


Chronic kidney disease: Definition, updated epidemiology, staging, and mechanisms of increased cardiovascular risk

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Chronic kidney disease (CKD) is a heterogeneous group of disorders that manifest in various ways depending upon the severity of disease and the underlying cause(s).¹

1 | CKD: DEFINITION

Chronic kidney disease is defined by the presence of kidney damage or decreased kidney function for at least three months, irrespective of the cause.² Kidney damage generally refers to pathologic anomalies in the native or transplanted kidney, established via imaging, biopsy, or deduced from clinical markers like increased albuminuria—*that is*, albumin-to-creatinine ratio (ACR) >30 mg/g (3.4 mg/mMol)—or urinary sediment alterations; decreased kidney function refers to a reduced glomerular filtration rate (GFR), which is usually estimated (eGFR) from the serum concentration of creatinine.³

2 | UPDATED CKD EPIDEMIOLOGY

According to the US Centers for Disease Control and Prevention (CDC), ~37 million people in the United States—~15% of adults—are estimated to have CKD. Of note, 90% of adults with CKD do not know they have it and 1 in 2 people with very low kidney function who are not on dialysis are not aware of the fact that they have CKD.⁴ Diabetes and hypertension are the major causes of CKD in adults: According to the CDC, 1 in 3 adults with diabetes and 1 in 5 adults with hypertension may have CKD. According to the current CDC statistics, CKD is more common in people aged 65 years or older (38%) than in people aged 45-64 years (13%) or 18-44 years (7%), and is slightly more common in women (15%) than men (12%); moreover, African Americans are about 3 times more likely than whites to develop ESKD.⁵

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3 | MECHANISMS LEADING TO CKD

In the Western world, the main risk factor for CKD development is diabetes, which is present in 30%–50% of CKD patients.⁶ Hypertension and smoking are other strong factors increasing the risk of CKD as well as the speed of its progression.⁶ Instead, in India, Asia, and Sub-Saharan Africa, the leading cause of CKD is glomerulonephritis, followed by CKD of unknown genesis, probably prompted by soil pollution with heavy metals and pesticides and excessive use of herbal-based traditional medicines.⁷ HIV contributes significantly to CKD due to the direct glomerular interstitial damage caused by HIV per se and to the significant nephrotoxicity of antiretroviral therapies.⁶

Despite the diverse etiologies, the main mechanism of CKD is believed to heavily rely on microvasculature dysfunction. Indeed, hypertension, dyslipidemia, and smoking act on the endothelium in glomeruli and interstitium, eventually resulting in the infiltration of macrophages and other inflammatory cells.⁶ Macrophages activate mesangial cells in glomeruli, facilitating their expansion and extracellular matrix production, which results in substitution of capillaries with matrix, thus reducing the surface through which the blood filtration occurs resulting in a net filtration decrease and accumulation of uremic toxins.⁸ At the same time, glomerulosclerosis is accompanied by dysfunction of podocytes, cells playing a central role in the proper function of the glomerular filtration barrier. As a result, proteinuria develops and tubular epithelium becomes exposed to proteins such as albumin, complement system components, and cytokines which further exacerbate the inflammatory response.⁸ Accumulation of damaged DNA in tubular epithelium through the chronic inflammation produces cell cycle arrest, accompanied by a switch to a specific type of secretory phenotype, which further facilitates pro-fibrotic modifications.⁸ Uncontrolled accumulation of extracellular matrix decreases the capillary density, thus obstructing oxygen and nutrient supply to tubular cells. Eventually, the kidney tissue ends up with tubular atrophy and ubiquitous fibrosis.

4 | CKD AND CARDIOVASCULAR DISEASE

The classification and staging of CKD are based on the cause(s), on the level of albuminuria, and on glomerular filtration rate (GFR).² Kidney failure represents the end stage of CKD (ESKD: end-stage kidney disease) and is defined as severely reduced kidney function or treatment with dialysis. CKD has been shown to lead to an increased risk for cardiovascular diseases, and cardiovascular complications remain the most common cause of death and disability in CKD patients.⁹ Even with a normal eGFR, patients with ACR > 30 mg/g have a significantly increased risk for all-cause and cardiovascular mortality, compared to subjects with a lower ACR.¹⁰

Vascular alterations reflect kidney dysfunction in CKD subjects, and arterial stiffness is considered one of its most common markers.¹¹ Arterial stiffness, characterized by a gradual degradation of the elastic lamellae within the vascular media alongside structural

changes in collagen cross-linking and calcification, is present in several cardiovascular and renal diseases, resulting in the reduced ability of arteries to respond to changes in blood pressure. In the current issue of the Journal, Guo and colleagues examined different parameters of arterial stiffness in CKD patients, proposing the 24-hour mean pulse pressure (PP) as the best marker to predict renal outcomes.¹²

5 | MECHANISMS UNDERLYING ARTERIAL STIFFNESS

Overall, arterial stiffness is a sign of structural and functional modifications of the vascular wall that eventually lead to organ damage. There are 2 main hemodynamic parameters of pressure and flow: a steady component and a pulsatile component. The first one is represented by mean arterial pressure (MAP), the product of cardiac output by vascular resistance, which is generally measured in hypertensive subjects. The second one is represented by the PP, which is mainly determined by stroke volume, aortic stiffness, and wave reflections. As confirmed by Guo and collaborators, PP is a useful parameter to evaluate arterial stiffness.¹² PP is divided into brachial PP and central PP; the difference between these two components is defined PP amplification and it is approximately 14 mmHg. PP amplification might be superior than PP to detect arterial stiffness in CKD patients, particularly in elderly populations.¹³

In patients with ESKD undergoing hemodialysis, clinical studies have shown that BP is frequently associated with an increase in systolic BP (SBP) alone, with normal or even low diastolic BP (DBP). These aspects could impact arterial stiffness because they are associated with increased stiffness of large conduit arteries and early wave reflections; importantly, an increased stiffness has been shown to be independent of MAP.¹⁴

In this context, pulse wave velocity (PWV) remains a widely used marker to evaluate arterial stiffness. PWV represents the pressure generated by the ventricular contraction along the aorta.^{13,15} Since pulse waves travel faster in stiffer arteries, arterial stiffness augments PWV, with normal values ranging between 3 and 5 m/s in young people but commonly increase with age.

Chronic kidney disease and creatinine levels are among the most critical determinants of PWV increase; in this scenario, a significant relationship has been observed between GFR reduction, proteinuria, and an increase in carotid-femoral PWV.¹⁶ Analyzing aortic PWV in 101 living kidney donors and their 101 corresponding recipients, Bahous and collaborators found that the major parameters associated with PWV were time since nephrectomy (donation date) in donors and renal rejection in recipients; additionally, plasma creatinine doubling secondary to chronic allograft nephropathy was significantly associated both to renal rejection and to donor PWV, independent of age.¹⁷

Several studies have demonstrated that an optimal control of blood pressure can prevent arterial stiffness.^{18–20} Furthermore, in 2005 Wang and coworkers demonstrated that a stepwise increase

in arterial stiffness reflects the stage of CKD²¹; in this study, a greater PWV was observed in patients with more advanced CKD from stages 1 to 5; SBP and the estimated GFR per 1.73 m² were the major clinical determinants of arterial stiffness in patients with CKD independent of conventional risk factors for cardiovascular diseases.²¹

6 | HOW TO QUANTIFY ARTERIAL STIFFNESS?

Arterial stiffness is commonly measured by PWV, which, as mentioned above, refers to the speed of a pressure wave's propagation across an arterial tree. With age, arterial walls become less distensible, leading to increased PWV. Carotid-femoral pulse wave velocity (cfPWV) is a well-validated measure of aortic stiffness that predicts the likelihood of future cardiovascular events. Indeed, cfPWV can predict future cardiovascular disease independently from conventional atherosclerotic risk factors (sex, age, smoking status, systolic blood pressure, dyslipidemia, and diabetes) in patients with ESKD.²² The cfPWV threshold of 10m/s, established by the 2013 European Society of Hypertension Guidelines,²³ is generally agreed upon as an indication of asymptomatic hypertension-mediated organ damage. cfPWV is measured by timing the movement of a pressure wave between the carotid and femoral arteries. Compared to peripheral measurements of PWV, cfPWV is more useful since central arteries appear most susceptible to age-related stiffening.²⁴ Additionally, brachial-ankle pulse wave velocity (baPWV) has been proposed as an alternate measure of arterial stiffness as a wider screening tool since it is easier and more convenient to conduct clinically. Other parameters to measure arterial stiffness include the augmentation index at heart rate 75 bpm (Alx@75)²⁵ and the ambulatory arterial stiffness index.²⁶

Changes in arterial stiffness may be hastened in hypertensive patients whose treatments fail to reduce their PWV. Moreover, failure to reduce PWV in hypertensive patients was a significant predictor of cardiovascular death in ESKD despite reasonable blood pressure control.²⁷

There is conflicting evidence that early atherosclerosis is linked to increased arterial stiffness. However, large arterial calcification present in advanced atherosclerosis is associated with increased PWV in CKD and ESKD.²⁸ This association may be more related to the plaque's contents (*i.e.*, degree of calcification) than its size.^{29,30} There are several direct hemodynamic consequences of increased PWV. For one, age-related widening of PP—the difference between systolic and diastolic blood pressure—is partly determined by arterial stiffening. Furthermore, arterial stiffening is linked to wave reflection arriving earlier at the aorta during systole due to increased PWV, likely affecting central PP. This aspect is significant since higher central PP results in increased left ventricular afterload, predisposition for ventricular hypertrophy, and decreased coronary blood flow.

CONFLICT OF INTEREST

None.

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