Osteopontin as a marker for assessment of vascular atherosclerosis in chronic hemodialysis patients

Thesis

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ABI : Ankle brachial index

ADMA : Asymmetrical dimethylarginine

ALK P : Alkaline phosphatase.

ADPKD :Autosomal dominant polyscytic kidney disease.

BMI : Body mass index

BP : Blood pressure.

BSP1 : Bone sialoprotein 1

BUN : Blood urea nitrogen

CAC : Coronary artery calcium

CIMT : Carotid intima media thickness

DD : Diastolic dysfunction

E/A ratio : Ratio of peak velocity flow in early diastole (the E wave) to peak velocity flow in late diastole caused by atrial contraction (the A wave)

EF : Ejection fraction

ETA1 : Eearly t-lymphocyte activation 1

HCV : Hepatitis c virus.

HDL : High density lipoprotein

iPTH : Intact parathyroid hormone

ICAM1 : Intercellular adhesion molecule 1

IHD : Ischemic heart disease

IMT : Intima media thickness .

ILs : Interleukiens

LDL : Low density lipoprotein

LVH : Left ventricular hypertrophy.

LVMI : Left ventricular mass index

M-CSF : Macrophage-colony stimulating factor.

MGP : Matrixγ-carboxyglutamicacid protein

MMPs : Matrix Metalloproteinases

NO : Nitric oxide

OC : Osteocalcin

OPG : Osteoprotegerin

OPN : Osteopontin

oxLDL : Oxidized lipids and LDL

L-RANK : Linked receptor activator for nuclear factor-K B ligand

RGD : Arginine-glycine-aspartic acid

SMCs : Smooth muscle cells

SPP1 : Secreted phosphoprotein 1

SVVYGLR : Serine-valine-valine-tyrosine-glutamate-leucine-arginine motif

TGs : Triglycerides.

TNF :Tumer necrosis factor.

URR : Urea reduction ratio

VC : Vascular calcification.

VCAM-1 : Vascular adhesion molecule-1

VSMC's : Vascular smooth muscle cells

α-SMA : α-smooth muscle actin

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Introduction

Cardiovascular disease (CVD) is the most common cause of morbidity and mortality in dialysis patients **(Go AS et al., 2014).**

Atherosclerosis is the dominant cause of cardiovascular disease including myocardial infarction, heart failure, stroke, and claudication **(Frostegård et al., 2013**).

However, the death rates from CVDs remain fivefold higher among hemodialysis (HD) patients than in general populations **(de Jager et al., 2009).**

Several factors related to end stage renal disease (ESRD), such as elevated calcium-phosphate product and vascular calcifications, inflammations, over activity of the rennin-angiotensin system, and volume overload can be related to arterial stiffness **(London et al., 2015).**

HD patients were shown to exhibit increased intima media thickness (IMT), common carotid plaque, arterial stiffness, and coronary artery calcification and advanced atherosclerosis in the carotid artery compared with age-matched healthy controls, assessment of the carotid intima media thickness (CIMT) using B-mode ultrasound is a

useful clinical tool for the measurement of atherosclerosis **(Abassi et al., 2016).**

CIMT≥0.9 mm has been shown to be a marker of generalized atherosclerosis and is associated with cardiovascular risk factors, increased CIMT may be one of the factors of access failure in HD patients **(Park et al., 2013).**

Carotid arteries are mirrors of coronary arteries, and left ventricular hypertrophy appears in approximately 40 %of patients with chronic renal insufficiency, and is even more frequent (75%) at the onset of ESRD **(Gluba-Brzózka et al., 2016).**

Many bone-associated proteins, including osteocalcin (OC), matrix γ-carboxyglutamic acid protein (MGP), osteoprotegerin (OPG), osteopontin (OPN) and fetuin A, are expressed in atherosclerotic plaques and participate in atherosclerotic calcification **(Gluba-Brzózka et al., 2014).**

Osteopontin (OPN) a 70 kDa, a bone-specific sialoprotein, that is highly negatively charged encoded on chromosome 4 in the human genome, it is acidic glycoprotein **(Rangaswami et al., 2006).**

OPN has several names including early T-lymphocyte activation 1 (ETA1) protein, secreted phosphoprotein 1 (SPP1) and bone sialoprotein 1 (BSP1), this plurality of names represent the multi-functionality of OPN, as well as its expression by various cell types including the kidney **(Pagel et al., 2014).**

In healthy kidneys, OPN is secreted into the urine it is thus conceivable that increases in circulating OPN are partly resulting from reduced urinary excretion; circulating osteopontin is closely and inversely related to GFR **(Lorenzen et al., 2010).**

OPN can promote adhesion and migration of vascular smooth muscle cells and play an important role in atherosclerosis and restenosis after angioplasty **(Fang et al., 2009).**

Osteopontin has a role in the development of atherosclerotic plaque, it has been shown to be chemotactic for inflammatory cells, there by promoting infiltration of macrophages and resultant release of proteolytic enzymes, as well as the expression of adhesion molecules and oxidative stress **(Golledge et al., 2004).**

It was shown that serum OPN was increased in patients with clinical and radiological features of carotid plaque **(Kadoglou et al., 2008).**

OPN is a marker of the atherosclerotic process; its plasma level not only associated with the extension of the disease but also with its activity, as OPN is higher in unstable plaques versus stable plaques **(Wolak, 2014).**

The higher OPN level is, the more sever the renal function damage is, both OPN and renal failure are the risk factors for atherosclerosis, which is reflected by the fact that the severity of atherosclerosis is obviously increased with increase of OPN level or exacerbation of renal function damage **(Chen et al., 2014).**