Cardiac Dysfunction Among Hemodialysis Patients with Metabolic Syndrome

Thesis

Submitted for Partial Fulfilment of Master Degree in

Internal Medicine

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Dedication

I WOULD LIKE TO DEDICATE THIS THESIS TO THE SOUL OF MY MOTHERAND TO MY FATHER; TO THEM I WILL NEVER FIND ADEQUATE WORDS TO EXPRESS MY GRATITUDE.

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List of abbreviations

1-ADMA	asymmetric-dimethyl arginine
ABPM	ambulatory blood pressure monitoring
ACR	Albumin: creatinine ratio
ADMA/DDAH	asymmetric dimethylarginine/ dimethylarginine dimethylaminohydrolase
AHA/NHLBI	American Heart Association/National Heart, Lung, and Blood Institute
AMPK	AMP activated protein kinase
APKD	Adult Polycystic Kidney Disease
apo(a)	apolipoprotein(a)
ASA	Acetyl salicylic acid
ASCOT-LLA	Anglo-Scandinavian Cardiac Outcomes Trial--Lipid Lowering Arm
AURORA	A Study to Evaluate the Use of Rosuvastatin in Subjects on Regular Hemodialysis
BMI	Body mass index
BP	Blood pressure
BV	Blood volume
CAD	Coronary artery disease
CETP	cholesteryl ester transfer protein
CKD	Chronic kidney disease
CVD	Cardiovascular disease
D.M	Diabetes mellitus
DBP	Diastolic blood pressure
DW	dry weight
ECV	extracellular volume
EF	Ejection fraction
EGIR	European Group for the Study of Insulin Resistance
ELFA	enzyme immunoassay sandwich method with a final flurescent detection
EPO	Erythropoietin
ESRD	end-stage renal disease
F.B.S	Fasting blood sugar
FFA	free fatty acid
GFR	Glomerular filteration rate
HD	Hemodialysis
HDL-C	High density lipoproteins-C
HF	Heart failure
HMG-CoA reductase	hydroxyl-3-methylglutaryl-CoA reductase
HMW	high molecular weight
HOMA-IR	Homeostatic Model Assessment of Insulin Resistance
HPS	Heart protection study
ICAM-1	Intercellular Adhesion Molecule 1
IDF	International Diabetes Federation
IDH	intra-dialytic hypotension
IDL	intermediate-density lipoprotein
IGF-1	Insulin-like Growth Factor-1
IHD	Ischemic heart disease
IL-6	Interleukine-6
iNOS	Inducible Nitric oxide synthases
IR	Insulin resistance
IVSd	Thickness of Interventricular septum
K/DOQI	the Work Group for Kidney Disease Outcomes Quality Initiative
KDIGO	Kidney disease improving global outcomes
LCAT	lecithin-cholesterol acyltransferase
LDL	Low density lipoproteins
LMW	low molecular weight
ln CRP	natural logarithm (geometric means)
Lp(a)	Lipoprotein (a)
LVH	Left ventricular hypertrophy
LVIDd	Internal diameter of left ventricle at end diastole
LVM	Left Ventricular Mass
LVMI	Left Ventricular Mass Index
MAP	Mean arterial pressure
MCP-1	Monocyte chemotactic protein-1
MDRD	Modification of Diet in Renal Disease study

MetS	Metabolic syndrome
NCEP-ATP III	National Cholesterol Education Program Third Adult Treatment Panel
NF-kB	nuclear factor kappa-light-chain-enhancer of activated B cells
NHANES III	The third National Health and Nutrition Examination Survey
NICE	National institute of clinical excellence
NO	nitric oxide
NS	nephrotic syndrome
PAI-1	plasminogen activator inhibitor-1
PCR	Protein:creatinine ratio
PD	Peritoneal dialysis
PG	Plasma glucose
PKCs	Protein Kinase-C
PPAR	peroxisome proliferator-activated receptors alpha
PRA	plasma renin activity
PTH	parathormone
PVD	Peripheral vascular disease
PWd	Thickness of posterior wall in end diastole
QUICKI	Quantitative Insulin Sensitivity Check Index
RAAS	rennin angiotensin-aldosterone system
RCTs	randomized controlled trials
ROS	reactive oxygen species
RPF	renal plasma flow
SBP	Systolic blood pressure
SERBP	sterol regulatory element binding proteins
SNS	sympathetic nervous system
SPR	solid phase receptacle
TG	Triglycerides
TGF-β	Transforming Growth Factor-β
TGF-β1	Transforming Growth Factor-ß1
TNF-*α*	tumor necrosis factor-α
U.A	Uric acid
VA-HIT	The Veterans Affairs HDL Intervention Trial
VLDL	Very Low Density Lipoproteins
VSMC	vascular smooth muscle cell
vWF	von Willebrand factor
WC	Waist circumference
WHO	World Health Organization

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Introduction

The number of chronic kidney disease (CKD) patients has been increasing throughout the world over the last decade and is expected to continue growing. A rise in the incidence of CKD in recent years paralleled with an increasing prevalence of metabolic syndrome **(Yu et al, 2010)**.

Metabolic syndrome is a medical condition with a clustering of major risk factors for cardiovascular diseases and type 2 diabetes. It arises from a constellation of derangements that includes hypertension, atherogenic dyslipidemia, central obesity and insulin resistance **(Park et al, 2010).**

There are several different definitions of metabolic syndrome. Although all of them include glucose intolerance, obesity, hypertension, and dyslipidemia as essential components, they differ in details. According to the definitions of the World Health Organization (WHO) and the European Group for the Study of Insulin Resistance (EGIR), glucose intolerance or insulin resistance are considered as essential metabolic syndrome components, whereas this is not the case for the National Cholesterol Education Program Adults Treatment Panel III (NCEP-ATPIII) (**Ucar et al., 2009)**.

Due to its simplicity and clinical relevance, the NCEP definition for metabolic syndrome is nowadays the one being most widely used in general populations **(Li et al, 2009).**

It requires three of the following five criteria:

• Abdominal obesity (waist circumference >102 cm in men and >88 cm in women);

• Fasting hypertriglyceridemia (≥ 1.7 mmol/L or 150 mg/dL);

• Low fasting HDL (<1.04 mmol or 40 mg/dL in men and<1.29 mmol/L or 50 mg/dL in women).

• High blood pressure (≥130/85 mmHg) or current treatment with antihypertensive medication; and
• High fasting glucose (≥6.1 mmol/L or 110 mg/dL) or current treatment with anti-diabetic medication.

Metabolic syndrome promotes the development of chronic kidney disease, and insulin resistance has been noticed as a result of impaired renal function; hence, patients with end-stage renal disease (ESRD) show a high prevalence of metabolic syndrome **(Johnson et al, 2007**, Young **et al, 2007)**. However, the exact prevalence of the metabolic syndrome in dialysis patients is unknown **(Elsaid et al, 2009).**

End-stage kidney disease (ESKD) patients requiring dialysis have a substantially elevated risk of CVD morbidity and mortality. Evidence is accumulating to suggest that the metabolic syndrome predisposes to cardiovascular disease (CVD). Recent studies associate metabolic syndrome with hospitalization and severe coronary artery disease in HD patients. Reports also show a relationship between metabolic syndrome and inflammation in patients on HD **(Chen et al, 2006 ,Yang et al,2007)**

In the general population, metabolic syndrome and its constituent components are known to increase risk for adverse effects, including cardiovascular disease and type 2 diabetes but data in the dialysis population are lacking **(Grundy, 2008, Park et al, 2010).** Evidence increasingly suggests, however, that some components of metabolic syndrome, including hypertension, hyperlipidemia and obesity, may favourably influence outcome in ESRD, an example of 'reverse epidemiology **(Chen et al,2006, Park et al, 2010).** In fact, hemodialysis patients with malnutrition had a lower rate of survival compared with those who had metabolic syndrome **(Stolic et al ,2010).**

Aim of the work

The aim of the present study is to compare cardiac function in hemodialysis patients with metabolic syndrome and those without metabolic syndrome.

Patients and methods

This study will be conducted on 100 adult stable regular hemodialysis patients, who had been on regular dialysis for more than 3 months at Mobaric and Elagoza Police Hospitals, after obtaining their informed consent.

Exclusion criteria will include patients who were younger than 18 years of age, had overt infections during the last 3 months prior to study enrollment or had a history of malignancy or other chronic inflammatory disease (e.g. rheumatoid arthritis or systemic lupus), or unwillingness to participate in the study.

The patients will be divided into 2 groups based on the presence or absence of metabolic syndrome:

Group I: will include 50 HD patients fulfilling the criteria of metabolic syndrome according to the NCEP-ATP-III.

Group II: will include 50 HD patients without metabolic syndrome.

All study population will be submitted to:

1. Full history taking with recording of clinical, demographic, hemodialysis data, detailed drug history and associated co-morbid diseases.
2. Through clinical examination including vital signs, body weight, height, BMI(weight (kg) divided by the height squared (m2),waist circumference measurement.
3. Blood samples for laboratory measurements of fasting blood glucose and fasting serum total cholesterol, HDL cholesterol , triglycerides ,serum albumin, and C-reactive protein (CRP)
4. M-mode and 2-dimensional Doppler Echocardiographic examinations will be done to all participants to evaluate LV measures and cardiac function .

5.Patients will be classified as having metabolic syndrome if they have three or more of the following criteria of NCEP-ATP-III: (1) SBP ≥130 mmHg and/or DBP ≥85 mmHg, (2) serum TG ≥150 mg/dl, (3) serum HDL cholesterol <40 mg/dl in men or <50 mg/dl in women, (4) fasting plasma glucose ≥110 mg/dl and (5) abdominal obesity according to waist circumference measured at the level of the umbilicus with the participant in the supine position defined as waist circumference >102 cm in men or >88 cm in women.