Review Article

Cardiovascular Disease in Chronic Kidney Disease Patients: A Review

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ABSTRACT

The link between Chronic Kidney Disease (CKD) and Cardio Vascular Disease (CVD) has long been established. This association was first suggested by Richard Bright in the early 19th century and has been substantiated in the intervening years. However, the subject has been gaining more attention in recent years. CKD has been termed cardiovascular risk equivalent, hence CKD is an independent risk factor for CVD. CVD is higher in CKD patients compared with the general population, the higher the CKD stage, the higher the CVD risk. CVD has been found to be the major cause of mortality and significant contributor to morbidity in CKD patients and it enhances the rapidity of progression of CKD in such patients. CKD patients are more likely to succumb to CVD than the CKD itself. In spite of these well-established facts, the prevention, diagnosis and treatment of cardiovascular disease in CKD are fought with various controversies. Many studies have shown that correction for the risk factors (both traditional and novel) did not counteract the effect of CKD on CVD risk.

Key Words: Chronic kidney disease, Cardio vascular disease, Anaemia

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INTRODUCTION

The world-wide incidence and prevalence of CKD continue to soar [1]. Global prevalence of CKD has been estimated to be between 11% and 13% of the world population [2]. The traditional and non-traditional risk factors in CKD predispose the patients to high cardiovascular complications. The high occurrence of cardiovascular disease in CKD patients requires careful assessment of possible risks, with the hope of mitigating the burden of the disease and its attendant consequences. Some of the numerous possibilities suggested for the wide distribution of CVD in CKD patients include: ageing population, increasing prevalence of hypertension and type2 diabetes, low detection rate, treatment inertia and reluctance in the early stages of CKD [1,3-9].

The risk factors for cardiovascular disease in CKD patients have been broadly divided into traditional and non-traditional risk factors [10]. These risk factors have synergistic effect and speeds up the process of atherosclerosis and evolution of CKD. It is important to accurately evaluate these risk factors with the ultimate aim of reducing the disease burden and minimizing complications [11,12]. The traditional risk factors for CVD are risk factors for CKD and are therefore common in CKD patients. Examples includes increasing age, hypertension, dyslipidaemia, diabetes, smoking and obesity [12]. They contribute in no small measure to the initiation of CVD in the early CKD stages and in turn worsen CKD progression [4].

The non-traditional or novel risk factors are uremia specific, or at least much more common in patients with CKD than in the general population. These include albuminuria, anaemia, hyperparathyroidism, metabolic bone disease, hyper homocysteinaemia, hyperuricemia malnutrition, apolipoprotein isoforms, inflammation, endothelial dysfunction and oxidative stress [10]. CKD develops over a relatively long period of time with a significant asymptomatic period in between. Hence the utility of biomarkers for early identification of the disease stage and its attendant consequences [13]. The use of biomarkers however, has not been without criticisms [12]. Renal biomarkers of note include cystatin C and serum creatinine which have been used to assess and predict renal function. Other notable markers of renal function include urine albumin, uric acid, and β2 micro globulin. Various novel biomarkers have also been suggested to improve risk assessment and early identification of kidney injury [2].

LITERATURE REVIEW

Biomarkers for CVD

Albuminuria has been considered a prognostic marker for cardiovascular disease, with or without renal involvement. Higher levels of albuminuria indicate a graded increase in risk for mortality independent of estimated Glomerular Filtration Rate (eGFR). Low eGFR and higher albuminuria has been linked with cardiovascular disease [13,14]. Hence the need for regular assessment of albuminuria in CKD patients.

Anaemia is commonly found in CKD patients and produces hyper dynamic circulation and generalized vasodilatation. It triggers neuro hormonal activation with resultant salt and water retention. Anaemia of CKD enhances the risk of cardiovascular morbidity and mortality by causing Left Ventricular Hypertrophy (LVH) and heart failure with Left Ventricular (LV) systolic dysfunction. Previous studies in patients on dialysis have shown that LVH is a potent predictor of morbidity and mortality. Correction of anaemia to an haemoglobin level of between 10 and 13 g/dl has therefore been recommended as a way of mitigating anaemia induced adverse cardiovascular outcomes in CKD patients [15,16].

CKD induces a chronic inflammatory state as a result of increased oxidative stress, enhanced production of pro-inflammatory cytokines and acidosis amongst other factors, further contributing to adverse overall and cardiovascular outcomes in these patients. Inflammatory states elaborate inflammatory markers which are inadequately cleared by the diseased kidney [17,18]. Interleukin-6 (IL-6) and C-reactive protein are among the most commonly measured inflammatory markers. While most studies have confirmed IL-6 as a classifier and predictor of prognosis in CKD patients, there have been divergent opinions on the utility of CRP in predicting the cardiovascular and all-cause mortality in this cohort of patients [19-22]. Asymmetric dimethyl arginine inhibits endogenous Nitric Oxide Synthase (NOS) resulting in endothelial dysfunction. Levels of ADMA increase with worsening renal dysfunction, and studies have associated increasing levels of ADMA with CKD progression and adverse CV outcomes [23]. Role of L-arginine, which competitively inhibits ADMA, antioxidants such as acetylcysteine and vitamin E, are worth further consideration and evaluation in counteracting the oxidative stress posed by ADMA in CKD patients.

Abnormal bone mineral metabolism with elevated calcium phosphorous product leads to vascular calcification that adversely affects the cardiovascular system. There is an elevated level of Fibroblast Growth Factor (FGF-23) in CKD patients which enhances the excretion of phosphate retained as a result of the decreased renal function. Current state of research has revealed that an association exists between FGF-

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23 and cardiovascular diseases in CKD patients, although it is not one of the conventional risk factors, numerous reports have linked elevated FGF23 to accelerated progression of kidney disease to End Stage Renal Disease (ESRD), CVD and death [24,25]. FGF is a highly sensitive biomarker of toxicity due to phosphate retention and it also, exerts a direct toxic effect on the heart. Several cross-sectional studies across the entire spectrum of varying degrees of renal dysfunction have demonstrated that elevated FGF23 levels correlate with higher LV mass index and LVH, with its attendant consequences. This was also demonstrated in the Homocysteine in Kidney and End Stage Renal Disease study in which elevated FGF23 levels overrode the traditional cardiovascular risk factors and increased the risk of myocardial infarction, commencement of maintenance haemodialysis and all-cause mortality. Higher FGF23 level results in impaired vessel reactivity, endothelial dysfunction and increased arterial stiffness.

An association between CKD and hyperuricemia has also been identified, although such evidence appears limited and inconsistent. Hyperuricemia has been found in some studies to raise the inflammatory markers, contribute to endothelial dysfunction and accelerate the kidney disease progression, hence adding to the negative consequences in CKD patients. Cardiac biomarkers have been suggested as potent elements to assess and better stratify the CVD risks in CKD patients however, this has not been without divergent opinions. Given the high prevalence, incidence and the adverse consequences of cardiovascular disease in CKD patients, it is understandable that regular assessments of the cardiac biomarkers are needed for accurate and prompt diagnosis. However, the interpretation of cardiac biomarkers in CKD can be complex since elevated levels of the biomarkers may not only imply an ongoing background cardiac damage or injury but may be a reflection of reduced urinary clearance [25].

Brain Natriuretic Peptide (BNP) and N-Terminal pro B type Natriuretic Peptide (NT proBNP) are cardiac natriuretic peptides released when there are alterations to cardiac pressure. NT ProBNP has been identified as a useful marker to predict cardiovascular events because of its stability and the less likelihood of it being removed by haemodialysis [12]. Several studies have affirmed BNP and NT proBNP as effective markers of cardiovascular risks in CKD patients [24-26]. They correlate and predict the severity and prognosis of left ventricular hypertrophy as well as heart failure, they guide treatment in CKD patients with heart failure and NT proBNP particularly has been established as independent predictor of all causes mortality in heart failure patients with significantly reduced eGFR [12].

Cardiac troponins are other useful cardiac biomarkers, found in the cardiac myocytes; they are regulatory proteins that facilitate cardiac contractions. Their presence in the blood suggests myocardial cell injury. There are 2 forms: Troponins T and I. Possible explanations advanced for the rise in cardiac troponins in pre-dialysis patients include increase in left ventricular mass, volume overload, myocyte apoptosis, kidney disease related subclinical cardiac damage and possibly reduced clearance [27,28]. Several studies have established the link between cardiac troponin and cardiovascular events as well as death in CKD patients although, the exact mechanism through which this occurs is still a subject of research. Cardiac Troponin T has been recognized as a predictor of coronary artery disease, end stage renal disease and ultimately all causes mortality in CKD patients [29].

Since interpretation of cardiac biomarkers in CKD patients can be confusing, research is underway to uncover novel markers that will improve the diagnostic yield and accuracy of cardiovascular outcomes in this group of patients [30]. Both the structural and functional cardiac impairments have contributed significantly to the poor prognostic outcome in CKD patients [31]. Left atria sizes, left ventricular hypertrophy, left ventricular mass are echocardiographic parameters that have been found to be significantly increased in CKD patients. Functional cardiac abnormalities such as heart failure have also been identified as a frequent finding [32].

Management of CVD in CKD

Given the significant effect of CVD in CKD patients and its invaluable contributions to mortality, it is convincing that preventing and treating CVD will go a long way to improve the clinical outcomes of these patients. However, the relationship is not usually that straightforward compared with what obtains with CVD risks in the general population [33]. Though CVDs are prevalent in CKD patients, there is scarce evidence on the optimal management strategy of this subgroup. This is because almost all the major trials on cardiovascular disease have excluded patients with renal dysfunction and those that have included them are small and underpowered. A review by Charytan and Kuntz which evaluated 86 trials with more than 4,00,000 patients, observed that 80% of the trials excluded ESRD subjects and baseline renal function was reported in less than 10% of the trials. Hence, the benefits obtained from standard medical therapy in non-CKD population cannot be directly extrapolated to the CKD population. This leads to the dilemma being faced while treating a patient with renal dysfunction [1]. The CKD cohort represents a unique subgroup and will require further investigation on this subject targeting the ranges of renal function.

The medical management of CVD hinges on aspirin, statins, and Angiotensin Converting Enzyme inhibitors (ACEi) or Angiotensin Receptor Blockers (ARBs) and β blockers. Optimizing glycaemic control to meet individual needs with an approximate glycated haemoglobin level of 7% has been recommended and the control of blood pressure to a target of <130/80 mm of Hg irrespective of the extent of proteinuria are critical in CKD patients [34,35].

ACEi or ARBs form the standard medical therapy in patients with CVDs in the general population

In patients with CKD, these medications have been found to derive benefits in the ability to lower blood pressure, reduce proteinuria, slow the progression to ESRD and reduce the overall cardiovascular events. However, the overall beneficial effect of ACEi or ARBs in renal insufficiency is still being debated. The Fosinopril in Dialysis (FOSIDIAL) trial failed to show any additional benefit in patients on dialysis [36]. Similarly, a Cochrane review in early non-diabetic CKD (stages 1–3) did not demonstrate any advantage in the overall cardiovascular events or all-cause mortality with ACEi [37].

However, Efrati, et al. in his study among dialysis patients found a 52% reduction in mortality and this benefit was reproduced by various other studies across the different stages of CKD [38-40]. In spite of the controversies, the NKF KDOQI recommends the use of ACEI or ARBs (with careful monitoring) in CKD patients while acknowledging its potential limitations [41].

DISCUSSION

In the past, β Blockers was not considered beneficial in CKD patients owing to reduced tolerability and adverse effect on metabolic profile however recent evidences support the use of newer vasodilatory β Blockers especially carvedilol and labetalol as add on to other anti-hypertensives for blood pressure reduction, they have also been found to contribute to reduction in albuminuria and sympathetic over activity which enhances cardiovascular events in CKD patients [42,43]. β Blockers use in CKD patients with systolic heart failure has also been recommended [44].

Although, the benefit of statin to reduce cardiovascular related mortality in the general population and CKD patients have been well established, the mortality advantage of statin in advanced CKD or CKD patients on

dialysis is yet to be reported. According to the Kidney Disease Improving Global Outcomes (KDIGO) 2013 guidelines, statin or statin/ezetimibe therapy is recommended in adults ≥ 50 years with reduced eGFR (<60 ml/min per 1.73 m2) but not on chronic dialysis and in those aged 18 and 49 years treatment with statin is recommended if there are other risk factors for CVD. Initiating statin is however, not recommended in those on chronic dialysis but can be continued if patient is already on it [45].

Anemia in CKD patients have been defined as Hb <13 g/dL in male, <12 g/dL in females [46]. Anemia contributes significantly to the adverse cardiovascular outcomes in CKD patients because of its association with left ventricular hypertrophy, ischemic heart disease and congestive cardiac failure. It has equally been identified as a marker of CKD progression. Management of anemia is therefore fundamental to reducing the cardiovascular burden and delaying disease progression in CKD patients. Appropriate treatment of anemia has therefore been recommended for cardiovascular benefits. The optimal target hemoglobin that will yield maximum benefits with minimal complication has been a subject of continuous study. KDIGO suggests that with erythropoietin therapy, target hemoglobin concentration should not be greater than 13 g/dL and that above this level risk of complications such as hypertension, heart failure and stroke increases [47]. For optimal cardiovascular and overall advantage hemoglobin level of between 10 and 13 g/dL should be the therapeutic target level [48]. Frequent testing to ensure early identification and prompt management of anemia has been recommended by KDIGO.

The management of Mineral Bone Disease (MBD) in CKD is still undergoing research. The aim of treatment of MBD is to maintain calcium and phosphate homeostasis. The currently used medications are phosphorus lowering agents and anti PTH agents are largely yet to produce the desired effectiveness in CKD patient [49].

Coronary artery disease is a common complication in CKD patients and has a negative prognostic implication [50]. Just like other forms of intervention in CKD patients, many of the trials that evaluated the intervention strategies in IHD have not been so inclusive of this cohort, hence the outcome cannot be extrapolated to the entire CKD cohort. In a 2 year trial comparing medical and revascularization therapy in insulin dependent diabetic patients with CKD and asymptomatic CAD showed superior outcome in the revascularization group. When the mammary artery is available as the bypass channel, coronary artery bypass grafting CABG with mammary artery graft is the revascularization option of choice [51,52]. Surgical reperfusion by (CABG) was considered the gold standard due to restenosis of Bare Metal Stents (BMS) used earlier. The presence of small diffusely diseased vessels coupled with vascular calcification in patients with CKD was responsible for high failure rates with balloon angioplasty in the present era [53].

CONCLUSION

In conclusion, cardiovascular complications are very common findings in CKD patients, causing acceleration of the kidney disease and accounting for premature death in about half the CKD population. However, there are evidences to support its relevance in those who are not candidates for surgery, especially when their symptoms persist despite optimal antianginal therapy. Early Identification of biomarkers will enhance early and prompt diagnosis of cardiovascular events which will in turn improve outcomes by improving the quality of life, reducing morbidity, mortality and reduce hospitalization rates.

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