.7 ± 15.6 years in 2005 to 53 ± 15.7 years in 2009. Regarding the co-morbid conditions found, 54.7% of the cases was hypertensives, 34.3 % were diabetics while 7.9% and 3.4% had chronic