Genetic Determinants of Increased Burdens of Cardiovascular Disease in Patients with Chronic Kidney Disease: A Narrative Review of the Literature

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ABSTRACT

Cardiovascular disease (CVD) is responsible for up to 37% of deaths among individuals with CKD, making it a leading cause of mortality among patients with CKD.[3] Also, the burden of CVD increases with worsening kidney function and CKD is regarded as a major CVD risk factor.Despite the high burden of CVD among individuals with CKD, the mechanisms underlying the increased prevalence of CVD burden in patients with CKD is not completely known. In addition, little is known about the genetic and environmental factors that determine the initiation and progression of CVD in patients with CKD. The incidence of CVD is rising in sub-Saharan African region and CKD is one of the major contributor to this increase.The excess burden of CVD in CKD suggests that both the traditional CVD risk factors and factors specific to kidney disease play important role in the rising burden of CVD in the population. Among the major kidney disease factors that contribute to the high burden of CVD are ***C**hronic **K**idney **D**isease – **M**ineral **B**one **D**isease* (CKD-MBD), anaemia, hypertension, albuminuria, endothelial dysfunction, dyslipidemia and peripherial arterial disease.Furthermore, the role of genetic factors in the excess burden of CVD in CKD is yet to be determined. Variants in the gene encoding Apolipoprotein 1 (*APOL1)* have been established as the major genetic risk factors for excess of CKD in individuals of African descent. However, their role in excess CVD burden is not clearly defined. This narrative review article examine and discuss thegeneticburden and aetiopathogenesis of CVD among patients with CKD.

Keywords: *APOL1variants,Cardiovascular Disease, Chronic Kidney Disease, CKD-MBD*

INTRODUCTION

Chronic kidney disease (CKD) constitute a signifcant disease burden worldwide with 11 – 13% of the world population affected [1]. Individuals of African descent are at higher risk of end stage kidney disease (ESKD) compared to people of European and Hispanic descents [2]. ESKD accounts for 8-10% of all medical admissions in Nigeria and recent community based studIes estimated the disease prevalence to

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be between 19 – 27% [3-5]. ESKD is associated with high morbidity and mortality. Mortality in sub-Saharan Africa (SSA) is particularly high as a result of very limited access to renal replacement therapy (RRT) [6]. Inhigh income countries (HICs), cardiovascular disease (CVD)(Defined as disorders of the heart and blood vessels and it include stroke, coronary artery disease, pheripheral arterial disease etc) contributes significantly to the huge morbidity and mortality associated with ESKD. In one study, CVD was reported to be responsible for 37% of deaths among individuals with CKD, making it a leading cause of mortality among patients with CKD [7-9]. The incidence of CVD is rising in sub-Saharan African region and CKD is one of the major contributor to this increase [10-12]. This suggests that the traditional CVD risk factors and factors specific to kidney disease play important role in the rising burden of CVD in the population [13]. Among the major kidney disease factors that contribute to the high burden of CVD are ***C**hronic **K**idney **D**isease – **M**ineral **B**one **D**isease* (CKD-MBD), anaemia, hypertension, albuminuria, endothelial dysfunction, dyslipidemia and peripherial arterial disease [14].

Contributions of CKD-MBD to excess cardiovascular disease burden in CKD

CKD-MBD arises from secondary hyperparathyroidm associated with CKD and is characterized by abnormal calcium and phosphate regulation, abnormal bone morphology and metastatic calcification of soft tissues and blood vessels [15]. The increased risk of CVD among individuals with CKD has been attributed to these abnormal calcium and phosphate metabolism and metastatic calcification of the arteries [16]. Studies have shown that CKD-MBD is associated with many cardiovascular sequalae, among which are the high prevalence of left ventricular hypertrophy (LVH), heart failure, coronary artery disease, transient ischemic attack, stroke and sudden cardiac death [17]. (Figure 1) The prevalence of CVD among patients with CKD-MBD could be as high as 80% and it is the leading cause of mortality in this group of patients [17-19]. Furthermore, CKD-MBD has a bidirectional relationship with CKD severity and increased severity of one increases the progression of the other [20]. The cumulative effects on CKD and CVD progression results in increased re-hospitalization, high morbidity and mortality. These burdens are particularly higher among people of African descent [21]. The genetic and environmental interactionspropagating this excess CVDburden among patients with CKD are currently unknown.

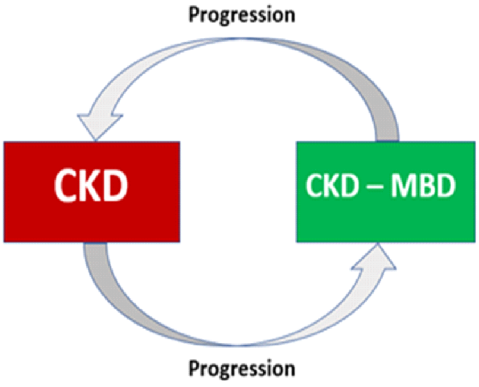

Figure 1: Relationship between CKD and CKD-MBD

Role of Apolipoprotein 1 (*APOL1)*genetic variants in excess cardiovascular disease burden in CKD

The genetic basis for excess of CKD in Africans was recently defined with the identification of risk variants in the gene encoding Apolipoprotein 1 (*APOL1)*. Using mapping by admixture linkage disequilibrium (MALD), the risk in African Americans (AA) with non-diabetic CKD was mapped to a region on chromosome 22q12 [22]. This region on chromosome 22q12 shows evidence of positive selection in individuals of West African descent which includes the majority of African Americans [22]. Subsequent fine mapping pointed to G1 (Ser342Gly or rs73885319) and G2 (rs71785313) variants in the nearest neighboring gene *APOL1* as the candidate variants associated with non-diabetic kidney disease [22]. The *APOL1* risk haplotype is present at high frequencies in populations of West African descent, but has low frequencies in other populations [23,24]. The clustering of CKD and CVD has led to studies to detemine whether *APOL1* genetic risk variants play a role in excess burden of CVD. Data among Africans in diaspora and other populations are conflicting, with some studies suggesting that *APOL1* risk variants are associated

with increased prevalence and progression of CVD in CKD patients, while others found no such association [25]. Ito *et al* found that among AA participants in the Jackson Heart Study (JHS), two *APOL1* risk alleles (G1 and G2) increased the risk of CVD, they reported 13.2% CVD events among participants with two *APOL1* high risk alleles compared with 6.6% in participants without *APOL1* risk allele (odds ratio (OR): 2.17, p=9.4 x 10-4) [25]. This finding was replicated by the same group, in the participants of Women's Health Initiative study, where CVD events was observed in 36.6% of the participants with two *APOL1* high risk alleles and 22.6% among participants without *APOL1* allele high risk variants [25]. In contrast to earlier findings, Freedman *et al* [26] reported that *APOL1* risk variants are associated with lower level of carotid artery plaque (β - 0.42, SE 0.18, dominant model), and marginally lower coronary artery plaque (β - 0.36, SE 0.21; dominant model), among 717 African participants of the American-Diabetes Heart Study. This study suggests that *APOL1* is protective against CVD risk. Similarly, the Systolic Blood Pressure Intervention Trial (SPRINT) found marginal association between *APOL1* risk variants and CKD (OR; 1.37, 95% confidence interval (CI) 1.08–1.73) but no association with CVD (OR;1.02, 95% CI; 0.82–1.27) [27]. Similar pattern was reported in the African American Study of Kidney Disease and Hypertension (AASK) study [28,29]. The contradicting reports from previous studies, most of which did not also assess the role of putative genetic modifiers of *APOL1* gene risk variants, makes it imperative to study the effects of *APOL1* on CVD end points among Western Africans who shared the *APOL1* ancestry with majority of the African Americans.

Genetic Determinants of CKD-MBD and its Role in Excess Cardiovascular Burden in CKD

Secondary hyperparathyroidism is a common component of CKD-MBD [30,31]. A key factor in the pathogenesis of CKD-MBD is Fibroblast Growth Factor 23 (FGF-23). FGF-23 is secreted by osteoblast and function to regulate phosphorus and vitamin D (Vit D) metabolisms. The primary activities of FGF-23 increases in hypophosphatemia arising from phosphorous wastage, hypocalcemia, low serum 1,25-dihyroxyvitamin D, rickets and osteomalacia. Whereas reduced activity of FGF-23 causes hyperphosphatemia, excessive level of 1,25-dihyroxyvitamin D, ectopic calcification and premature death [31]. In normal homeostasis, FGF-23 regulates and maintains a normal serum phosphorous [31]. Elevated FGF-23 has been reported to be an independent predictor of death among patients with CKD [31]. The abnormal calcium and vitamin D metabolism occurs as early as stage 2 of CKD, and it is accompanied by progressively increasing risk of CVD [31]. Identification of FGF-23 protein as a marker of CKD-MBD has provided insight into the pathogenesis of CVD in patients with CKD and variants in *FGF23 gene* CVD identified [32]. FGF-23 protein down-regulates expression of the sodium dependent phosphate cotransporters (NPT2a) in the renal proximal tubule, decreasing reabsorption of phosphate and, thereby, decreasing blood phosphate concentrations [32,33,34]. The NPT2a protein is encoded by *SLC34A1* gene and two variants in the gene have been associated with CKD-MBD and its cardiovascular sequalea [34]. The calcium-sensing receptor (CaSR) is a G-protein coupled receptor family mostly found in the parathyroid gland and the renal tubule, it maintains serum calcium level via its regulation of parathyroid hormone (PTH) secretion and urinary calcium execretion [35]. Variants in *CASR* gene have been associated with increased risk of metastatic calcifications and CVD in patients with CKD [36]. Similarly, polymorphisms in the Vitamin D resistant (VDR) gene has also been implicated in CKD-MBD [37]. A genome wide association study by Kestenbaum *et al* [38] identified three loci near *SLC34A1, CASR and FGF23* as being associated with CKD-MBD [39,40], however, the role of these variants in development of CVD in Africans with CKD with and without *APOL1* high risk genotype is unknown (Figure 2).

Future Direction

Advances in genetics and genomic science have increased our ability to investigate the interractions between environment and genetic predisposition to CKD and its cardiovascular complications in different populations. *APOL1* genetic variants have been shown to confer increased risk of kidney disease among individuals of African descent [41]. Studies among the West African population have reported higher prevalence of the *APOL1* allele risk variants

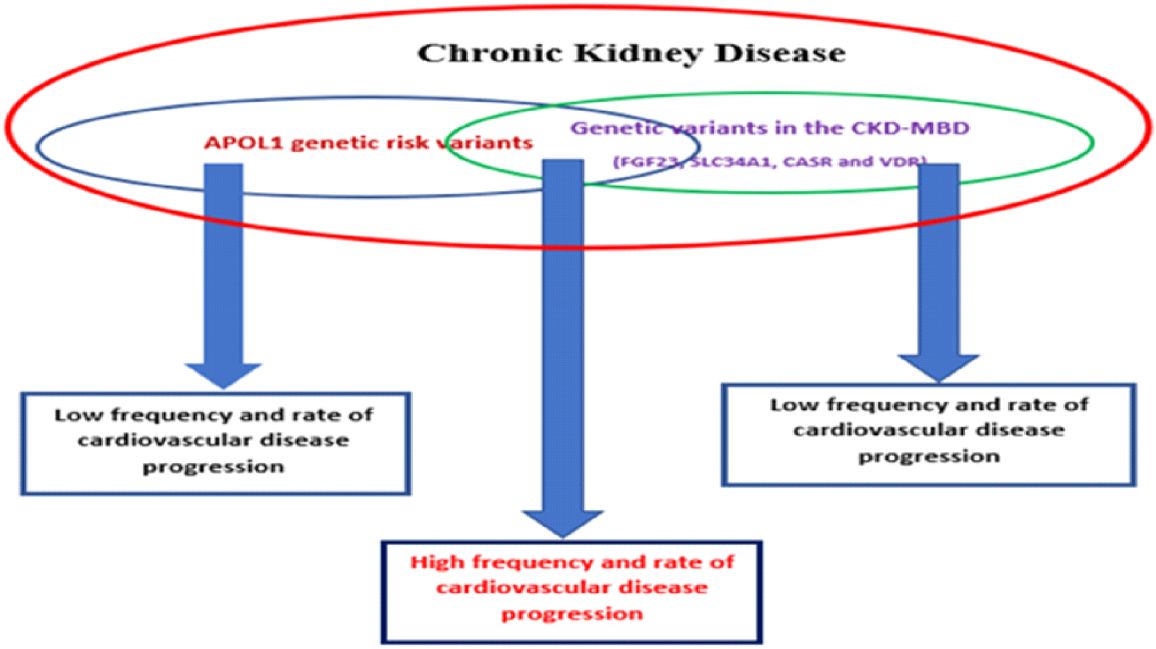

Figure 2: The study hypothesis that interactions between *APOL1* high risk variants and the variants in CKD-MBD associated genes leads to high frequency and rate of progression of cardiovascular disease.

compared to the African Americans [23,24,42]. The role of *APOL1* allele risk variants in the pathogenesis of kidney disease and its progression among individuals of African descent have been well estabilished [23,24,43]. However, its role in CVD burden is not clear cut. Furthermore, the interractions between *APOL1* and the genetic determinants of CKD-MBD have not been studied especially in Africans. Polymorphisms of *FGF23, SLC34A1, CASR and VDR* genes have been associated with calcium and phosphorus metabolisms and its various sequelea including CVD [39-49,44,45]. Therefore, studiesthat will investigate gene xgene and gene **x**environmentinteractions in the development and progression of CVD are needed to unravel factors that propagate the excess burden of CVD among individuals with CKD.

CONCLUSION

The narrative review examines the determinants of excess burden of CVD among individuals with CKDwith the aim of understanding the pathogenesis of CVD and its progression among patients with CKD. Unraveling the mechanisms underlying the high CVD burdens has the potential of providing insight into the development of novel strategies to prevent or retard the progression of CVD among individuals with CKD.

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