40 *Cardiorenal Syndrome— A New Emphasis*

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Abstract: The advancement of Renal Replacement Therapy in the management of patients of CKD has resulted in an increased life expectancy in patients of dialysis. However, this theoretical analogy does not hold good as CVD takes its toll. It has been estimated that age adjusted CVD mortality is about 30 times higher in CKD than in general population. So the risk of dying because of cardiovascular causes in patients of ESRD is much higher than in the general population and this has led to the concept of cardiorenal syndrome. The cardiovascular risk factors namely diabetes, hypertension, anemia, dyslipidemia, oxidant stress, inflammation, hyperhomocysteinemia, neuroheumoral over activity or activated RAS have a much adverse prognostic significance than in patients of CVD with no ESRD.

The pathogenesis and pathophysiology of the cardiorenal syndrome is discussed and its effect on the various risk factors and their importance has been highlighted with regard to how early detection can help in formulating a strategy for primary and secondary prevention of this disease. The role of some of the newer therapies is also discussed and the direction of future therapies is presented.

Advancements in renal replacement therapy (RRT) and growing awareness on the opportunity to live longer with RRT is encouraging more and more patients to opt for RRT. Nevertheless life expectancy of patients on dialysis continues to be reduced. Among the cause of deaths, Cardiovascular Disease (CVD) is emerging as the most common cause of death in patients with End Stage Renal Disease (ESRD).[1] Age adjusted CVD mortality is about 30 times higher in ESRD than in the general population. The risk of dying of cardiac complications is 65 times higher in dialysis patients between 45-54 years and 500 times higher than the general population in the younger cohort . This observation has lead to the creation of a new entity of CARDIORENAL SYNDROME which is well defined from the kidney disease seen in cardiac failure. It represents the presence of renal disease and cardiovascular disease together.[2] The multifold increased CV risk may be related to the primary disease causing Chronic kidney disease (CKD), e.g. Diabetes Mellitus (DM), Hypertension (HT) and /or presence of one or more of associated risk factors like anemia, dyslipidemia, divalent ion abnormalities, increased oxidant stress, inflammation, hyperhomocysteinemia, neurohumoral over activity or activated renin angiotensin system. Studies (Framingham Heart study, HOPE, HDFP, MRFIT, HOT) show that this increased cardiovascular risk begins quite early in renal insufficiency. About 1/3rd of patients with mild renal impairment (glomerular filtration rate (GFR) < 50 ml/mt) were found to have a history of overt CVD.[1,2]

While the evidence is alarming, there is a ray of hope of enabling reduction in the CV mortality and morbidity and prolonging life expectancy by instituting early detection and prevention strategies. It is essential hence to understand the pathophysiology of CVD in CKD.

The specific risk factors related to CKD causing CVD besides the traditional risk factors and the probable mechanisms of their CV toxicity to effectively protect the heart and save the life of renal failure patients. Pre-transplant CVD is a risk marker of post transplant CVD and is responsible for loss of precious lives with functioning renal grafts.

Pathophysiology of Cardiorenal Syndrome

Traditional risk factors for CVD are frequently present in patients with CRF (Table 40.1). A few more risk factors specific to CKD and associated with increasing CV risk are listed in Table 40.2.

Reversing the increased cardiovascular risk in CKD is the greatest challenge of the day.

Anemia—A Crucial Factor in the Viscious Cycle of Cardiorenal Syndrome

The kidney being the main source of erythropoietin, anemia is apparently an integral part of advancing renal failure. Anemia exerts an independent effect on CVD in CKD. For every 1gm/dl drop in mean hemoglobin, the risk of cardiac failure (de novo) increases by 25%, echo-cardiographically demonstrable LVH by 42% and risk of death increases by 14%.[3]

Low hemoglobin results in low oxygen delivery, reduced blood viscosity, reduced peripheral resistance leading to increased sympathetic activity and venous return. The resultant high cardiac output and high arterial volume lead to adaptive left ventricular hypertrophy and arterial hypertrophy and defective cardiac remodeling (see Fig. 40.1).[3]

In heart failure there is reduced blood pressure, increased sympathetic activity, and decreased renal blood flow. It induces cytokines which depress the bone marrow. The erythropoietin levels which should be 1000 times normal, barely go up because of the inhibitory effect of TNF and renal disease. The cytokines -TNF and interleukin-6 can decrease erythropoietin production in the kidney, increase erythropoietin resistance in the bone marrow and decrease the release of iron from the reticuloendothelial system. TNF also interferes with the iron absorption in the gut.[4,5]

Proteinuria itself causes loss of erythropoietin, iron, and transferrin, one reason why patients with nephrotic syndrome become anemic. In diabetics, glycosylation of the interstitial cells that produce erythropoietin lead to inappropriately low hemoglobin that what is referred to as diabetic myocardiopathy in many cases may simply be the anemia not treated adequately.[4,5]

Blood Pressure Changes in CKD Leading to CVD

Hypertension is a strong predictor for LVH, cardiac dilatation, cardiac failure, ischemic heart disease and worsening of atherosclerosis. There is a blunting of the nocturnal dip in blood pressure in uremics. Whether the non dipping leads to LVH or LVH is the cause of the blunted nocturnal dip, this puts the patients at higher risk for vascular diseases. Even chronic hypo-tension is associated with increased CV mortality. Impairment of cardiac perfusion during diastole, particularly in the presence of LVH or decreased aortic compliance leads to ischemic myocardial damage. For any given systolic pressure a pulse pressure more than 50 mmHg correlates with increased risk of death.[6-9]

Calcium, Phosphorus and Parathormone (PTH) in CKD

Progressive nephron loss is associated with phosphate retention and hypocalcemia. This triggers increased parathormone activity. The secondary hyperparathyroidism along with hyperphosphatemia and increased calcium phosphate ion product are identified as independent cardiovascular risk factors.[10] Decreased cardiac contraction, LVH and valvular calcification culminates. An increase in calcium-phosphorus product > 60 mg^2/dl^2 promotes metastatic calcification. Vascular calcification begins 10-20 years earlier than in the general population.[11]

Recent studies point to the alternative possibility of deficiency in calcium regulatory proteins - X_2 Hereman Schmid glycoprotein and matrix GIa protein (MGP) representing important mechanisms causing extrosseous calcification.

Proteinuria in CKD

Prolonged protein loss leads to hypoalbuminemia, hyperlipidemia and coagulation abnormalities following hyperfibrogenemia, increase in Factor III and Von Willebrand factor. Proteinuria may reflect renal involvement due to systemic disease like systemic lupus erythematosus wherein cardiac involvement is a part of the systemic onslaught. Drugs, commonly used, e.g. steroids, used to treat the glomerular diseases can produce vascular changes leading to CV disease. Micro-albuminuria occurring in early diabetic nephropathy or essential HT is a marker of vascular endothelial dysfunction.[12]

Hypoalbuminemia

Hypoalbuminemia is emerging as a powerful risk factor for CV mortality besides all cause mortality, especially in HD patients. Malnutrition also can lead to low folate, B12 levels and low arginine intake leading further to hyperhomocysteinemia and impaired nitric oxide synthesis. Low level of antithrombotic proteins leads to hypercoagulability. Expansion of plasma volume as seen in HD patients is yet another cause for hypoalbuminemia. Albumin itself is a negative acute phase protein. HD patients with hypoalbuminemia have reduced albumin synthesis and increased level of acute phase proteins.[13] Inflammation also causes decrease in albumin synthesis and increase in albumin fractional catabolic rate. This inflammatory response alters the endothelium and plasma protein composition in ways favoring vascular injury.[14]

Malnutrition—Inflammation—Atherosclerosis Syndrome (MIA)[15]

Uremia is a state of chronic inflammation. Reduced renal clearance of cytokines, accumulation of Advanced Glycation End Products (AGE) and unrecognised persistent infections are some of the causes. Additional causes in patients on dialysis include graft and fistula infections, peritonitis in CAPD, bio-incompatibility of dialyser membranes and exposure to endotoxins from contaminated dialysate. Levels of pro-inflammatory cytokines such as IL_1, IL_6, Tumor necrosis factor alpha (TNFα) are increased 8 to10 fold in ESRD patients. IL_6 is an important pro-atherogenic cytokine shown to alter insulin sensitivity and endothelial function. It is a strong stimulant of the adhesion molecules (VCAM, ICAM) which mediate attachment and migration of leucocytes across the endothelial surface. IL_6 down regulates albumin mRNA, inhibits albumin synthesis and inhibits appetite directly and indirectly through leptin, promoting malnutrition. The sustained inflammatory reaction promotes endothelial dysfunction (ED), oxidative stress; complement activation and leads to increased cardiovascular mortality.

Role of ADMA (Asymmetric Dimethyl Arginine)

ADMA[16] is a new emerging cardiovascular risk factor considered in uremic patients. It is a competitive NO synthase inhibitor leading to decreased nitrous oxide availability. ADMA is degraded by dimethyl arginine dimethyl aminohydrolase—an enzyme rich in renal tissue. With advancing renal failure and loss of renal mass ADMA accumulates. In ESRD it is the second strongest predictor of CV mortality, after age, among the traditional risk factors. ADMA is reduced by angiotensin converting enzyme inhibitors (ACEI), angiotension receptor 1 blockers (ARB) and insulin sensitizers.

Angiotensin II

The renin angiotensin system is activated in most of the renal diseases especially in the diabetics and hypertensives. Emerging evidences suggest that the resultant increased Angiotensin II is not only a vasoactive peptide but also a true cytokine that regulates cell growth, inflammation and fibrosis. Ang-II increases TNFα production which regulates various cell processes including cell proliferation and production of other cytokines and adhesion molecules. It also up regulates other pro-inflammatory mediators—IL-6, NF-kB and thus plays an active role on the inflammatory response in renal diseases. It stimulates superoxide lipid peroxidation and inactivation of NO producing oxidative stress. Atherosclerosis is promoted by Ang-II by production of lipid into the foam cells of the vessel wall and by ED. It induces endothelial cell apoptosis, which has dramatic effects on the platelet cell binding and on the inflammatory process. The various metalloproteinases induced by Ang-II —MMP-1, MMP-9, etc. lead to proliferation, migration and hypertrophy of vascular smooth muscles and promote matrix expansion and fibrosis.[17]

Hyperhomocysteinemia

Hyperhomocysteinemia is a strong predictor of CVD in the general population. In CRF, homocysteine levels range from moderate (16-30 μmol/L) to intermediate 30-100 μmol/L). Hyperhomocysteinemia enhances vascular smooth muscle proliferation, increases platelet aggregation and act on the coagulation cascade and fibrinolysis directly inducing a pro-thrombotic environment or by acting in a synergistic manner with other risk factors. It activates coagulation factors V, X, XII along with decreased activation of protein C and cell surface thrombomodulin and modulation of tissue plasminogen activator binding to its endothelic receptor—annexin II.[18]

The proposed mechanisms of homocysteine toxicity are oxidative stress through production of reactive oxygen species, binding to nitric oxide, production of homocysteinylated/acylated proteins and accumulation of its precursor S-adenosyl homocysteine—a potent inhibitor of transmethylation reactions.

Lipids

Renal dyslipidemia[19] is reflected in an abnormal apolipoprotein (apo) profile-reduced concentration of Apo-A containing lipoprotein in HDL and increased concentration of intact or partially metabolized triglyceride rich Apo-B containing lipoprotein in VLDL, intermediate density lipoprotein (IDL) and LDL. There is preferential increase in levels of IDL and small dense LDL. A significantly decreased Apo A-II to Apo C-III ratio is the hallmark of altered lipoprotein composition in renal disease. Reduced catabolism and clearance of triglycerides rich Apo-B containing lipoprotein are the main causes. While HD moderately attenuates the dyslipidemia, PD aggravates it.

Thus various factors endogenous[20]—Ang II, ox LDL, lipopolysaccharides, AGE, cytokines, homocysteine and exogenous—dialysis and access-related toxins, induce increased oxidative stress. Excessive oxidative stress causes ED, promotes abnormal vascular and accelerated atherosclerosis.[21]

Diagnosis of CVD in CKD Patients

A high index of suspicion is necessary for early detection of the cardiovascular disease in renal failure patients as it occurs early in the course of the disease. They are asymptomatic especially in diabetics. Cardiac enzymes like Troponin T may be elevated even in the absence of active myocardial injury. 64 slice CT has come as a boon to detect asymptomatic coronary arterial disease.[22]

C-reactive Protein— A Risk Marker or Risk Factor[23]

Data from the Framingham during instability in coronary artery disease (FRISC) trial has convincing data on the prognostic support of CRP not only for short term outcomes but also for long-term outcomes.

Besides a risk marker, there is increasing evidence that CRP may be directly involved in atherothrombogenesis. CRP present in the vessel wall induces expression of adhesion molecules E selectin, VCAM-1 and ICAM-1 by endothelial cells which serves as a chemo-attractant for monocytes, mediated by MCP-1. It opsonises LDL and facilitates native LDL entry into macrophages. CRP binds to plasma membrane of damaged cells and activates complement via the classical pathway. It decreases nitric oxide synthesis and thus induces ED favoring progression of atherosclerosis. It sensitizes the endothelial cells to destruction by cytotoxic CD_4 T cells. Thrombogenesis is facilitated by stimulation of tissue factor biosynthesis by macrophages. Conclusive evidence is lacking.

Prevention of CVD in CKD[24]

Primary Prevention

Lifestyle modification towards maintenance of ideal weight, avoidance of smoking, regular dynamic exercises are unquestionable measures to be implemented. Diabetes and Hypertension are the two major etiologies of CKD, both being capable of causing ED and accelerating atherosclerosis. Tight control of diabetes mellitus with fasting blood sugar < 100 mg/dl, 2 hrs postprandial sugar < 120 mg/dl, pre-dinner blood sugar < 110 mg/dl and HbA_1C around 6% will have lasting impact not only on CVD but also in slowing the progression of CKD itself. Tight control of blood pressure involves keeping the blood pressure around 120/75 mmHg. Dietary modification and statins will aid to control dyslipidemia and the associated vascular damage.

Secondary Prevention[24]

Secondary prevention involves strategies to reduce the hypervolemia, blocking of the angiotensin system, sympathetic overactivity, correction of anemia and the divalent ion abnormalities besides reversing dyslipidemia and controlling diabetes. Hypervolemia can be effectively countered with regulated fluid balance and adequate dialytic support.

Various trials (HOPE, REIN) have evidence based proof that ACEI and ARB must be an integral part of the therapeutic armamentarium in CKD to counter the villain—ANG-II. These drugs, besides aiding in the control of blood pressures, have demonstrated blood pressure independent reduction of LVH. ACEI also suppress catabolic cytokines. ARBs reduce IL_6 and TNFα and thus are anti-inflammatory too. Therefore, dual blockade will be much better than either alone.

Sympathetic over-activity has been demonstrated in CKD. This consideration postulates the wider use of β blockers and central sympathetic blocking drugs to protect the heart.

The effective correction of anemia with adequate erythropoietin dosing to keep the hemoglobin > 12 gm/dl and packed cell volume > 36% has proved beyond doubt by evidence based medicine. Iron supplementation is required in many cases.

Secondary hyperparathyroidism has to be effectively countered by maintaining the calcium and phosphorus product < 50 mg^2/dl^2 with phosphorus < 5 mg/dl and calcium around 10 mg/dl. Besides low phosphorus diet, the phosphate binders are used. Calcium salts are effective. Newer phosphate binders are sevelamer, iron salts and Lanthanum carbonate.[25]

Anti-oxidants like Vitamin-E have earned their place to counter the oxidant stress. Reducing the inflammation by early identification and appropriate treatment of infections, use of more biocompatible membranes can help in reducing the cytokine load and slow the trigger on ED.

Treatment with statins[26] has been proven to reduce the mortality and morbidity in CVD both in primary and secondary prevention settings. Observational registry data report reduction in total and CV mortality by 32 and 36% among ESRD patients receiving statin. Rosuvastatin is a

potent highly effective statin that is not metabolized by cytochrome P_{450} $3_{A4.}$ In doses of 10 to 80 mg/day it reduces LDL cholesterol by approximately 45 to 65%. The Study of Heart and Renal Protection (SHARP) trial has demonstrated that lowering LDL cholesterol by about 1 mmol/L for 4-5 years reduces risk of coronary event and strokes by about 20%.[27]

Ezetimibe is a cholesterol absorption inhibitor which selectively inhibits the passage of dietary and biliary cholesterol across the intestinal wall. In patients with CKD, combination of ezetimibe 10 mg and simvastatin 20 mg reduce mean LDL cholesterol around 1/5 as compared to simvastatin alone.

Newer Therapies

Similar to ACE, NEP (neutral endopeptidase) is an endothelial cell surface metalloproteinase involved in the degradation of several regulatory peptides including the natriuretic peptides. NEP inhibition thus augments vasodilation and natriuresis through increased levels of atrial natriuretic peptide, by inhibiting the RAS and potentiating natriuretic peptide system. A combination of NEP/ACE inhibitors are the VASOPEPTIDASE INHIBITORS. Omapatrilet is a vaso-peptidase inhibitor. It decreases proteinuria by 20% in CKD. While no dose adjustment is required in renal insufficiency, its major disadvantage is angio-edema, especially when it is combined with ACEI.[28]

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