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The burden and consequences of chronic disease are increasing rapidly throughout the world with no end in sight. Cardiovascular disease (CVD) is progressing relentlessly in all communities and is responsible for excessive morbidity and premature mortality. The spectrum of CVD ranges from asymptomatic ischemia in vital organs to the development of systemic vascular disease. Thus, the manifestations of CVD include coronary artery disease (CAD), congestive heart failure (CHF), left ventricular hypertrophy (LVH), transient ischemic attack (TIA), cerebrovascular disease (CeVD), aortic aneurysms, and peripheral arterial disease (PAD). Therefore, the impact of CVD on life expectancy is of critical importance. The risk factors for CVD are well established and the disease occurrence and progression can be interrupted by early identification and aggressive control of the risk factors.

The prevalence of CVD is quite high in patients with chronic kidney disease (CKD). Unfortunately, CVD and CKD are closely inter-connected, often co-exist, and can initiate and perpetuate the morbidity. The CVD-CKD circuit is a vicious cycle. The onset of CVD in patients with CKD occurs much earlier and more extensively compared to the general (non-CKD) population. It is clear that CVD

can be extensive and extremely dangerous in patients with CKD. From a patho-physiological point, CKD is a powerful risk factor and a signal for the development of CVD. The CVD-CKD connection is of serious importance in clinical medicine. For a practicing clinician, CKD should, therefore, be considered as a precursor for CVD. The diagnosis of CKD signifies simultaneous presence of CVD. It has been postulated that for every 10 mL/min decrease in glomerular filtration rate (GFR), the risk of mortality from CVD increases by 6%! (1). In patients with end-stage renal disease (ESRD), CVD is the principal reason for premature death, excess morbidity, and hospitalization.

RISK FACTORS AND MARKERS OF CVD IN PATIENTS WITH CKD

The pathophysiological risk factors for CVD in patients with CKD in many ways are similar to the patients without CKD. However, uremic toxins likely play an additional role in “igniting” and “fuming” CVD in patients with CKD. Beyond the traditional risk factors for CVD, patients with CKD have other adverse factors such as --- hemodynamic volume overload, anemia, oxidative stress, vascular inflammation, uremia, calcium-phosphate product, endothelial malfunction, enhanced activity of the sympathetic nervous system (SNS), renin-angiotensin-aldosterone system (RAAS), and insulin resistance. Hence, both the traditional and non-traditional risk factors contribute to the burden of CVD in the presence

Table 1: Confluence of traditional and non-traditional CVD risk factors in CKD	
Traditional	Non-Traditional
Male gender	Anemia
Family history	Uremia
Physical inactivity	Volume overload
Obesity	Oxidative Stress
Hypertension	Vascular inflammation
Hyperlipidemia	Calcium-Phosphate Product
Diabetes	Catabolic State
Tobacco use	Endothelial dysfunction
Excessive alcohol consumption	↑ Activity of SNS and RAAS
	↑ Thrombogenic factors

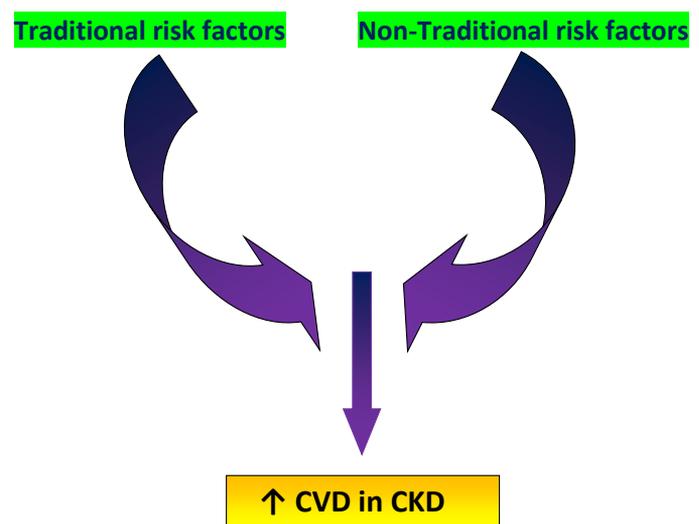


Fig. 1: Pathophysiology of CVD in CKD

654 of CKD. In patients with ESRD, the cardiovascular milieu is further deranged and becomes complex. While it is possible to demonstrate cardiovascular risk markers such as C-reactive protein (CRP), IL-6, TNF- α , asymmetric dimethyl arginine, and endothelial dysfunction, clinical utilization of these indices in patients with CKD is not widely available. Thus, the focus on CVD prevention in patients with CKD remains on tackling the conventional risk factors (Table 1 and Figure 1).

PREDISPOSING RISK FACTORS FOR CVD IN PATIENTS WITH CKD

Hypertension

Patients with CKD are likely to have antedating chronic hypertension which is aggravated with declining renal function. More than 90% of patients with CKD have hypertension. The pathophysiology of blood pressure elevation in CKD includes but not limited to---sodium retention, volume expansion, and enhanced activities of SNS and RAAS. In the elderly patients with CKD, renovascular resistance is increased.² As CKD worsens, the blood pressure control mechanisms get deranged and patients have significant nocturnal hypertension (non-dipping).³ Persistence of nocturnal hypertension aggravates target organ damage---LVH, CHF, and atherosclerosis. In patients with ESRD, systolic blood pressure increases disproportionately causing systolic hypertension and the wide pulse pressure poses a significant hazard.⁴ Uncontrolled hypertension worsens CKD progression and enhances CV mortality. Aggressive blood pressure control may halt the progression of CKD (5). While the recommended blood pressure targets should be aimed for in patients with CKD, even a modest reduction in the blood pressure level may be helpful to lower the CVD burden.⁶

Dyslipidemia

Elevated level of LDL and a lower level of HDL---are attributable to CVD risk in the general population. The association between dyslipidemia and CVD is particularly strong and fully expressed in patients with CKD.⁷⁻⁹ While there is an agreement about the CV risk from dyslipidemia in patients with CKD, routine use of statins has not been advocated. Therapy therefore, has to be individualized. Fibrates are relatively contra-indicated in patients with CKD due to the risk of rhabdomyolysis. The pathophysiology of lipid metabolism in patients with CKD is extremely complex. For example, uremia decreases the activity of triglyceride lipase which leads to retention of triglycerides and lipoprotein lipase activity is also impaired in CKD. Additionally, dialyzer membrane dialysate itself, and heparin use alter lipid catabolism in patients with CKD. Urea accumulation (in CKD) causes formation of carbamylated LDL which is an independent risk factor for systemic vascular disease.¹⁰

The benefits of statin therapy to prevent CVD in patients with CKD have not been conclusively demonstrated. For example, atorvastatin showed no composite benefits on CVD in patients with ESRD;¹¹ in the Aurora study,

rosuvastatin reduced the LDL in patients with ESRD but had no significant effect on CVD outcomes.¹² However, in the SHARP trial¹³ statin therapy (along with ezetimibe) reduced the CV events in ESRD patients. Meta-analysis provides sufficient evidence for the ultimate benefits of statin therapy in patients with ESRD.¹⁴ Statin therapy reduced CV morbidity and mortality in kidney transplant patients.¹⁵ The AHA/ACC guidelines recommend (high-intensity) statin therapy for patients with CKD except in ESRD.¹⁶

Diabetes

Diabetes is a paramount risk factor for nephropathy and CKD. A majority of patients with diabetes also have hypertension. Therefore, diabetes by itself or any combination with hypertension leads to CKD and its progression to ESRD. The vascular pathology in diabetes is likely mediated in part by advanced glycation end products (AGEs). AGEs accumulate in the vascular wall and provoke inflammation leading to atherosclerosis. AGE deposition in the vessel subsequently causes cross-bridging of the proteins, matrix formation, collagen synthesis, loss of elasticity and an increase in the arterial stiffness. These abnormal biophysical pathways triggered by AGEs causes vascular dysfunction in diabetes and CKD.^{17,18} The resultant endothelial damage may be responsible for proteinuria in patients with diabetic renal disease. CV mortality goes up steeply after the onset of proteinuria.

Microalbuminuria correlates with manifestations of CVD-LVH, increased intima-media thickness, and CAD.¹⁹⁻²¹ Patients with microalbuminuria/proteinuria might also have other CV risk factors. Diabetes causes endothelial dysfunction, coagulation abnormalities and vascular inflammation.²²⁻²⁴ Microalbuminuria predicts transformation to proteinuria and progression of CKD.²⁵

Tobacco Consumption

Smoking is known to cause CVD but increases the risk of CKD. Tobacco causes hemodynamic and intra-renal abnormalities.²⁶ SNS activation may play a contributory role in the development of CKD. Kidney response to increasing levels of blood pressure may be impaired in people who smoke cigarettes.²⁷ Tobacco abstinence should be recommended to prevent CKD in the community.

Obesity

High body mass index and obesity increase the CV event rates in patients with CKD.^{28,29} Metabolic syndrome imparts CVD risk in general population and this association may also be applicable to patients with CKD. Adiponectin is an established biomarker for CV risk in metabolic syndrome. Lower levels of adiponectin were noted in CKD patients with cardiovascular mortality.³⁰

Deranged Calcium/Phosphate metabolism

Hyperphosphatemia and hyperparathyroidism cause vascular stiffness and calcification. These abnormalities cause LVH, systolic hypertension, and myocardial ischemia. These biological and biophysical abnormalities

are present in patients with CKD making them easily vulnerable to CVD.³¹

Anemia

Renal insufficiency leads to chronic anemia due to decreased synthesis of erythropoietin. Anemia is a common feature of CKD and is implicated in the pathogenesis of LVH. Correction of anemia may cause regression of LVH in patients with CKD.³² Paradoxically, however, full correction of anemia has been associated with increased CV mortality in CKD patients with CAD or CHF.³³ Higher iron stores may have an adverse effect on coronary perfusion. The current guidelines recommend correction of anemia but not overshoot the normal hemoglobin level.

Inflammation

CKD typifies an example of vascular inflammation.³⁴⁻³⁶ Vascular inflammation has a pathogenetic role in CV syndromes in patients with CKD. Progression of CKD is associated with endotoxemia and CVD burden.³⁷ C-reactive protein (CRP) mediates critical processes in the pathogenesis of atherosclerotic disease. IL-6 excess in patients with CKD is a potent stimulus for CRP.³⁸ There appears to be a close correlation between the degree of vascular inflammation and CKD stages.³⁹ High levels of CRP are associated with increased mortality in patients with CKD. It is not clear whether possible benefits of statin therapy in CKD are due to their anti-inflammatory actions.

A high ratio of neutrophil-to-lymphocyte is an indirect marker of vascular inflammation. Patients with CKD demonstrate a high neutrophil-to-lymphocyte indicating the underlying contributory role of inflammation in the clinical outcome of patients with CKD.⁴⁰ CKD by the virtue of its manifold mechanisms (including inflammation) unfolds the patho-physiology of CVD. Oxidative stress is linked to vascular inflammation. Uremic solutes like cysteine, homocystein, β_2 -microglobulin, and AGEs promote oxidative stress in CKD.⁴¹ In some studies, antioxidants have been shown to reduce CVD events.^{42,43} However, guidelines do not comment on the role of antioxidants in CKD patients to reduce the CVD burden.

SPECTRUM OF CVD IN PATIENTS WITH CKD

The strong link between CVD and CKD is not surprising because of shared predisposing risk factors for both the entities. However, CKD by itself is an independent risk factor for CVD. On the other hand CVD presence portends a decline in the renal function. Thus the CVD-CKD loop is a vicious cycle.^{44,45} Atherosclerotic lesions in patients tend to be extensive, heavily calcified, and more unstable. The morphologic features of atherosclerosis in patients with CKD are distinctive and “malignant” in nature.

A common cardiac structural abnormality of patients with CKD is LVH. As the renal function declines there is a reciprocal increase in LVH.⁴⁶ A majority of patients with CKD demonstrate LVH. It is important to recognize that LVH is a strong and independent risk factor for CVD burden in patients with CKD.

The manifestations of CVD (CAD, LVH, CHF, hypertension, atrial fibrillation, ventricular arrhythmias, cardiomyopathy, and sudden cardiac death) are accentuated and fully expressed in CKD patients. CVD mortality in ESRD patients is 20-30 times higher compared to the general population. CAD in patients with CKD tends to be severe and “violent” with high mortality. Unfortunately, ACS may be missed in patients with CKD because chest pain may be absent and EKG may be misleading due to LVH. The Uremic milieu drastically reduces the success of coronary and other vascular interventions in patients with CKD. Herein lies the deadly paradox--- CVD is not only extensive in patients with CKD but also less responsive even to aggressive and early therapeutic options. Ironically, patients with CKD may have ischemic heart disease (without visible occlusive coronary artery disease) due to microcirculatory disturbances and LVH. Another structural pathologic lesion--- arterial calcification---is frequent in patients with CKD. A high coronary artery calcification is common in patients with CKD.⁴⁷

CHF is a major pathophysiological and clinical problem in patients with CKD. While the predisposing factors for CHF in patients with CKD are conventional in nature, LVH, declining GFR, and anemia further contribute to the development of CHF in patients with CKD/ESRD. Sudden cardiac arrest is a highly feared (and prevalent) complication in patients with CKD. Renal disease increases the risk of sudden cardiac arrest. There is an inverse relationship between GFR and sudden cardiac arrest.^{48,49}

CONCLUSIONS

Clinical experience prospective and retrospective studies, and outcome observations confirm and reinforce the critical importance of CVD in patients with CKD. Evidence suggests that the intensity of CVD in patients with CKD is due to the confluence of traditional and non-traditional clustering of risk factors. The prognosis of CVD in patients with CKD is considerably poor compared to patients without CKD. The entire spectrum, breadth, length, and depth of CVD are maximally expressed in patients with CKD.

CKD and its progression cause an exponential increase in the CVD burden. Recognition of this adverse association essential to formulate evidence based preventive and therapeutic strategies at the community level. It is imperative to identify and control the traditional and non-traditional CV risk factors in patients with CKD while acknowledging that CKD by itself is an independent powerful risk factor for CVD. A broad approach, therefore, is to diagnose and manage the risk factors for CVD and CKD in an aggressive manner and the community clinical practice level. This mandates public awareness and medical education to combat the horrible consequences of CVD in patients with CKD.

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