دراسة العلاقة بين البروتين التفاعلي (سى) وتصلب الشريان السباتى الرئيسي في مرضى الفشل الكلوي المعاشين على الاستصفاء الدموي

توطئة للحصول على درجة الماجستير في أمراض الكلى

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٢٠١٠

Study of the Relation Between
C. Reactive Protein and Carotid

Atherosclerosis in Hemodilalysis Patients

Thesis
Submitted For Partial Fulfillment
For MSC. Degree of Nephrology

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List of contents

List of Figures

List of Figures (Cont.)

List of Tables

List of Abbreviations

ADMA	:	Asymmetric dimethyl argenine
AHSD	:	Alpha 2- heremans schmid glycoprotein
MIA	:	Malnutrition, inflammation and athero sclerosis
AMI	:	Acute myocardial infarction
BMI	:	Body mass index
BP	:	Blood pressure
C.K.D	:	Chronic kidney disease
Ca	:	Calcium
CIMT	:	Carotid intima media thickens
CRP	:	c-reactive protein
CTMT	:	Carotid intina media thickness
CVD	:	Cardio vascular disease
ESRD	:	End stage renal disease
ET-1	:	Endotheline-1
GFR	:	Glomerular filtration rate
HD	:	Hemodialysis
HDLC	:	High density lipoprotein cholesterol
HS-CRP	:	High sensitivity C-reactive protein
LD	:	Lumen diameter
LDLC	:	Low density lipoprotein cholesterol
LVH	:	Left ventricular hypertrophy
MAP	:	Mean arterial pressure

List of Abbreviations (Cont.)

No	:	Nitric oxide
P.T.H	:	Parathyroid hormone
PO_4	:	Phosphorus
PWV	:	Pulse wave velocity
RAS	:	Renin angiotensinogen system
ROS	:	Reactive oxygen species
T_1DM	:	Type one diabetes mellitus
T_2DM	:	Type two diabetes mellitus
TG	:	Triglyceride
URR	:	Urea reduction ratio
VSMc	:	Vascular smooth muscle cells

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First of all, all gratitude is due to **God** *almighty for blessing this work, until it has reached its end, as a part of his generous help, throughout my life.*

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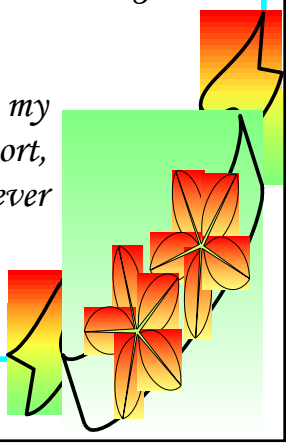
Adel Saied Mohamed Ibrahem



الملخص العربي

ترتفع نسبة أمراض القلب والأوعية الدموية لدى مرضى الفشل الكلوى تحت الاستصفاء الدموي، ويعتبر مرض تصلب الشرايين هو الأكثر شيوعاً من ناحية المضاعفات بين مرضى الفشل الكلوي.

والغرض من الرسالة هو توضيح العلاقة بين البروتين التفاعلي سي ومؤشرات تصلب الشرايين في مرضى الفشل الكلوى تحت الاستصفاء الدموي، ولتحقيق هذا الهدف تم اختيار أربعين مريضاً بالفشل الكلوي تحت الاستصفاء الدموي، بالإضافة لعشرة من الأصحاء كعينة مقارنة وشملت مجموع المرضى خمسة وعشرون من الرجال وخمسة عشر امرأة ومجموعة المقارنة شملت ستة رجال وأربعة نساء.

وتم فحص المرضى والأصحاء بعناية وتم عمل التحاليل اللازمة لهم وعمل البروتين التفاعلي سي (العالي الحساسية) وتم فحصهم جميعاً بالأيكو دوبلر على شرايين الرقبة (الشريان السباتي).

وكان سبب الفشل الكلوي في المرضى الذين تم فحصهم تحت الاستصفاء الدموي هو ٣٠% التهابات مناعية بالكلى ، ٣٠% ارتفاع بضغط الدم والتهابات مزمنة بالكلى في ٢٧% من الحالات، بينما لم يتم التعرف على السبب في حوالي ١٢,٥%.

وبالنسبة لتحاليل الدم التي تم إجراؤها وجد نسبة الألبومين منخفضة في مرضى الغسيل الكلوي تحت الاستصفاء الدموي وكذلك ارتفاع نسبة الكوليسترول والدهون منخفضة الكثافة وكذلك انخفاض نسبة الدهون العالية الكثافة مقارنة بالمجموعة الثانية (بدون فشل كلوي).

كما وجد ارتفاع بالبروتين التفاعلي (سي) العالي الكثافة في مرضى الفشل الكلوي تحت الاستصفاء الدموي مقارنة بمجموعة الأصحاء.

كما وجدت اختلافات واضحة في الأيكو دوبلر على شرايين الرقبة (الشريان السباتي) ما بين مجموعة المرضى تحت الاستصفاء الدموي ومجموعة الأصحاء .

Introduction

C-reactive protein (CRP) is a known risk factor for cardiovascular diseases, but the association of CRP with the early phase of atherosclerosis has been insufficiently investigated ***(Tirmenstajn-Janković and Dimković, 2005).***

Cardiovascular disease (CVD) is still the major cause of morbidity and mortality in hemodialysis (HD) patients. The characteristics of major arterial changes, atherosclerosis and related risk factors in HD patients remain unclear ***(Kiykim et al., 2004).***

According to ***Seyrek et al., (2003)*** metabolic, inflammatory, and hemodynamic alterations cause structural changes and vascular complications in end stage renal disease. Binding of CRP to lipids (especially lecithin) and to atheromatous plaques in combination with complement was reported by some authors ***(Pepys and Hirschfield, 2003).***

CRP has also been reported to have procoagulant effects ***(Cermak et al., 1993).*** In their study, ***Kiykim et al., (2004)*** stated plasma CRP levels were correlated with the CIMT (Carotid intima media thickness) measurements and plaque presence, significantly. CIMT as an atherosclerotic process indicator is thicker in asymptomatic HD patients than healthy subject. They concluded that in addition to various classical risk factors, uremic environment may also contribute to acceleration of the atherosclerotic process.

In patients on chronic hemodialysis, CRP is independently associated to carotid atherosclerosis and appears to be explained by IgG antichlamydia pneumoniae antibodies level. These data lend support to the hypothesis that inflammation plays a role in the pathogenesis of arteriosclerosis in these patients ***(Zoccali et al., 2000).***

Hommels et al., (2005) concluded that high sensitivity CRP (Hs-CRP) concentrations are related to atherosclerotic lesions in the renal arteries and abdominal aorta. While this supports the view that atherosclerotic renal artery stenosis is a part of systemic inflammatory vascular disease. Concentrations of CRP may also coincide with decreased renal function.

Aim of the Study

The aim of the present study is to investigate the relation between CRP and indicators of uncomplicated atherosclerosis in hemodialysis patients; intima-media thickness, lumen-diameter and cross-sectional intima-media area (CSIM area) of the common carotid artery.

Cardiovascular Disease in ESRD

Despite the improvement in the global care of patients with end-stage renal disease (ESRD), the mortality rate among hemodialysis (HD) patients remains unacceptably high (10–22%) ***(Rayner et al., 2004).*** The leading cause of death in this group of patients is cardiovascular disease (CVD). Traditional CVD risk factors alone do not account for the high incidence of cardiovascular mortality among these patients, as mortality from cardiovascular causes is on average 10–20 times higher than in the general population ***(Levin, 2003).*** According to the 10-year data from the Hong Kong Renal Registry, up to 50% of the mortality in dialysis patients is accounted for by cardiovascular causes ***(Wang et al., 2004).***

Indeed, the association between kidney failure and increased cardiovascular risk has been extensively reported in the literature. A pooled analysis of data from four community-based studies including the Atherosclerosis Risk in Communities Study, Cardiovascular Health Study, Framingham Heart Study, and Framingham Offspring Study has clearly demonstrated that chronic kidney disease is a risk factor for the composite endpoint of all-cause mortality and cardiovascular disease in the general population ***(Anavekar et al., 2004; Weiner et al., 2004).***

In another study by ***Go et al., (2004)*** an independent graded association was observed between a reduced estimated glomerular filtration rate and the risk of death, cardiovascular events and hospitalization in a large community-based population. This indicates that kidney dysfunction is an independent predictor of an enhanced cardiovascular risk and that the more severe the kidney dysfunction, the greater the cardiovascular risk. In a recent observational, prospective study by ***Almeida et al., (2010)*** on 334 HD patients who were studied for three years, global mortality rate was 21.6% (72

patients) and cardiovascular mortality constituted 41.7% (30/72) of the global mortality.

In ESRD patients, it is important to consider two primary categories of cardiovascular complications, namely vascular disease and myocardial disease ***(Wang et al., 2004).***

Vascular Disease In ESRD

Vascular disease in uremia encompasses two main subtypes, including atherosclerosis and vascular calcification, which lead to large-vessel remodeling or arteriosclerosis ***(Wang et al., 2004).***

- ***Vascular/valvular calcification***

Vascular calcification is present in a large proportion of maintenance hemodialysis patients, most frequently in the abdominal aorta ***(Wang et al., 2009).*** Screening for arterial calcifications in chronic kidney disease patients is suggested even in the early pre-dialysis period ***(Gelev et al., 2008).***

The presence of vascular and valvular calcification is associated with both atherosclerosis and arteriosclerosis in ESRD patients. Calcification occurring within the intimal layer and plaque area is characteristic of atherosclerotic disease and is associated with luminal stenosis and distal ischemia. On the other hand, calcification present within the medial layer, also known as Monckeberg's calcinosis, has been largely attributed to uncontrolled hyperphosphatemia and increased calcium-phosphorus product. It has a classic tram-line appearance on plain radiographs and is associated with stiffening of the arteries and loss of vascular compliance. Compared to non-uremic patients with only the intimal type of calcification, uremic patients frequently exhibit both intimal and medial types of calcification, but the intimal calcification is usually more extensive and of greater severity ***(Ketteler et al., 2005).***