Introduction

Atherosclerotic cardiovascular disease is a major cause of morbidity and the leading cause of mortality in End Stage Renal Disease (ESRD) patients on maintenance hemodialysis (HD) ***(Elena et al., 1994).***

Endothelial dysfunction had constantly been observed in chronic renal failure (CRF) patients, and results in impaired modulation of vascular growth, dysregulation of vascular remodeling and altered anti-coagulant and anti-inflammatory properties of the endothelium ***(Kosch et al., 2003).***

Chronic inflammation is a common feature of ESRD ***(Stenvinkel, 2001).*** It plays a key role in atherogenesis and atheroma development**.** Inflammatory mechanisms with atherosclerotic plaque formation can be triggered, maintained and enhanced by multiple factors such as oxidized low density lipoproteins (LDLs), increased reactive oxygen species and activated macrophages that induce synthesis of neopterin ***(Roxbourgh et al., 1999).***

Plasma neopterin originates as the oxidation product of 7,8-dihydroneopterin secreted by γ-interferon stimulated macrophages within atherosclerotic plaques, and is increasingly being used as a marker of inflammation during clinical management of patients with a range of disorders including atherosclerosis ***(Gieseg et al., 2008).***

Neopterin is expressed in endothelial cells, kidney epithelial cells, fibroblasts and vascular smooth muscle cells. Most studies dealing with effects of neopterin, provided evidence that interactions with reactive oxygen intermediate and the promotion of oxidative stress are fundamental principles of neopterins mode of action ***(Hoffmann et al., 2003).***

Neopterin levels have been shown to be elevated in patients with coronary artery disease (CAD) and associated with its severity, the complexity of atherosclerotic lesions and an increase in cardiovascular risk ***(Sugioka et al., 2010).***

Recent studies have shown a strong association of neopterin with cardiovascular disease (CVD). **Sasaki et al., (2010)** showed association of high levels with increased cardiac events rates. In a cross-sectional study, neopterin levels correlated with the extent of atherosclerosis, especially coronary and peripheral vascular disease (PVD) ***(Hermus et al., 2011).***

Neopterin has been identified as a potential risk factor for CVD in dialysis patients ***(Avci et al., 2008).***

Aim of the Work

The aim of the study is to evaluate the association between serum neopterin level and carotid atherosclerosis in chronic kidney disease patients.

Astherosclerotic Cardiovascular Disease

Patients with chronic kidney disease (CKD) are at substantially higher risk for the development of CVD than those in the general population without CKD ***(US Renal Data System: URSDS 2011).***

CVD accounts for approximately 50% of deaths in patients receiving renal replacement therapy (RRT). The risk of death due to CVD is 10–20 times higher in patients receiving dialysis than in the age, gender, and race-matched general population. CVD is particularly lethal in younger patients receiving renal replacement therapy, approaching an incidence 100 times that of the age matched general population ***(Smink et al., 2012)***.

Approximately 60% of cardiovascular (CV) deaths in dialysis patients are due to sudden cardiac arrest. Sudden cardiac arrest is frequently, but not invariably associated with alterations in cardiac structure and function that evolve during the course of CKD ***(US Renal Data System: URSDS 2011).***

Abnormal CV pathology in patients with CKD may be classified as vascular (atherosclerosis, arteriosclerosis, and vascular calcification) and myocardial (left ventricular hypertrophy (LVH) and dilated cardiomyopathy) ***(Smink et al., 2012)***.

The clinical sequelae to these alterations in pathology such as myocardial infarction (MI), heart failure and sudden cardiac arrest contribute to the high risk of CV mortality in those with CKD and particularly in those receiving dialysis. CVD in patients with CKD is multifactorial in origin .A variety of traditional and non-traditional risk factors (Table 1) begin to take their toll relatively early in the course of CKD and are facilitated by dialysis-related CV risk factors in those receiving RRT ***(Nusair et al., 2012).***

Moreover, there is increasing evidence that CKD itself is an independent CV risk factor ***(Matsushita et al., 2010).***

Although there is substantial overlap between risk factors for vascular disease and those predisposing to myocardial disease, the following review will focus on the ways in which these risk factors contribute to atherosclerosis.

Table 1

Risk factors for atherosclerosic CVD in patients with CKD

Traditional
Older age
Male sex
Hypertension
Diabetes mellitus
Dyslipidemia
Cigarette-smoking
Physical inactivity
Family history of premature CVD
Non-traditional
Hyperhomocysteinemia
Increased oxidative stress
Endothelial cell dysfunction
Inflammation
Activation of the renin–angiotensin–aldosterone system
Activation of the sympathetic nervous system
Abnormal calcium and phosphate metabolism*
Anemia (co-factor)
Possible CVD risk markers in patents with CKD
Hyperuricemia
Increased cystatin C levels
Increased pentraxin 3 levels
Increased beta-2 microglobulin levels
Increased beta-trace globulin levels
Reduced bone mineral density
Increased fibroblast growth factor 23 levels
CKD as an independent risk factor for CVD
Proteinuria, macroalbuminuria or microalbuminuria
Reduced GFR with or without proteinuria, macroalbuminuria or microalbuminuria
Secondary renal parenchymal hypertension
Uremia

Abbreviations: CVD, cardiovascular disease; CKD, chronic kidney disease; GFR, glomerular filtration rate.

* Contributes to vascular calcification and calcification in existing atherosclerotic plaques [26].

Table 1: ***(Matsushita et al., 2010).***

Traditional CV risk factors

Traditional risk factors for CVD in patients with CKD are similar to those for the general population. They include older age, male sex, hypertension, diabetes mellitus (DM), dyslipidemia, cigarette-smoking, physical inactivity, and a family history of premature CVD ***(Smink et al., 2012)***.

Older age

Although older age is frequently listed as a risk factor for CVD in patients with CKD, the evidence-basis for this conclusion is inferred primarily from studies of the general population such as the Framingham Heart Study. Most studies assessing cardiovascular outcomes in CKD adjusted for age. ***Muntner et al., (2005)*** reported that in the Atherosclerosis in Communities Study (ARIC) the median age was 55.8 years in those with CKD and incident coronary heart disease (CHD) during a 10.5 year period of follow-up compared with 58.8 years in those with CKD, but no CHD ($P < 0.001$) ***(Muntner et al., 2005).***

Additionally, elderly HD patients have also increased risk of acute coronary event and mortality after this event. In one study, it was demonstrated that elderly HD patients (>65 years old) have an odds of 3.289 for acute coronary syndrome and odds of 1.693 for death ***(Afsar et al., 2014).***

Gender

In the ARIC study 54.7% of patients with CKD and incident CHD during follow-up were men vs. 29.5% ($P < 0.001$) in those with CKD, but no CHD. In this study, the adjusted relative risk for a major CHD event in those with CKD was 3.96 (CI: 2.52–6.21). Notably, the percentage of men decreased progressively with declining renal function from 41.9% in those with normal renal function to 33.0% in those with stages 3 and 4 CKD ***(Muntner et al., 2005).***

Women are affected by CAD to a great extent. CAD is the leading cause of death for both men and women in the United States. More women than men die of CAD. More women have died from CAD than of cancer (including breast cancer), chronic lower respiratory disease, Alzheimer disease, and accidents combined. From 1998 to 2008, the rate of death attributable to CAD declined 30.6%, but the rates are increasing in young women ***(Roger et al., 2012).***

Hypertension

More than 85% of patients with CKD are hypertensive at some time during the course of their disease and its prevalence in CKD exceeds 50%. HTN affects many organ systems and causes end-organ damage to heart, blood vessels, brain and kidney. More than 20% of patients with systemic HTN have hypertensive nephropathy. Fortunately,

only a minority of these patients progress to advanced CKD or ESRD **(*US Renal Data System: URSDS 2011*).**

The renal changes in HTN are often classified as benign versus malignant nephrosclerosis. Benign nephrosclerosis is a gradual and prolonged process. It is far from benign, as it results in progressive renal injury in some patients. Malignant nephrosclerosis occurs in presence of malignant HTN (DBP > 130 and accelerated end-organ damage) and progresses at an alarming rate and, if untreated, may lead to death from stroke, heart attack or renal failure within months **(*D'Agati and Mengel, 2013*).**

Several studies have assessed outcomes in patients with HTN and CKD. The HTN Detection and Follow-up Group treated 10 940 hypertensive patients. Those whose serum creatinine was ≥1.7 mg/dl had an eight year mortality rate > 3 times that of patients with lower serum creatinine levels. ***(Shiffrin et al., 2007).***

It is now well-established that there is a 'J' curve with regard to blood pressure and mortality in patients with CKD. Systolic blood pressures ≥160 mm Hg or <120 mm Hg are associated with higher mortality rates than those with systolic blood pressures between 120 and 160 mm Hg. Current guidelines suggest that a blood pressure <130/80 mm Hg in patients with stable CKD may be an acceptable target. In patients with proteinuria and CKD, the target is <125/75 mm Hg. While decreased CV mortality has

accompanied more effective treatment of HTN in the general population, no such epidemiologic observations exists in patients with CKD ***(Shiffrin et al., 2007).***

The European Society of Hypertension/European Society of Cardiology 2013 guidelines for the treatment of HTN recommend lowering the systolic blood pressure to less than 140 mm Hg in patients with diabetic or non-diabetic CKD. In elderly patients with a systolic blood pressure of 160 mm Hg or higher, the systolic blood pressure should be lowered to 140-150 mm Hg . A diastolic blood pressure target of less than 90 mm Hg is recommended in patients with CKD ***(Mancia et al., 2013).***

The 2012 International Society of Nephrology guidelines for treatment of blood pressure in patients with non-dialysis-dependent CKD recommend that adults with CKD without diabetes mellitus or with diabetes mellitus with HTN and albuminuria less than 30 mg per 24 hours should have their blood pressure lowered to ≤140/≤90 mm Hg with a class I B indication. If albuminuria greater than 30 mg per 24 hours is present, lowering of the blood pressure to ≤130/≤80 mm Hg has a class II D indication ***(KDIGO ,2012).***

The eighth report of the Joint National Committee for the management of high blood pressure in adults (JNC 8) recommended that patients with CKD younger and older than 60 years of age should have their blood pressure

decreased to less than 140/90 mm Hg. These guidelines also recommended that ACEIs or ARBs should be used to treat HTN in patients with CKD regardless of ethnic background either as first-line therapy or in addition to first-line therapy **(*James et al., 2014*).**

Diabetes mellitus

DM is a common cause of CKD, and is often accompanied by proteinuria ***(Smink et al., 2012)***.

The prevalence of DM in CKD is 20% and is higher still in ESRD. DM is also a potent risk factor for CVD morbidity and mortality in the general population. The risk for adverse CV outcomes is particularly high in patients with diabetic nephropathy ***(US Renal Data System: URSDS 2011).***

Type 2 DM is one of the major risk factors associated with carotid atherosclerosis. It has been suggested that patients with type 2 diabetes have thicker and stiffer carotid arteries and are more likely to suffer from cerebrovascular events ***(Giannarelli et al., 2012).***

The World Health Organization Multinational Study for Study of Vascular Disease in Diabetes showed a nearly twofold increase in mortality rate in diabetics with microalbuminuria compared to the general population. The

mortality rate for those with microalbuminuria and HTN was nearly threefold higher than that of the general population ***(Shiffrin et al., 2007).***

In patients without CKD, DM is considered a CHD equivalent as CV mortality rates are similar to those of non-diabetic who have suffered a MI. Current guidelines suggest that a hemoglobin A1c level <7% is desirable in all diabetics. Excellent control of HTN in such patients may be even more important to preserve renal function ***(Shiffrin et al., 2007).***

Dyslipidemia

Dyslipidemia is frequently encountered in patients with CKD. Hypertriglyceridemia is the most common form of dyslipidemia in dialysis patients and has been attributed to retention of intermediate density lipoprotein and other atherogenic particles ***(Smink et al., 2012)***.

Hypertriglyceridemia is often, but not invariably associated with low high density lipoprotein (HDL) cholesterol levels. Most dialysis patients have normal or low total and LDL cholesterol levels, but 20–30% have total cholesterol levels >240 mg/dl and 10–45% have LDL cholesterol levels >130 mg/dl. In patients with the stage 3 and 4 CKD, the nephrotic syndrome and in peritoneal dialysis and renal transplant patients, total and LDL

cholesterol levels are commonly elevated, sometimes quite severely and hypertriglyceridemia is often present ***(Attman and Samuelsson, 2009).***

Dyslipidemia in CKD is caused in part by damage to the glomerular filtration barrier resulting in proteinuria. Compensatory up regulation of hepatic protein synthesis, which includes lipoproteins, occurs. Dyslipidemia in patients with CKD is thought to contribute to atherosclerosis through a variety of mechanisms, although the association is not as well-established as it is in the general population ***(Smink et al., 2012)***.

Reversible secondary causes of hypertriglyceridemia in CKD patients should be treated. Pharmacotherapy of hypertriglyceridemia should be reserved for those with levels ≥ 500 mg/dl to prevent pancreatitis. In those with lower levels of hypertriglyceridemia, non-pharmacologic measures such as diet, exercise, and weight loss are recommended ***(Smink et al., 2012).***

Cigarette-smoking

As in the general population, cigarette smoking contributes to the already high risk of atherosclerotic complications of CKD including a 22% greater risk of developing CHD and an increase in carotid intimal-medial thickness (IMT) ***(Van der Zee et al., 2009)***. No studies exist that show improved CV outcomes in CKD patients with

smoking cessation. Nevertheless, based on reduced CV events associated with smoking cessation in the general population as well as non-CV benefits, smoking cessation is strongly advocated in patients with CKD.

Physical inactivity

Unlike the general population, regular exercise has not been shown to improve CV outcomes in CKD patients, including those on dialysis. Regular exercise does however, help to reduce blood pressure and insulin resistance in some patients with CKD. For those reasons and for general well-being, regular physical exercise is advocated in CKD patients who do not have contraindications based on co-morbidities, recognizing that many stages 4 and 5 CKD patients may be unable to exercise effectively due to malnutrition or to musculoskeletal and CV disorders ***(Van der Zee et al., 2009)***.

Non-traditional CV risk factors

Hyperhomocysteinemia

Multiple epidemiologic and angiographic studies have demonstrated an association between mild to moderate hyperhomocysteinemia and the development of CAD, and to a lesser extent cerebrovascular disease in the general population. However, studies assessing the effects of folic acid, pyridoxine and vitamin B12 in such patients have

failed to demonstrate a reduction of CV and cerebrovascular events ***(Kendrick and Chonchol, 2008).***

Mild to moderate hyperhomocysteinemia is commonly encountered in stages 1 and 2 CKD and becomes progressively more severe as renal function deteriorates (>90% of dialysis patients have hyperhomocysteinemia). The effect of lowering homocysteine levels on CV and cerebrovascular outcomes in early stage CKD is unknown. However, the Homocysteine in Kidney and ESRD Study, which followed stages 4 and 5 CKD patients for a median of 3.2 years, showed no significant difference in the incidence of the composite end point of total mortality, MI, stroke and amputation between patients treated with daily oral doses of folic acid (40 mg), pyridoxine (100 mg), and vitamin B12 (2 mg) compared to those who received a placebo. For this reason, routine treatment with these medications is to improve vascular outcomes in patients with CKD is not recommended ***(Jamison et al., 2007)***.

Increased oxidative stress

A major cause of inflammation in CKD and particularly in ESRD is increased oxidative stress. Activation of NADPH, and other oxidative enzymes coupled with reduced activity of anti-oxidant systems results in enhanced production of reactive oxygen species (ROS) ***(Kendrick and Chonchol, 2008).***