American Journal of Hypertension Research, 2013, Vol. 1, No. 1, 1-5
Available online at http://pubs.sciepub.com/ajhr/1/1/1

DOI:10.12691/ajhr-1-1-1

Main Points of Coronary Artery Disease in Chronic Kidney Disease

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Received January 15, 2013; Revised February 23, 2013; Accepted March 15, 2013

Abstract Cardiovascular diseases are the most common cause of mortality and morbidity in patients with chronic kidney disease (CKD) and end-stage renal disease (ESRD) receiving hemodialysis and peritoneal dialysis. Beside traditional risk factors including hypertension, diabetes, dyslipidemia, advanced age novel risk factors such as endothelial dysfunction, hyperphosphatemia, hyperparathyroidism, vascular calcification, increased oxidative stress and inflammation are highly prevalent and seem to play a more important role for vascular disease in CKD and ESRD patients compared to general population. This review briefly discuss classical and recent epidemiologic, pathophysiologic and clinical aspects of coronary artery disease in ESRD patients.

Keywords: *chronic kidney disease (CKD), cardiovascular disease (CVD), atherosclerosis*

1. Introduction

Despite the improvements in diagnostic tools and medical applications, cardiovascular diseases (CVD) remain the most common cause of morbidity and mortality in patients with chronic kidney disease (CKD) and end-stage renal disease (ESRD) receiving hemodialysis (HD) and peritoneal dialysis (PD) [1]. The main factors for the heightened risk in this population, beside advanced age and a high proportion of diabetes and hypertension, are malnutrition, chronic inflammation, accelerated atherosclerosis, highly prevalent endothelial dysfunction (ED), coronary artery calcification (CAC), left-ventricular structural and functional abnormalities, and CKD-MBD abnormalities [2,3,4]. Chronic kidney disease is now recognized as an independent risk factor for coronary artery disease (CAD) in community-based studies as well as in high cardiovascular (CV) risk populations. In community-based studies, decreased glomerular filtration rate (GFR) and proteinuria were both found to be independently associated with CAD [5,6,7]. Growing evidence suggest that a gradual fall in GFR is also independently associated with CV events in patients with preexisting CVD [8,9,10,11]. This review will discuss classical and recent epidemiologic, pathophysiologic and clinical aspects of CAD in CKD patients.

2. Epidemiology

Epidemiologic studies have repetetively showed the close relationship between CV events and CKD. The largest population-based study done by Go et al. [12] demonstrated that a decline in GFR was the main independent risk factor for CV events, including hospitalization secondary to peripheral artery disease (PAD), CAD, congestive heart failure (CHF) or stroke even after the elimination of confounding risk factors, in more than 1.1 million adults. Similar findings were also reported in a systematic review considering approximately 1.4 million adults from 42 different cohorts [13]. According to this review's results, the risk of all-cause mortality was highest in patients with lowest baseline GFR and vice versa. The gradual fall of GFR was also found to be associated with a gradual increase of death.

Cardiovascular risk is increased even in the early stages of CKD, particularly in the elderly. In a study including approximately 30.000 older CKD patients with estimated GFR of less than 90mL/min/1.7m^2, the rate of mortality at five years was 19.5%, 24.3%, 45.7% in those with CKD stage 2, 3, or 4, respectively [14].

Considering the depth and the quality of the epidemilogical evidence, to date, both the American College of Cardiology/American Heart Association (ACC/AHA) and the National Kidney Foundation (NKF) recommend that CKD be considered as equivalent of CAD [15,16].

3. Pathophysiology of CAD in CKD

According to the AHA guidelines, coronary atherosclerotic plaques constitute most of the CVD in

general population [17]. However, the pathophysiology of vascular disease in CKD is quite different from that related to atherosclerosis, in the general population [18]. Beside traditional risk factors including hypertension, diabetes, dyslipidemia, advanced age novel risk factors such as endothelial dysfunction (ED), chronic kidney diseases-mineral bone disorders (CKD-MBD) abnormalities (hyperphosphatemia, hyperparathyroidism and vascular calcification), increased oxidative stress and inflammation are highly prevalent and seem to play a more important role for vascular disease in CKD and ESRD patients compared to healthy subjects. [4,19,20,21]. Several studies demonstrated that systemic persistent inflammation particularly could be the main factor responsible for this increased risk in ESRD patients regardless of the renal replacement therapy [22]. To prove this hypothesis, several biomarkers including C-reactive protein, interleukin (IL)-1β, IL-6, tumor necrosis factor-α (TNF- α) were considered in CVD and CKD populations [22,23].

Beside the factors mentioned above, why the CKD patients are more prone to worse CV outcomes is still unclear. In the general population, many patients with CAD develop coronary collateral circulation to overcome obstruction of the atherosclerotic coronary arteries. Charytan et al hypothesized that CKD patients might have less collateral blood supply to ischemic area of the myocardium and this hypothesis might partially explain why CKD patients have much worse CV outcomes and death. However, this study was failed to prove this hypothesis because both CKD patients and subjects without CKD had similar culprit artery collateral supply (25% vs 27.2%, respectively, p=0.76) [24].

4. Vascular Calcification

Vascular calcification (VC) is very common and becoming more prevalent with the worsening of kidney function in patients with CKD and ESRD. The importance of this process has been demonstrated by the tight relationship between VC and increased cardiac mortality in this population [25]. The hemodynamic consequences of VC include a decrease in coronary microcirculation and arterial elasticity, an increase in pulse wave velocity and increased left ventricular hypertrophy [26,27]. VC may develop in the intimal or the medial layer of the vessel wall. The latter is also named as 'Monckeberg's sclerosis' which is much more common in patients with CKD compared to general population [26]. The main differences between these two types of VC are as follows; i) intimal calcification is highly associated with inflammation and focal occlusion secondary to the plaque formation, however, medial calcification are characterized by diffuse pipe type calcification of muscular arteries, ii) intimal calcification is commonly seen in coronary, carotid arteries and aorta, whereas medial calcification is commonly observed in tibial and femoral arteries [27,29].

Malnutrition–inflammation–atherosclerosis/calcification (MIAC) syndrome has been defined as the interaction between increased levels of proinflammatory cytokines, malnutrition and atherosclerosis/calcification in ESRD patients [30,31). Stenvinkel et al. [32] hypothesized that malnutrition, inflammation and atherosclerosis cause a vicious cycle, and that proinflammatory cytokines play a central part in this process. The presence of MIAC components was found to be associated with increased mortality and morbidity in ESRD patients receiving PD [32] or HD [33]. The coronary artery calcification is a part of the extended state of vascular calcification which can be detected even in the early decades of patients with ESRD [23,28] that reflects the severity of atherosclerotic vascular disease and predicts cardiovascular events [34,35]. Wang et al. [31] showed an important association between malnutrition–inflammation–atherosclerosis and valvular and vascular calcification in PD patients. In a recent study, the correlation of coronary artery calcification score (CACS) with coronary flow velocity reserve (CFR) was investigated in HD patients [36]. According to the results of this study HD patients with CACS >10 had a significantly lower CFR and the functional deterioration of coronary arteries started from low levels of CACS.

Epicardial adipose tissue (EAT) is the true visceral fat depot of the heart that accounts for approximately 20% of total heart weight and covers 80% of the cardiac surfaces, and is mostly in the grooved segments along the paths of coronary arteries [37,38,39]. Recent studies showed a close relationship between CAD and EAT using multidetector computed tomography (MDCT) and echocardiography in healthy subjects and patients at a high risk of CAD [40,41,42,43]. Although the pathophysiologic role of EAT is not clear to date, the researchers suggest that EAT may act as an extremely active organ that produces several bioactive adipokines as well as proinflammatory and proatherogenic cytokines such as tumor necrosis factor (TNF)-α, monocyte chemotactic protein (MCP-1), interleukin (IL)-6 and resistin [42,44,45,46,47]. In a recent study, we demonstrated the relationship between MIAC syndrome and EAT in ESRD patients receiving HD or PD [48]. Taken together, these factors may contribute to premature CVD and the markedly increased mortality in patients with ESRD. Treatment of CAD in patients with CKD is beyond the scope of this review.

5. Clinical Studies of CAD in CKD Patients

Baber et al. [49] was aimed to determine the impact of CKD on atherosclerotic plaque composition, morphology, and outcomes in patients with CAD. According to the results of this study, authors demonstrated that CKD patients had more extensive and severe atherosclerotic plaques composed of greater necrotic core and less fibrotic tissue. They also concluded that in the following 3-years, CKD patients had significantly higher rate of acute myocardial infarction, cardiac arrest and death compared to patients without CKD although there were no significant difference in the rates of events adjudicated to nonculprit lesions. Similarly, Kawai et al. [50] demonstrated that the prevalance of severe coronary artery stenosis (≥70% of luminal diameter) defined by 320-row area computed tomography was significantly higher in 131 patients with mild CKD (eGFR≥60mL/min) compared with patients without CKD (35.1% vs 19.4%, p=0.0003, respectively), although there were no

significant difference in the prevalance of high-risk plaque (13.0% vs 9.8%, p=0.3189, respectively).

In a substudy of Acute Catheterization and Urgent Intervention Triage strategy (ACUITY) trial, Acharji et al. [51] aimed to show the prognostic value of baseline troponin levels of 2179 CKD patients with moderate and high-risk of ACS. Of 2179 CKD patients 1291 had elevated baseline troponin (59.2%). CKD patients with higher baseline serum troponin levels had significantly higher rates of death, MI or unplanned revascularization at 30 days and 1 year compared with CKD patients without baseline troponin elevation. Another important result of this study confers that baseline elevation of troponin independently predicts death or MI at 30 days and 1 year (HR=2.05 (1.48-2.83), p<0.0001 and HR=1.72 (1.36-2.17), p<0.0001, respectively). However, diagnosis of ACS in the patients with CKD based on troponin levels should be interpreted cautiously.

Among all dialysis patients, a cardiac mortality has been estimated as 40%. Additionally this high rate reaches up to 50% in diabetic ESRD patient without any ACS symptoms. Accurate diagnosis of ACS is quite different in this population. In a study of 274,777 subjects (CKD, non-CKD and patients receiving dialysis) enrolled from the US Renal Data System and the Third National Registry of Myocardial Infarction, outcomes were reported for several subgroups, including patients with advanced CKD (baseline serum creatinine≥2.5mg/dL) and ESRD patients receiving dialysis and patients without CKD [52]. On admission, chest pain, ST elevation and diagnosis other than ACS were seen in 40.4%, 15.9%, and 44% of patients with advanced CKD; 41.1%, 17.6% and 47.7% of ESRD patients receiving dialysis; 61.6%, 32.5%, 25.8% of patients without CKD, respectively. In addition, mortality rates, unexpected cardiac arrest, and congestive heart failure were seen in 23%, 8.9%, 41% of patients with advanced CKD; 21.7%, 12.3%, 25.8% of ESRD patients receiving dialysis; and 12.6%, 6%, 21.1% of patients without CKD, respectively (p<0.0001 for all comparisons).

There has been a strong relation between CKD and hypertension whereby each can cause or aggravate the other. Control of blood pressure is fundamental to avoid the progression of CKD hence several clinical practice guidelines have been published on this topic by many authoritatives over the last 10 years [53,54]. Since hypertension in the patients with chronic kidney disease contributes to the particularly high risk of CV morbidity and mortality, ambulatory blood pressure measurement (ABPM) is one of the important diagnostic tools especially in patients with poorly controlled hypertension [55]. Anderson et al [56] showed that, approximately 30% of CKD patients had office BP measurements higher than ABPM, whereas 28% of the patients had office BP measurements underestimated ABPM. ABPM showed a strong correlation with left ventricular mass index (LVMI) [57] and proteinuria than single casual office BP measurementsin patients with CKD [58] and in general population [59]. A study comparing the prognostic value of office BP and home BP monitoring showed that home measurements were superior to office BP and predicted ESRD independently of other risk factors [60].

In hypertensive CKD patients, inappropriate left ventricular hypertrophy may occur which can be estimated by the ratio of observed to predicted left ventricular mass (LVM). Recently, the ratio of observed to predicted LVM was found to be independently associated with increased CV events in patients with CKD stages 3-5 [61].

Recently, Kidney Disease Improving Global Outcomes (KDIGO) published a guideline regarding the management of blood pressure in CKD [62]. According to this report they recommended that non-diabetic adults with CKD patients who had urine albumin excretion≤30mg/24hours and office BP>140/90mmHg should be treated with antihypertensive agents especially with angiotensin converting enzyme inhibitors or angiotensin receptor blockers. They also suggested that blood pressure target should be ≤130/80mmHg in those who had urine albumin excretion (UAE) 30-300mg/24hours and UAE≥300mg/24hours.

6. Prognosis of CAD in Patients with CKD

CKD patients with CAD have a worse prognosis than patients with preserved kidney functions. In-hospital complication rates and long term mortality were found to be highest among patients receiving hemodialysis [63]. Previous studies showed that there was an adverse association between GFR decline and cardiovascular prognosis even in CAD patients who undergone percutaneous coronary intervention [64] or coronary artery bypass grafting [65]. The proposed explanations of this poor prognosis are as follows;

i). CKD patients have a burden of multiple cardiovascular risk factors including hypertension, diabetes, advanced age, hypervolemia, inflammation, oxidative stress and etc. Thus, the detrimental effects of these risk factors may explain the hightened mortality rates in this population.

ii). A second explanation of this worse prognosis may be the misdiagnosis of the underlying kidney disease in patients admitted with CAD because of the usage of formulas depending on baseline serum creatinine to define GFR. Thus, AKI or acute reversible elevations of serum creatinine may conflict the results of the studies about predicting CV mortality in patients with ACS admitted to emergency room.

7. Conclusion

The risk of CAD unexpectedly high in patients with CKD and ESRD. Beside the traditional ones, novel risk factors commonly seen in CKD patients including chronic inflammation, oxidative stress, and hyperparathyroidism might provoke the underlying pathophysiological mechanisms of CAD. To date, we know more about the the genesis of CAD in this population, however, much remains unknown. Further experimental and randomised controlled clinical studies are needed to define the exact pathophysiological and clinical aspects of CAD in CKD population.

Conflict of Interest

None of authors have conflict of interest

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