The Relationship between Adhesion Molecules and Parameters of Inflammation and Dyslipidemia in Uremic Patients

Thesis
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Abstract

Cardiovascular diseases are the leading cause of morbidity and mortality among patients with renal failure. Systemic inflammation caused by renal failure per se and by the process of hemodialysis are important risk factors for cardiovascular disease in this patient population. This study was conducted in order to compare the level of three inflammatory markers: soluble vascular cell adhesion molecule (sVCAM-I) and monocyte chemoattractant protein (MCP-1) and C- reactive protein (CRP) in three different groups of individuals: patients with renal failure on hemodialysis, in patients with renal impairment, and persons without renal impairment. It was also planned to detect the relationship between the level of these markers of inflammation with dialysis adequacy, and nutritional parameters and finally to clarify the relationship between the previously mentioned two markers with the diastolic function and ventricular wall thickness.

Our study was conducted on 41 subjects divided into three groups: Group I included 23 patients with end stage renal disease on regular hemodialysis, group II included 10 patients with chronic renal impairment, and group III included 8 normal control subjects.

Laboratory tests in the form of urea, creatinine, total protein, serum albumin, cholesterol, triglycerides, serum level of VCAM, MCP-I, and CRP were done for all participants. Dialysis adequacy and post dialysis VCAM-1, MCP-1, and CRP were assessed for group I patients. Echocardiography was

done for all patients to determine diastolic function and ventricular wall thickness.

In our study, VCAM-1 MCP-1 and CRP levels were significantly higher after the dialysis procedure in patients of group I compared to pre dialysis levels ($p < 0.05$). Our results have also shown that the blood level of pre-dialysis VCAM-1 was significantly higher in patients on hemodialysis compared to normal controls ($p = 0.0001$) and to pre ESRD patients. CRP negatively correlated to serum albumin (r -0.43, p0.04). As regards the echocardiographic findings we found that patients with diastolic dysfunction had significantly higher levels of MCP-1.

Key words: VCAM-1, MCP-1, inflammation, atherosclerosis, CVD, CKD, ESRD, hemodialysis.

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List of Abbreviations

ADH=	Anti Diuretic Hormone
ADMA=	Asymmetric dimethylarginine
AF=	Atrial fibrillation
AGE=	Advanced glycation end products
ANP=	Atrial Natriuretic Peptide
AOPPs=	Advanced oxidative protein products
APC=	Antigen presenting cell
APR=	Acute phase reaction
AVC=	Aortic valve calcification
ATP III=	Adult Treatment Panel III
BP=	Blood pressure
CAD=	Coronary artery disease
CCR2=	Chemokine receptor 2
CHD=	Coronary heart disease
CHF=	Congestive heart failure
CKD=	Chronic kidney disease
CRI=	Chronic renal impairment
CRP=	C- reactive protein
CVD=	Cardiovascular disease
EBCT=	Electron beam computed tomography.
EC=	Endothelial cell
eNOS=	Endothelial form of nitrous oxide
EPO=	Erythropoietin
ESRD=	End stage renal disease

Abbreviations

HD=	Hemodialysis
HDL=	High density lipoprotein
HF=	Heart failure
ICAM-1=	Intercellular adhesion molecule-1
IFN-γ= =	Interferon gamma
IL-1,2,6,8,10	Interleukin-1, 2, 6, 8, 10
iNOS=	Inducible form of nitrous oxide
LDL=	Low density lipoprotein
LP(a)=	Lipoprotein (a).
LPS=	Lipopolysaccharides
LVH=	Left ventricular hypertrophy
MAC=	Membrane attack complex
MCP-1=	Monocyte chemoattractant protein-1
MCPIP=	Monocyte chemoattractant protein induced protein
MD=	Maintenance dialysis
MDA=	Malonyldialdehyde
MSCT=	Multislice spiral computed tomography
MVC=	Mitral valvular calcification
NE=	Norepinephrine
nNOS=	Neuronal form of nitrous oxide
NO=	Nitrous oxide
OH=	Hydroxyl group
oxLDL=	Oxidized LDL
PAI=	Plasminogen activator inhibitor
PD=	Peritoneal dialysis
PEM=	Protein energy malnutrition

Abbreviations

PMNs=	Polymorphnuclear cells
PWT=	Posterior wall thickness
RAS=	Renin angiotensin system
ROS=	Reactive oxygen species
RRT=	Renal replacement therapy
sdLDL=	Small density LDL
SWT=	Septal wall thickness
TCC=	Terminal complement complex
TGF-β=	Transforming growth factor- beta
Th1=	T helper 1 (T helper cell subpopulation)
Th2=	T helper 2 (T helper cell subpopulation)
TNF-α=	Tumor necrosis factor- α
USRDS=	United States Renal Data System
VC=	Vascular calcification
VCAM-1=	Vascular cell adhesion molecule-1
VLDL=	Very low density lipoprotein
VSMC=	Vascular smooth muscle cell

Introduction

And

Aims

Of The Study

Introduction & Aims of the study

Cardiovascular disease, in general, with coronary heart disease being the most prevalent 40% is the single most accurate predictor of mortality in patients with end-stage renal disease on regular hemodialysis **(Cheung et al., 2004)**.

Coronary heart disease (CHD) represents an important cause for overall morbidity and mortality among patients with chronic kidney disease (CKD) as well as among hemodialysis patients. Chronic renal dysfunction is an independent risk factor for the development of coronary heart disease and is also associated with an adverse effect on prognosis from cardiovascular disease **(Kaysen et al., 2004; Muntner et al., 2002).**

Inflammation is thought to play a central role in the pathogenesis and outcome of atherosclerosis and cardiovascular events in patients with chronic kidney disease as well as dialysis patients **(Shlipak et al., 2005).**

There is evidence that acute phase reaction with activation of cytokines such as C- reactive protein (CRP), interleukin-1 (IL-1), and interleukin- 6 (IL-6) and others is associated with the vascular pathology both in the general population and in dialysis patients. The vascular wall is particularly the main target of the inflammatory process **(Santoro and Mancini, 2002).**

In ESRD patients on regular hemodialysis, membrane bioincompatibility and water quality may be seen as the major culprits in the

development of acute phase reaction, during dialysis, transmembrane passage of intact endotoxins or low molecular weight bacterial products including bacterial DNA may account to some extent for the acute phase reaction **(Santoro and Mancini, 2002).**

Chronic inflammation is considered, based on several studies, to be the major determinant of the 'dialysis syndrome' characterized by malnutrition, cachexia and vasculopathy and responsible for the high mortality and morbidity rate in dialysis patients **(Amore and Coppo, 2002).**

Inflammation stimulates the activated endothelial cells to express a number of cytokines such as vascular cell adhesion molecule-1 (VCAM-1) and macrophage colony stimulating factor that encourage the differentiation of monocytes into macrophages and encourage them also to infiltrate the plaque, which is the critical step for the development of atherosclerosis and accordingly coronary heart disease **(Hansson 2005).**

The aim of this study was to

a) Compare the level of two inflammatory markers: an adhesion molecule (sVCAM-I) and a chemokine (monocyte chemoattractant protein-1) (MCP-1) and C-reactive protein (CRP) in three groups of individuals: patients with renal failure on hemodialysis, in patients with renal impairment (pre-ESRD) and in persons without renal impairment

b) To detect any association between the level of these markers of inflammation with dialysis adequacy, and nutritional parameters

c) To clarify the relationship between the markers of inflammation and nutrition on one hand and cardiovascular parameters viz. diastolic cardiac function, and ventricular wall thickness on the other hand.

Review

Of The

Literature

Cardiovascular Disease in Patients with Renal Insufficiency

Cardiovascular Diseases In Patients with Renal Insufficiency

Cardiovascular diseases are the leading cause of mortality in patients with renal insufficiency as well as in hemodialysis patients, accounting for 50% 0f overall mortality according to the U.S.Renal Data System, **USRDS 2003.**

Approximately 22% of the deaths from cardiac causes are attributed to acute myocardial infarction **(Kessler et al., 2002)**.

It is also an important source of morbidity, as the annual probability of hospital admission for heart failure (HF) and/or myocardial ischemia is approximately 20 percent in these patients (**Trespalacios et al., 2003)**.

Coronary heart disease and hypertension occur with increased frequency and are important causes of myocardial dysfunction in end-stage renal disease. In addition, there is evidence supporting a direct role for the uremic milieu and/or an indirect role for enhanced cardiovascular calcification **(London, 2003)** as it is increasingly appreciated that chronic renal dysfunction alone is an independent risk factor for the development of coronary artery disease **(Kaysen et al., 2004)**.

The relationship between hypertension and cardiovascular mortality in patients with end-stage renal disease is complicated because of the high prevalence of co morbid conditions and underlying vascular pathology. Although a positive correlation has been found in many studies **(Amar et al., 2000)**

Improved survival and better cardiovascular outcomes due to adequate blood pressure control have been demonstrated in those studies with the longest duration of follow-up and with the best design **(Takeda et al., 2005).**

A higher mortality may be due to the presence of left ventricular hypertrophy (on ECG or echocardiography), which is associated with increases in the incidence of heart failure, ventricular arrhythmias, death following myocardial infarction, sudden cardiac death, aortic root dilation, and a cerebrovascular event. Some evidence suggests that partial regression of hypertrophy due to adequate hypertensive therapy lowers the risk of mortality among dialysis patients **(London et al., 2001).**

The presence of HF independently predicts early mortality in end-stage renal disease as it does in nonuremic patients **(Trespalacios et al., 2003)**. According to the United States Renal Data System Dialysis Morbidity and Mortality Study, the mortality rate was 83 percent at three years among those with HF **(Trespalacios et al., 2003)**.