



شبكة المعلومات الجامعية
التوثيق الإلكتروني والميكروفيلم

بسم الله الرحمن الرحيم



MONA MAGHRABY



شبكة المعلومات الجامعية
التوثيق الإلكتروني والميكروفيلم



شبكة المعلومات الجامعية التوثيق الإلكتروني والميكروفيلم



MONA MAGHRABY



شبكة المعلومات الجامعية
التوثيق الإلكتروني والميكروفيلم

جامعة عين شمس

التوثيق الإلكتروني والميكروفيلم

قسم

نقسم بالله العظيم أن المادة التي تم توثيقها وتسجيلها
علي هذه الأقراص المدمجة قد أعدت دون أية تغيرات



يجب أن

تحفظ هذه الأقراص المدمجة بعيدا عن الغبار



MONA MAGHRABY



THE EFFECT OF HEMODIAFILTRATION ON INFLAMMATORY BIOMARKERS IN COMPARISON TO HIGH FLUX DIALYZERS IN PREVALENT HEMODIALYSIS PATIENTS

Thesis

Submitted for partial fulfillment of M.D degree in Internal Medicine

Presented by

Walid Abdalla Attya Salem
(M.B., B.Ch) M.Sc, (Internal Medicine)

Supervised by

Prof. Dr. Gamal Elsayed Mady

Head of department of Nephrology
Professor of Internal Medicine and Nephrology
Faculty of Medicine, Ain Shams University

Ass. Dr. Walid Ahmed Bichari

Assist. Professor of Internal Medicine and Nephrology
Faculty of Medicine, Ain Shams University

Dr. Mostafa Abdel Nasier Abdel Gawad

Lecturer of Internal Medicine & Nephrology
Faculty of Medicine, Ain Shams University

Dr. Lina Essam Khedr

Lecturer of Internal Medicine & Rheumatology
Faculty of Medicine, Ain Shams University

Dr. Khaled Mohamed Rezk

Lecturer of Internal Medicine & Nephrology
Faculty of Medicine_ Ain Shams University

Faculty of Medicine
Ain Shams University

2020

بِسْمِ اللَّهِ الرَّحْمَنِ الرَّحِيمِ

قالوا

لسبحناك لا علم لنا
إلا ما علمتنا إنك أنت
العليم العظيم

صدق الله العظيم

سورة البقرة الآية: ٣٢



Acknowledgement

First and foremost thanks to **ALLAH**, the Most Merciful.

I wish to express my deep appreciation and sincere gratitude to **Prof. Dr. Gamal Elsayed Mady**, Head of department of Nephrology, Professor of Internal Medicine and Nephrology, Ain Shams University, for her close supervision, valuable instructions, continuous help, patience, advices and guidance. He has generously devoted much of her time and effort for planning and supervision of this study. It was a great honor to me to work under her direct supervision.

I wish to express my great thanks and gratitude to **Dr. Walid Ahmed Bichari**, Assist. Professor of Internal Medicine and Nephrology, Ain Shams University, for her kind supervision, indispensable advice and great help in this work.

I wish to express my great thanks and gratitude to **Dr. Mostafa Abdel Nasier Abdel Gawad**, Lecturer of Internal Medicine & Nephrology, Ain Shams University, for her kind supervision, indispensable advice and great help in this work.

I wish to express my great thanks and gratitude to **Dr. Lina Essam Khedr**, Lecturer of Internal Medicine & Rheumatology, Ain Shams University, for his kind supervision, indispensable advice and great help in this work.

I wish to express my great thanks and gratitude to **Dr. Khaled Mohamed Rezk**, Lecturer of Internal Medicine & Nephrology, Ain Shams University, for her kind supervision, indispensable advice and great help in this work.

Last and not least, I want to thank all my family, my colleagues,, for their valuable help and support.

Finally I would present all my appreciations to my patients without them, this work could not have been completed

CONTENTS

• List of Abbreviations	I
• List of Table	III
• List of Figures.....	IV
• Introduction	1
• Aim of the work.....	4
• Review of literature.....	
Chapter (1): Inflammation and Inflammatory Biomarkers	5
Chapter (2): Inflammation in chronic kidney disease and hemodialysis.....	21
Chpater (3): Hemodialysis vs Hemodiafiltration and their impact on inflammatory biomarkers	44
• Subjects And Methods	57
• Results	63
• Discussion.....	88
• Summary	93
• Conclusions	95
• Recommendations	97
• References	98
• الملخص العربي	-

LIST OF ABBREVIATIONS

AGEs	: Diabetes mellitus
b2-MG	: B2-microglobulin
BMI	: Body mass index
CANTOS	: Canakinumab anti-inflammatory thrombosis
CAPD	: Continuous ambulatory peritoneal dialysis
CKD	: Chronic kidney disease
CKD-	: Chronic Kidney Disease–Mineral and Bone Disorder
COX-2	: Cyclooxygenase-2
CRF	: Chronic renal failure
CRIC	: Chronic Renal Insufficiency Cohort
CRP	: C-reactive protein
CTRA	: Conserved transcription response to adversity
CVD	: Cardiovascular disease
DM	: Advanced glycated end products
eGFR	: Estimated glomerular filtration rate
ELISA	: Enzyme linked immunosorbent assay
eNOS	: Endothelial NO-synthase
ESRD	: Coronary heart disease
GFR	: Glomerular filtration rate
HD	: Hemodialysis
HDF	: Hemodiafiltration
HDL	: High density lipoproteins
HIF	: Hypoxia-inducible factor
hs-CRP	: High-sensitivity CRP
HTN	: Hypertension
IL	: Interleukin
IL-1	: Interleukin-1
IL-23	: Interleukin 23
IL-6	: Interleukin 6
iNOS	: Inducible nitric oxide synthase
KDIGO	: Kidney disease improving global outcomes

List of Abbreviations

MDRD	: Modification of diet in renal disease
MMP-9	: Matrix metalloproteinase-9
MMPs	: Matrix metalloproteases
NF-κB	: Nuclear factor kappa-B
OL-HD	: Online hemodiafiltration
OL-HDF	: Online hemodiafiltration
PAMPs	: Pathogen-associated molecular patterns
PD	: Peritoneal dialysis
PHDs	: Prolyl hydroxylases
ROS	: Reactive oxygen species
SNS	: Sympathetic nervous system
STAT3	: Signal transducer and activator of transcription 3
TC	: Total cholesterol
TGs	: Triglycerides
TNF-α	: Tumour necrosis factor alpha
VLDL	: Very low-density lipoproteins
β	: Beta

LIST OF TABLE

Tab. No.	Subjects	Page
Table 1:	Comparison between acute and chronic inflammation.....	9
Table 2:	Comparison between group A and group B as regard some demographic and biochemical data:	63
Table 3:	Comparison between group A and group B as regard lipid profile:	65
Table 4 :	Comparison between group A and group B as regard some biochemical data using Independent-samples T test before 3 months:	66
Table 5:	Comparison between group A and group B as regard some biochemical data using Independent-samples T test after 3 months	67
Table 6:	Comparison between group A and group B as regard inflammatory markers (CRP and IL6) using Independent-samples T test before and after 3 months.....	68
Table 7:	Comparison between CRP before and after 3 months in group A using Chi-Square test	69
Table 8:	Comparison between CRP before and after 3 months in group B using Chi-Square test	70
Table 9:	Comparison between IL6 before and after 3 months in group A using Chi-Square test	70
Table 10:	Comparison between IL6 before and after 3 months in group A using Chi-Square test	71
Table 11:	Correlation between CRP (mg/dl) before 3 months and all studied parameters in all groups	72
Table 12:	Correlation between CRP (mg/dl) after 3 months and all studied parameters in all groups	76
Table 13:	Correlation between IL6 (mg/dl) before 3 months and all studied parameters in all groups	80
Table 14:	Correlation between IL6 (mg/dl) after 3 months and all studied parameters in all groups	84

LIST OF FIGURES

Fig. No.	Subjects	Page
Figure 1:	Activation, resolution, and the process leading to chronicity of inflammation.....	7
Figure 2:	Pathways linking inflammation and cancer	11
Figure 3:	Cytokines, chemokines and their receptors.....	12
Figure 4:	IL6 is a pleiotropic cytokine.	14
Figure 5:	Factors contributing to the progression of CKD and CVD	24
Figure 6:	Factors contributing to increased inflammation in chronic dialysis patients	27
Figure 7:	Pathophysiology of accelerated atherosclerosis in CKD	28
Figure 8:	Adverse clinical outcomes associated with increased inflammation in chronic dialysis.....	29
Figure 9:	Schematic representation of the causes of protein energy wasting and pathophysiologic interactions in chronic kidney disease.	35
Figure 10:	Pharmacological and nonpharmacological strategies to reduce inflammation in chronic dialysis.	40
Figure 11:	Clinical correlation between kidney and heart disease.	48
Figure 12 :	Comparison between group A and group B as regard lipid profile	65
Figure 13:	Comparison between group A and group B as regard some biochemical data using Independent-samples T test before 3 months.....	66
Figure 14:	Comparison between group A and group B as regard some biochemical data using Independent-samples T test after 3 months.....	67
Figure 15:	Comparison between group A and group B as regard inflammatory markers (CRP and IL6) using Independent-samples T test before and after 3 months.....	68

Abstract

Introduction Inflammation in patients with ESRD undergoing HD is an increasing concern for physicians and has been related to increase the rates of morbidity and mortality. Interestingly, patients with ESRD in conventional HD have frequent infections and a suboptimal response to vaccines; this is probably related to an immune inflammatory disorder associated either with uremia and /or nutritional status.

Objective The aim of this study is to detect, prospectively, the effect of 3 months dialysis with Hemodiafiltration on inflammatory and nutritional biomarkers in comparison to conventional dialysis with high flux dialyzer in stable HD patients.

Patients and methods 30 adults aged 20-75 years who were selected from Dialysis Unit, Kobary El-Kobba Military Hospital. 30 male patients known to have chronic kidney disease and are on dialysis with high flux dialyzer more than 3 months were divided into 2 groups: 15 Patients are shifted to be on dialysis with HDF and 15 Patients are continued to be on Regular Hemodialysis with high flux dialyzer. Full medical history and clinical examination.

Results The current study was conducted on 30 patients with chronic kidney disease on regular dialysis. The patients were divided into two groups A representing patients on hemodiafiltration (n=15) and group B representing patients on dialysis with high flux dialyzer (n=15). A high statistical significant difference ($P < 0.01$) was found regarding K 4.3 ± 0.6 meq/l in group A while it is 5.2 ± 0.5 meq/l in group B, a high statistical significant difference ($P < 0.01$) was found regarding phosphorus 4.6 ± 1.0 mg/dl in group A while it is 6.1 ± 0.9 mg/dl in group B and no statistical significant difference ($P > 0.05$) was found as regard the uric acid.

Conclusion The present study revealed that there was no significant change in CRP and IL6 in patients on HDF compared to patients undergoing hemodialysis with high flux dialyzer before 3 months but there was a significant decrease in CRP and IL6 in patients on HDF compared to patients undergoing hemodialysis with high flux dialyzer after 3 months.

INTRODUCTION

Inflammation has been recognized as an essential part of chronic kidney disease (CKD). In the late 1990s and it was linked to cardiovascular disease, protein-energy wasting, and mortality. In the Chronic Renal Insufficiency Cohort (CRIC) study, biomarkers of inflammation (IL-1 β , IL-1 receptor antagonist, IL-6, TNF- α , CRP, and fibrinogen) were inversely associated with the measures of kidney function and positively with albuminuria (***Gupta et al., 2012***).

Despite recent advances in CKD and end-stage renal disease (ESRD) management, morbidity and mortality in this population remain high. Persistent low-grade inflammation has been recognized as an important component of CKD, playing a unique role in its Pathophysiology and being accountable in part for cardiovascular and all-cause mortality, as well as contributing to the development of protein-energy wasting (***Akchurin and Kaskel, 2015***).

CKD and especially dialysis patients are prone to additional inflammatory stimulations due to infectious and thrombotic events such as, catheter-related bloodstream infections, access site infections, thrombosed fistulas and grafts, and episodes of peritonitis in PD patients. (***Ruospo et al., 2014***)

As renal function deteriorates, worsening of appetite and a decline in the nutritional state is frequently observed in patients with chronic kidney disease (CKD). Protein Energy Wasting (PEW) describes a state of decreased body protein and energy stores. PEW is defined as the presence of three out of the following four categories: decreased serum albumin or cholesterol levels, low or a fall in body mass, decreased muscle mass or unintentional loss of dietary protein (and calorie) intake (**Pieter and Denis, 2015**).

Pro-inflammatory cytokines may directly cause anorexia via influence on the brain. In addition, inflammatory markers, particularly IL-6, may be associated with depression in CKD and ESRD, which by itself is a predictor of morbidity and mortality (**Taraz et al., 2014**).

Inflammation has been proved to have a role in the pathophysiology of anemia and bone disorders. TNF-alpha is an inducer of the NF-κB ligand (RANKL) which is a key trigger of osteoclast activation and bone resorption (**Panuccio et al., 2012**).

For ESRD patients, two main approaches to decrease inflammatory load related to the dialysis procedure were proposed. First, elimination of factors triggering inflammation, second, removal of inflammatory mediators. Interventions that were tested include the use of biocompatible membranes, purity standards for

hemodialysis (HD) water, ultrapure dialysate, increased dialysis frequency, and Hemodiafiltration (***Santoro and Mancini, 2014***).

Recent meta-analysis demonstrated that the use of ultrapure dialysate in HD patients results in a decrease in markers of inflammation and oxidative stress, an increase in serum albumin and hemoglobin and a decrease in erythropoietin requirement. Hemodiafiltration may decrease inflammatory activity via additional clearance of middle molecules by convection (***den Hoedt et al., 2014***).