INTRODUCTION

Cardiovascular diseases (CVD) are a major cause of morbidity and mortality in patients with end stage renal disease (ESRD). Left ventricular hypertrophy (LVH), determined by echocardiography, is frequent cardiac changes observed in ESRD and is independent risk factors for mortality ***(Cerasola et al., 2011)*.**

In the haemodialysis (HD) population left ventricular dysfunction is common with a rate 10–30 times greater than that in the general population. Among patients with ESRD, nearly 15% have systolic dysfunction, 40% have heart failure and more than 75% LVH. Also left ventricular diastolic dysfunction is very frequent among chronic kidney disease (CKD) patients and may be associated with the subsequent development of heart failure and with mortality ***(Sood et al., 2008).***

LVH in ESRD is a disorder of multifactorial origin. Hypertension, anemia, hyperparathyroidism, chronic volume expansion, inflammation and hyperhomocysteinemia are risk factors for LVH ***(Glassock et al., 2009).***

NO controls the growth of the myocardium and is influential in the development of cardiac remodeling, which in turn has an antiproliferative effect on the myocardium, as a peripheral vasodilator, it additionally reduces both afterload and preload. This hemodynamic effect of NO helps the prevention of LVH ***(Tirziu and Simons, 2008)*.**

NO also prevents incidents that can trigger the development of atherosclerosis, such as leukocyte adhesion, platelet aggregation, vascular smooth muscle cell proliferation, and controls vascular regeneration through angiogenesis, thus protecting against the development of atherosclerosis ***(Tirziu and Simons, 2008).***

Evidence indicates that NO deficiency contributes to cardiovascular events and progression of kidney damage. Nitric oxide production is reduced in renal disease, which may be caused by substrate (L-arginine) limitation and increased levels of circulating endogenous inhibitors of nitric oxide synthase (NOS), particularly Asymmetric dimethylarginine (ADMA) ***(Baylis, 2006).***

ADMA is a naturally occurring amino acid that competitively inhibits the activity of NOS. ADMA is produced by methylation of arginine residues in intracellular proteins via protein arginine N-methyltransferases (PRMT). Only 20% of ADMA is excreted in the urine. About 80% of ADMA is cleared by enzymatic degradation of dimethylamine dimethylaminohydrolase (DDAH) ***(Kielstein et al., 2007).***

An increase in serum ADMA levels is often observed in subjects with hypercholesterolemia, insulin resistance, diabetes mellitus, hypertension, and chronic renal disease. These conditions are associated with vascular oxidative stress, which is known to impair DDAH activity ***(Kielstein et al., 2007).***

Plasma concentrations of ADMA are associated not only with endothelial dysfunction and atherosclerosis but also predict mortality and cardiovascular complications in patients with CKD or ESRD ***(Jacobi and Tsao et al., 2008).***

Recently, it has been claimed that residual renal function (RRF) has positive effects on cardiovascular events and LVH ***(Haksun et al., 2008).***

AIM OF THE WORK

The aim of this work is to:

- Correlate plasma ADMA level with LVH and function in ESRD patients on regular hemodilaysis.
- Correlate both plasma ADMA and LVH with residual renal function in ESRD patients on regular hemodilaysis.

CARDIOVASCULAR DISEASES IN PATIENTS WITH ESRD

Cardiovascular diseases (CVD) are a major cause of morbidity and mortality in patients with end-stage renal disease (ESRD). Cardiovascular mortality is 10 to 20 fold higher in ESRD patients than in general population. The high prevalence of established traditional risk factors for atherosclerosis in these patients undoubtedly contributes to the accelerated rate of vascular disease. In addition, growing evidence has been gathered over the last years regarding the role of uremia related risk factors such as inflammation, oxidant stress and endothelial dysfunction in the pathogenesis of atherosclerosis in subjects with renal failure ***(Helal et al., 2010).***

Epidemiology:

The risk of a cardiovascular event is, on average, 20 times higher for dialysis patients than for pre-dialysis ones. Furthermore, in hemodialysis (HD) patients, the overall mortality is estimated at about 25% per year in the US, and ranges from 13.3 to 18.6% in Europe ***(Iliou et al., 2005).***

Moreover, data from epidemiologic studies have confirmed that even a moderate reduction in kidney function is associated with a significant increase of cardiovascular risk, and that the level of kidney function itself is an independent predictor of cardiovascular outcome and all cause mortality ***(Cerasola et al., 2011).***

The major increase in risk for heart disease and death occurs at a GFR of <50 to 60 ml/min (Figure 1), coronary artery disease (CAD) defined as >50% stenosis in the coronary artery was present in as many as 53% of a cohort of asymptomatic dialysis patients ***(Ohtake et al.,2005).***

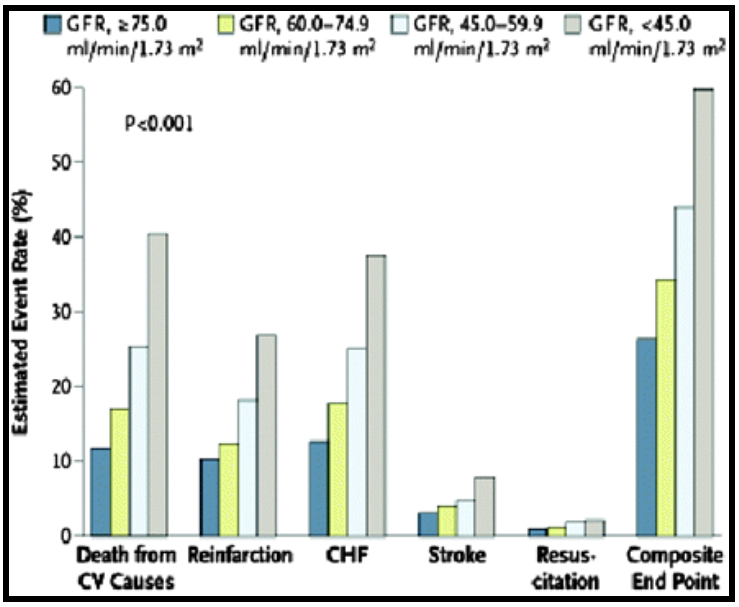

Figure (1): Kaplan-Meier estimates of the rates of death at 3 yr from cardiovascular (CV) causes, re infarction, congestive heart failure (CHF), stroke, resuscitation after cardiac arrest, and the composite end point, according to the estimated GFR at baseline ***(Anavekar et al., 2004).***

Cardiac death as a function of all causes of death in dialysis patients was 38.8% (AMI 5.3%, CHF 5.2%, Arrythmia/cardiac arrest 26.10% and other cardiac 2.2%) ***(USRDS, 2010).***

Moreover ,Anomalies of left ventricular structure and function are very frequent Among patients with ESRD, nearly 15% have systolic dysfunction, nearly 40% have

heart failure and more than 70% have left ventricular hypertrophy (LVH) which considered a strong predictor of mortality ***(Cerasola et al., 2011).***

The difference in cardiovascular prognosis among dialysis patients compared to those without renal disease is related in part to the nature of new patients being started on HD. Based upon the Choices for Healthy Outcomes in Caring for ESRD (CHOICE) study, a large percentage of incident dialysis patients have traditional risk factors for cardiovascular disease ***(Longenecker et al., 2002).***

These factors include diabetes (54 percent), low serum HDL cholesterol (33 percent), hypertension (96 percent), left ventricular hypertrophy by electrocardiographic criteria (22 percent), and increased age, with the average patient age at the commencement of dialysis being nearly 60 years ***(Longenecker et al., 2002).***

Many dialysis patients have more than one of these risk factors, resulting in an even higher risk of adverse outcomes. As an example, among 373,539 United States dialysis patients, nearly 40 percent had both diabetes and hypertension, resulting in a five to six fold increased risk of having heart disease compared to those with neither condition ***(Mailloux et al., 2009).***

Risk factors of cardiovascular disease in ESRD:

The etiology of cardiovascular disease in ESRD is multifactorial. As shown in (Figure 2), there are several modifiable, nonmodifiable, and specific uremia related factors that contribute to cardiovascular morbidity and mortality ***(Henrich et al., 2009).***

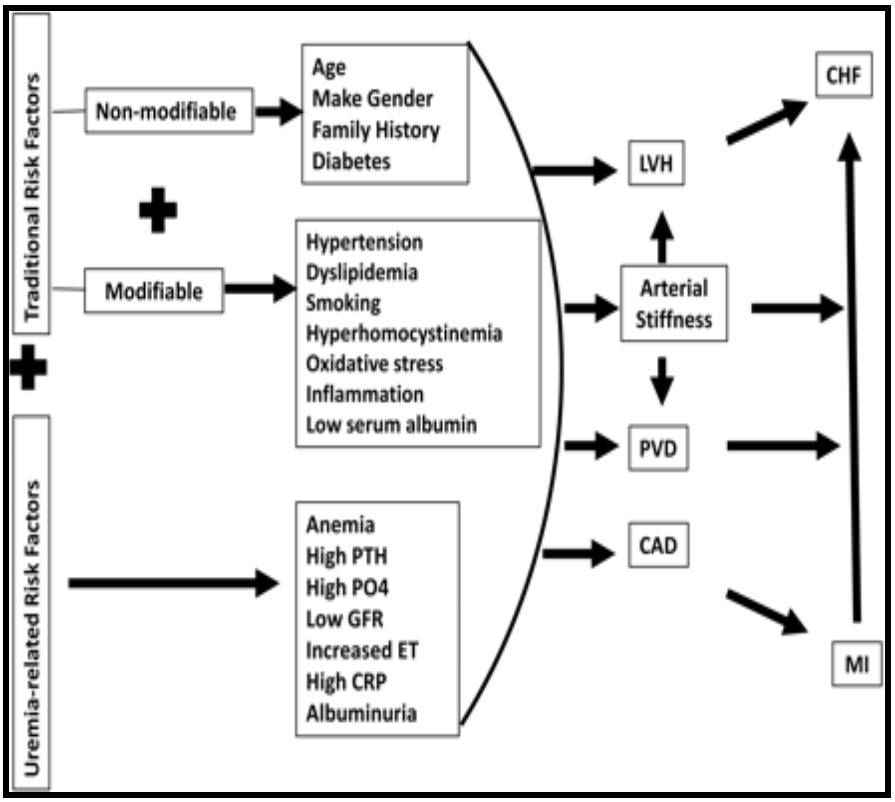

Figure (2): Factors in cardiovascular disease for ESRD patients ***(Henrich et al., 2009).***

Anemia:

Anemia is usually observed in patients with GFR <60 mL/min/ 1.73m2. Anemia prevalence rates are approximately 25% in patients with creatinine clearance (CrCl) >50 mL/min, and approximately 44% in those with GFRs in the 15-29 mL/min/1.73m2 range (anemia defined as a hemoglobin (Hb) of <12 g/dL in men and <11.0 g/dL in women).

By stage 5 CKD, approximately 90% of patients are anemic. Several studies suggest that anemia is a major risk factor contributing to poor CVD outcomes, including LVH, worsening CHF, and myocardial ischemia ***(Pendse et al., 2008).***

Hb concentration was found to be an independent risk factor for the development of LVH, with a 32% increased risk for LVH for every 0.5 g/dL decrease in Hb. Similarly, CrCl was also found to be associated with an increased risk of LVH development, with a 3% increase in risk of LVH for every 5 mL/min decline in GFR (P=0.0168) ***(Pendse et al., 2008)***.

A study based on data from Medical Evidence Forms (Health Care Financing Administration 2728, now the Centers for Medicare and Medicaid Services – CMS), found that erythropoietin treatment given prior to dialysis

initiation was associated with survival improvement as compared with non treated patients ***(Fink et al., 2001).***

Hyperphosphatemia and hyperparathyroidism

These constitute the second cardiovascular risk factor commonly seen in patients with chronic renal insufficiency. hyperparathyroidism is associated with a history of myocardial infarction and heart failure, and strong association has been described between hyperphosphatemia and incident cardiovascular events in ESRD patients ***(Cozzolino et al., 2005).***

Calcium phosphorous management in CKD has shifted to concerns about significant increases in CV risk associated with extra skeletal calcification, particularly in the coronary vasculature. A study in ESRD patients assessed valvular calcifications by electron beam computed tomography (CT), and found aortic and mitral calcification rates of 55% and 59%, respectively ***(Goldin et al., 2000).***

A serum product of calcium and phosphorous (CaP) >55 was associated with a significant increase in mortality. Those individuals in the highest quintile of CaP (>72) had an increased risk of death compared with those with a Ca P in the 42 to 52 range ***(Pendse et al., 2008).***

Furthermore, patients with calcification were found to be older (26 ± 3 vs 15 ± 5 years, P<0.001) and had been

on dialysis for a longer duration (14 ± 5 vs 4 ± 4 years, P<0.001) ***(Goldin et al., 2000).***

Another large observational study 25 of 40 538 patients on HD hyperphosphatemia, hypercalcemia, and moderate to severe hyperparathyroidism PTH ≥ 600 pg/mL were associated with an increased Risk of death ***(Block et al., 2004).***

Dyslipidemia

Lipid profiles in patients with kidney disease, particularly with ESRD, are different from those in individuals without kidney disease. Total and low-density lipoprotein cholesterol (LDLC) levels are often within the normal range, while high density lipoprotein cholesterol (HDL-C) levels are decreased and plasma triglycerides are increased. In addition, patients with renal disease also have greater oxidative stress, resulting in higher levels of oxidized glutathione and advanced glycation end products, as well as increased oxidation of lipoproteins ***(Iliou et al., 2005).***

The oxidative change in LDL may be the initial and requisite step in the development of atherosclerosis. It results from the ingestion of oxidized LDL by scavenger monocytes, the subsequent enrichment of these cells with cholesterol esters, and the consequent formation of foam cells, the primary step in atherosclerosis ***(Pendse et al., 2008).***

Hypertriglyceridemia is the most common lipid disturbance but is not usually treated with pharmacologic therapy. Whether this approach is beneficial in patients with renal failure is not known, but it should be considered for those with fasting triglycerides ≥ 500 mg/dL (≥ 5.65 mmol/L) that cannot be corrected by removing an underlying cause, treatment with lifestyle changes and a triglyceride lowering agent should be considered ***(Pendse et al., 2008).***

An important observation among dialysis patients is that a low (and not a high) serum cholesterol concentration is associated with increased mortality.

This probably reflects the profound adverse effect of malnutrition and chronic inflammation upon mortality, resulting in a paradoxical risk factor reversal ***(Kilpatrick et al., 2007).***

On the other hand, among those without markers of inflammation/malnutrition, higher cholesterol levels were associated with higher mortality. Small trial, atorvastatin produced a significant reduction in serum CRP ***(Kilpatrick et al., 2007).***

Lipoprotein a:

Lipoprotein a (Lp[a]; a similar lipoprotein to LDL, but with the addition of a glycosylated protein, apolipoprotein) has been linked with the development of atherosclerosis and

elevated levels are found in the ESRD population ***(Iliou et al., 2005).***

Studies indicate that there are up to 6-fold higher levels in patients with severe nephritic syndrome and up to 4-fold higher concentrations in dialysis patients, compared with healthy controls. There was association between elevated levels and mortality from CVD in HD patients. Lp(a) levels have been shown to decrease by 45%-75% in patients who have undergone renal transplantation, further supporting an association with renal disease ***(Iliou et al., 2005).***

The 2 postulated mechanisms for this increase in Lp(a) are: hepatic overproduction of albumin and other proteins produced by the liver (eg, apolipoproteins), secondary to reduced oncotic pressure stimulation resulting from hypoalbuminemia; or, alternatively, a reduction in catabolism if, in fact, the kidney plays a role in this process. Other mechanisms possibly play a role in the development of atherosclerotic plaque mediated by Lp(a)**.**

Lp (a) is ingested by macrophages, resulting in the formation of foam cells, and it can be oxidized, which increases its atherogenicity. Lp(a) also impairs the activation of plasminogen, resulting in enhanced vascular smooth muscle cell proliferation. Numerous studies have evaluated the role of Lp(a) in CV risk stratification ***(Iliou et al., 2005).***

Hyperhomocysteinemia

Homocysteine (Hcy) is a sulfur-containing amino acid that is produced as a result of the transmethylation of methionine. Initial evidence suggested that elevations in plasma Hcy levels were associated with increased risks of ischemic heart disease or stroke ***(Zoccali et al., 2006).***

Elevations in plasma Hcy levels are a common metabolic consequence of renal failure. The mechanism linking hyperhomocysteinemia to CV disease remains somewhat obscure; however, it appears to include direct endothelial injury, an increase in the oxidation of LDL, an increase in thromboxane-mediated platelet aggregation, a decrease in thrombomodulin expression and protein C activation, and an increase in smooth muscle cell proliferation ***(Pendse et al., 2008).***

Plasma Hcy concentration increases as renal function worsens associated with a higher risk of coronary heart disease death. Seven prospective observational studies in ESRD, including more than 1000 HD and 176 continuous ambulatory peritoneal patients. Hcy was strongly associated with incident atherothrombotic events ***(Zoccali et al., 2006).***

C-reactive protein and other atherogenic mechanisms triggered by inflammation

In ESRD, CRP is strongly associated with increased risk of death and cardiovascular events. Inflammation, a fundamental promoter of atherosclerosis, interacts with many pathophysiologic pathways that lead to vascular damage ***(Henrich et al., 2009).***

In vitro, inflammatory cells (monocyte-macrophage) potentiate alkaline phosphatase activity of osteoclast-like cells in the vascular system; this suggests that inflammation favors vascular calcification. The cardiac valve calcifications are much more frequent in ESRD patients with high CRP levels than in those with relatively lower levels. Inflammation also interacts with several pro-atherogenic mechanisms ***(Wang et al., 2003).***

One major inflammatory molecule, interleukin-6, stimulates fibrinogen synthesis via a specific interleukin-6-sensitive sequence in the fibrinogen gene; this pathway leads to thrombosis. Fibrinogen is at center stage in mediating the cardiovascular damage seen in ESRD patients ***(Henrich et al., 2009).***

Plasma fibrinogen was directly related to LVH and all cause death and incident cardiovascular events in HD patients. Thus multiple mechanisms, both inflammation dependent and independent, cooperate in determining the high atherothrombotic risk of ESRD ***(Zoccali et al., 2006).***