Obesity Related Hypertension in Prevalent Hemodialysis Patients

Thesis

Submitted for Partial Fulfillment of M.Sc. Degree inInternal Medicine

by

Ismail Ibrahim Muhammad Alsharkawy

M.B.B.Ch.,

Faculty of Medicine- Tanta University

Supervised by

Prof. Dr. Yasser Soliman Ahmad

Professor of Internal Medicine and Nephrology

Faculty of Medicine- Ain Shams University

Dr. Waleed Anwar Abdel Mohsen

Assistant Professor of Internal Medicine and Nephrology

Faculty of Medicine- Ain Shams University

Faculty of Medicine

AinShamsUniversity

Cairo 2014

Acknowledgement

First of all thanks to "ALLAH" for helping me to complete this study…

I have the greatest pleasure to express my deepest gratitude to ***Prof. Dr. Yasser Soliman Ahmad,*** *Professor of Internal Medicine, Faculty of Medicine, Ain Shams University, for his most valuable advises and support all through the whole work and for dedicating much of his precious time to accomplish this work,his generous encouragement, supervision, reading and critical discussions during the writing and preparation of the manuscript of this thesis.*

I wish to also to express my sincere thanks to Assistant ***Prof Dr.Waleed Anwar Abdel Mohsen,*** *Assistant Professor of Internal Medicine, Faculty of Medicine, Ain shams University, for his supervision, tutorial guidance, continuous assistance, valuable support, unfailing interest in the progress of the work, and his critical review of the thesis.*

Ismail Ibrahim Alsharkawy

Contents

List of Abbreviation

Abb.	Meaning
A1 AGP	Alpha-1 Acid Glycoprotein
ADMA	Asymmetrical dimethyl arginine
Ag	Antigen
AGE	Advanced glycatedendproducts
AHI	Apnea-hypopnea index
AIDS	Acquired Immune Defeciency Disease
ANG	Angiotensinogen
ApoE	Aoplipoprotein E
BMI	Body mass index
Ca	Calcium
c-GMP	Cyclic guanosine monophosphate
CHF	Congestive heart failure
CKD	Chronic kidney disease
CNS	Central nervous system
CRP	C-Reactive protein
CVD	Cardiovascular disease
DBP	Diastolic blood pressure
eKt/V	Equilibrated Double Pool
ELISA	Enzyme-linked immunosorbent assay
eNOS	Endothelial Nitric Oxide Synthase
ESRD	End stage renal disease
ETA	Endothelin receptor type A
ETB	Endothelin receptor type B
FFA	Free fatty acid
GFR	Glomerular filtration rate

List of Abbreviations (Cont.…)

Abb.	Meaning
HD	Hemodialysis
HDL	High density lipoprotein
HRP	Horseradish peroxidase) enzyme
HsCRP	High sensitivity C-reactive protein
HTN	Hypertension
ICAM	Intercellularadhesion molecule
IGF	Insulin-like growth factor 1
IL-6	Interleukin-6
LDL	Low density lipoprotein
LVH	Left ventricular hypertrophy
MCP-1	Monocyte Chemo attractant Protein-1
MSA	Multisystem atrophy
Na	Sodium
NHANES III	Third National Health and Nutrition Examination Survey
NO	Nitric Oxide
OHS	Obesity hypoventilation syndrome
OSA	Obstructive sleep apnea
P	Phosphorus
PAI-1	Plasminogen activating inhibitor-1
pg	Picogram
PGE2	Prostaglandin E2
PGI2	Prostacyclin
PINI	Prognostic Inflammatory and Nutritional Index
PREVEND	Prevention of Renal and Vascular End Stage Disease

List of Abbreviations (Cont….)

Abb.	Meaning
RAAS	Renin-angiotensin-aldosterone system
REM	Rapid eye movement
SBP	Systolic blood pressure
SNP	Single nucleotide polymorphism
SNS	Sympathetic nervous system
SREBP-1	Sterol regulatory element binding protein
TMB	Tetramethylbenzidine
TNFα	Tissue necrosis factor-alpha
VCAM	Vascular adhesion molecule
WC	Waist circumference
WCRF	World Cancer Research Fund
WHO	World Health Organization
WHR	Waist-to-hip ratio

List of Tables

List of Tables (Cont….)

List of Tables (Cont….)

List of Figures

Introduction

Obesity is the epidemic of 21th century. In developing countries, the prevalence of obesity continues to rise and obesity is occurring at younger ages. The world health organization estimates that globally there were>1 billion overweight adults {body mass index (BMI) ≥25}, 300 million of whom are obese {body mass index (BMI) ≥30}. This poses a major public health issue due to increased risk of several serious chronic diseases such as type2 diabetes, cardiovascular disease, hypertension and stroke **(Greenberg and Obin, 2006)**.

Adipose tissue is a dynamic endocrine organ that secretes a number of factors that are increasingly recognized to contribute to systemic and vascular inflammation. Several of these factors, collectively referred to as adipokines, have now been shown regulate, directly or indirectly a number of the processes that contribute to the development of atherosclerosis including hypertension, endothelial dysfunction, insulin resistance and vascular remodeling. Several adipokines are preferentially expressed in visceral adipose tissue and the secretion of pro-inflammatory adipokines is elevated with increasing adiposity **(Lyon and Law, 2003)**.

Hypertension is a common finding in dialysis patients. Based upon multiple studies, over 50 to 60% of hemodialysis patients (up to 85% in some reports) are hypertensives. These values are lower than the 80% incidence of hypertension at initiation of dialysis due largely to better volume control in most patients **(Henrich, 2012).**

The high mortality rate seen in dialysis patients is related to longstanding high blood pressure and presence of other traditional and non-traditional risk factors for cardiovascular disease. Risk factors of hypertension in hemodialysis patients may include extracellular fluid volume expansion, increased endothelin level synthesis, activation of rennin angiotensin and sympathetic nervous system and hemoconcentration induced by erythropoietin treatment. Hypertension is associated with increased risk of left ventricular hypertrophy, coronary artery disease, congestive heart failure and cerebrovascular complications. Optimal blood pressure in dialysis patients is not different from recommendations for general population **(Horl and Horl, 2002)**.

Large longitudinal studies showed the epidemiological link between obesity and hypertension. During last years, multiple possible mechanisms involved

in this association were identified. Adipose tissue has an important role in the genesis of hypertension in obese patients through several pathways: insulin resistance, leptin, rennin-angiotensin-aldosterone system and mediators of inflammation; tumor necrosis factor-alpha (TNF-α) and interleukin-6 (IL-6). Adipocyte may be the major player in the development of insulin resistance and hypertension, elements of metabolic syndrome, responsible for cardiovascular complications **(Blaj et al., 2003)**.

An activated inflammatory response is a common feature of end-stage renal disease (ESRD) patients and predicts outcome. Although various factors related to the dialysis process may contribute to inflammation, such as bio-incompatibility and non-sterile dialysis fluids, a number of non-dialysis related factors also are of importance. Adipose tissue secretes a number of pro-inflammatory adipokines such as leptin, resistin, tumor necrosis factor-alpha (TNF-α) and interleukin-6 (IL-6) which have pleiotropic activities and can enhance adhesion molecules, expression on endothelial cells, stimulate Ag presentation and stimulate synthesis of inflammatory mediators as PGE2 from fibroblasts **(Pauletto , 2006)**.

Patient with end-stage renal disease present with an immunodeficient state paradoxically co-exisisting with

signs of activation of immune system cells and that is accentuated rather than corrected by replacement dialysis therapy. There is an increased production of the cytokines IL-1, TNF-alpha and IL-6 by activated monocytes **(Descamps-Latscha, 1997)**.

In contrast to general population, a higher BMI is associated with better survival among hemodialysis patients, referred to as reverse epidemiology. Chronic hemodialysis patients frequently have a low energy intake and are underweight. A greater caloric intake by hemodialysis patients to engender a better survival outcome has been hypothesized because of obesity paradox. Nonetheless; obesity is also associated with increased risk of developing insulin resistance which may contribute to accelerated cardiovascular disease which is the major cause of death among chronic hemodialysis patients. Hence the protective effects of excess weight in hemodialysis patients remain debatable and need to be tested with an appropriately designed prospective study **(Hung and Tang, 2009)**.

Substantial evidence has been accrued that inflammation is a major factor in the high mortality of ESRD patients, and a variety of experimental and epidemiological studies coherently indicate that cytokines

and other inflammatory proteins are not only conducive to cardiovascular damage in experimental models but also predictive of cardiovascular events in patients with ESRD.We recently reported that IL-6, a key player in acute phase response, is the strongest predictor of mortality among inflammation markers **(Zoccali et al., 2003)**.

IL-6, the major mediator of acute-phase response, is elevated in most but not all ESRD patients. A number of factors prevalent in patients with ESRD such as hypertension, adiposity, and insulin resistance could all be associated with elevated IL-6 level **(Memoli, 2001)**.

There is currently great excitement surrounding acute-phase reactant CRP for the insights it is providing into etiologic relationships between inflammation and clinical vasculopathic syndromes, its usefulness as a clinical marker and evidence for a direct pathogenic involvement. Elevated CRP levels are unquestionably associated with obesity and increased risk of cardiovascular disease. CRP, a hepatic acute phase protein, is largely regulated by circulating levels of IL-6 **(Berg and Scherer, 2005)**.