TRADITIONAL AND NONTRADITIONAL CARDIOVASCULAR RISK FACTORS IN CHRONIC KIDNEY DISEASE: AN INTRODUCTION

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Abstract
Chronic kidney disease is associated with a significantly elevated risk of cardiovascular morbidity and mortality. While traditional cardiovascular risk factors such as hypertension, diabetes, and dyslipidemia play a critical role, non-traditional risk factors unique to Chronic kidney disease further contribute to this heightened risk. This abstract explores both traditional and non-traditional cardiovascular risk factors in Chronic kidney disease. Traditional risk factors in Chronic kidney disease include hypertension, diabetes mellitus, dyslipidemia, and smoking. These factors accelerate the progression of atherosclerosis and increase the likelihood of cardiovascular events and are intricately linked to Chronic kidney disease pathophysiology, impacting significantly cardiovascular health. The interplay between traditional and non-traditional risk factors is complex. For instance, Chronic kidney disease -related mineral and bone disorders contribute to vascular calcification, which independently predicts adverse cardiovascular outcomes. Similarly, chronic inflammation, common in Chronic kidney disease, promotes atherosclerosis and endothelial dysfunction, further heightening cardiovascular risk. Understanding the collective impact of traditional and non-traditional risk factors is crucial for effective cardiovascular risk stratification and management in Chronic kidney disease patients. Cardiovascular risk assessment tools tailored specifically for Chronic kidney disease populations should encompass both traditional and non-traditional risk markers. Moreover, interventions targeting these multifaceted risk factors, such as optimal blood pressure control, glycemic management, lipid-lowering therapies, and novel Chronic kidney disease -specific treatments, are imperative to mitigate cardiovascular risk in this vulnerable population.

In conclusion, Chronic kidney disease is characterized by a distinct cardiovascular risk profile that extends beyond traditional risk factors. Non-traditional risk factors associated with Chronic kidney disease pathophysiology significantly contribute to cardiovascular morbidity and mortality. Future research should focus on elucidating the mechanisms underlying these non-traditional factors and developing targeted interventions to improve cardiovascular outcomes in Chronic kidney disease patients.

Keyword: Chronic kidney disease, Traditional risk factors, Nontraditional risk factors, Cardiovascular disease.

FAKTORËT TRADICIONALË DHE JO-TRADICIONALË TË RREZIKUT KARDIOVASKULAR NË SËMUNDJEN RENALE KRONIKE: NJË HYRJE

Abstrakt

Sëmundja Renale Kronike lidhet me një rrezik të rëndësishëm të sëmundshmërisë dhe vdekshmërisë kardiovaskulare. Ndërsa faktorët tradicionalë të rrezikut kardiovaskular si hipertensioni, diabeti dhe dislipidemia luajnë një rol kritik, faktorët e rrezikut jo-tradicionalë të veçantë për Sëmundjen Renale Kronike kontribuojnë më tej në këtë rrezik të rritur. Ky abstrakt eksploron të dy faktorët tradicionalë dhe jo-tradicionalë të rrezikut kardiovaskular në Sëmundjen Renale Kronike. Faktorët tradicionalë të rrezikut në Sëmundjen Renale Kronike përfshijnë hipertensionin, diabetin mellitus, dislipideminë dhe duhanpirjen. Këta faktorë përshpejtojnë progresionin e aterosklerozës dhe rrisin mundësinë e ngjarjeve kardiovaskulare. Megjithatë, Sëmundja Renale Kronike shoqërohet me faktorë rreziku shtesë jo-tradicionalë si: çrregullimet minerale dhe kockore, inflamacionin, stresin oksidativ, aneminë, toksinat uremike dhe kalcifikimin vaskular. Njohja këtyre faktorëve, është e rëndësishme për vlerësimin sa më të plotë të riskut kardiovaskular, stadifikimin dhe menaxhimin e pacientëve me Sëmundje Renale Kronike. Mjetet e vlerësimit të riskut kardiovaskular të përshtatura specifikisht për këtë grup popullate duhet të përfshijnë si shënuesit tradicionalë ashtu edhe ata jo-tradicionalë. Për më tepër, ndërhyrjet tek këta faktorë rreziku të shumëfishtë, si kontrolli optimal i shifrave të tensionit arterial, menaxhimi i glicemisë, terapitë për uljen e lipideve dhe trajtimet e reja specifike për Sëmundjen Renale Kronike, janë të domosdoshme për të zvogëluar riskun kardiovaskular në këtë grup vulnerabel popullsie.
Si përfundim, Sëmundja Renale Kronike karakterizohet nga një profil i vecantë rreziku kardiovaskular që shkon përtej faktorëve tradicionalë të riskut. Faktorët e rrezikut jo-tradicionalë të lidhur me fizpatologjinë e SRK kontribojnë në mënyrë të konsiderueshme në morbiditetin dhe mortalitetin kardiovaskular. Hulumtimet e ardhshme duhet të përqëndrohen në zbulimin e këtyre mekanizmave fizpatologjikë të këtyre faktorëve dhe në zhvillimin e ndërhyrjeve të duhura për të përmirësuar rezultatet kardiovaskulare tek pacientët me Sëmundje Renale Kronike.

Fjalë kyçe: Sëmundja Renale Kronike; Faktorët tradicionalë të rrezikut; Faktorët jo-tradicionalë të rrezikut; Sëmundja kardiovaskulare.

Introduction

Chronic kidney disease is increasingly recognized as a global public health problem(1) imposing huge medical and financial burdens on societies and health care systems with an estimated prevalence of 13.4% globally (2). Projections made by the global health burden of disease epidemiologists forecast that in 2040, Chronic kidney disease will be the 5th disease in rank responsible for death in the world.(3) In the 2012 KDIGO, defined Chronic kidney disease as abnormalities of kidney structure or function present for ≥3 months, with implications for health (4). In clinical practice, the main diagnostic criteria for Chronic kidney disease are the presence of an eGFR below 60 mL/min/1.73 m^2, and/or elevated albuminuria, i.e. UACR over 30 mg/g. Cardiovascular (CV) death in patients with CKD prevents these patients from reaching kidney failure (stage G5, i.e., the stage where dialysis and renal transplantation are needed) (5).

Cardiovascular disease (CVD) is the primary cause of morbidity and mortality in chronic kidney disease (CKD). CVD mortality risk doubles and triples in CKD stages 3 and 4, respectively (6). This relationship is complex and bidirectional, with each condition increasing the incidence and progression of the other (8,9) Indeed, the heart and kidney are inextricably linked, as exemplified by the cardiorenal syndrome, whereby dysfunction of one organ induces and advances dysfunction in the other (9,10).
In general, in addition to traditional risk factors, two major mechanisms are thought to contribute to the development of CVD in CKD. As renal function deteriorates, non-traditional risk factors play an increasing role in both glomerular filtration rate (GFR) loss and cardiovascular damage. On the one hand, the kidney can release hormones (11-13), enzymes, and cytokines (14,15) in response to kidney injury or kidney insufficiency, which leads to characteristic changes in the vasculature. On the other hand, CKD-associated mediators as well as hemodynamic alterations contribute to cardiac damage,(16) as discussed in the following sections. Understanding cardiovascular risk factors in chronic kidney disease is essential because these patients often face therapeutic nihilism, where appropriate modification and intervention of risk factors is lacking despite awareness of their high cardiovascular risk, therefore, educational efforts are needed to bridge this therapeutic gap. Identifying these risk factors is crucial for the prevention and treatment of chronic heart disease in CKD patients.

In this review, we will focus on whether or not early CKD is an important risk factor for the presence, severity, and progression of CVD. Specifically, we will examine both traditional and novel risk factors for both CKD and CVD and how they relate to each other (figure 1,2).

Figure 1: Changing Cardiovascular Disease Risk in Progressing Chronic Kidney Disease

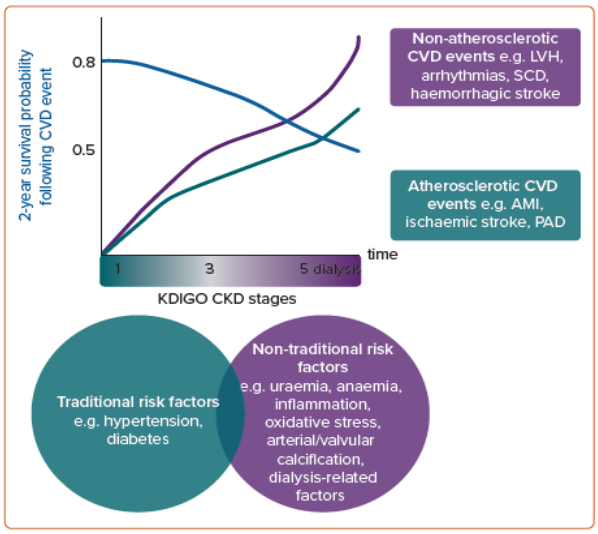

Figure 1: Warrens H, Banerjee D, Herzog Ch, Cardiovascular complications of chronic kidney disease: an indroduction;https://doi.or/10.15420/ecr.2021.54

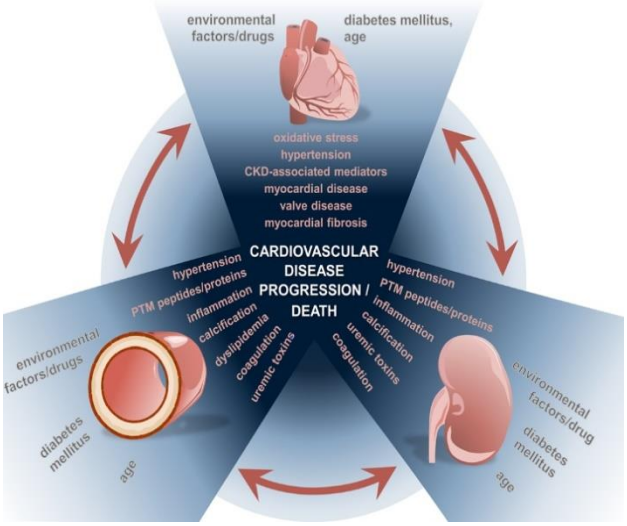

Figure 2: Jankowski J, Floege J, Fliser D, Bohm M, Marx J, Cardiovascular Disease in Chronic Kidney Disease, Pathophysiological Insights and Therapeutic Options https://doi.org/10.1161/CIRCULATIONAHA.120.050686Circulation. 2021;143:1157–117

Traditional cardiovascular risk factors

Traditional cardiovascular risk factors are highly prevalent in patients with CKD, and their contribution to atherosclerotic vascular disease is particularly important in earlier CKD stages (17). The number of cardiovascular risk factors appears to correlate with the severity of kidney dysfunction. Among others, hypertension, insulin resistance/diabetes, dyslipidemia, and smoking contribute not only to atherosclerotic cardiovascular and cerebrovascular sequelae but also to CKD progression because of their effect on large (e.g., kidney artery stenosis) and smaller (e.g., nephrosclerosis) kidney vessels (18). High blood pressure, glucose, and lipid levels, as well as tobacco use, can aggressively be modified.

Hypertension: Hypertension is both a cause and a consequence of CKD. In CKD, impaired kidney function leads to sodium and water retention, volume expansion, and activation of the renin-angiotensin-aldosterone system (RAAS), all of which contribute to hypertension. Conversely, hypertension accelerates the progression of CKD by increasing intraglomerular pressure and promoting renal injury. Additionally, uncontrolled hypertension is a major risk factor for CVD, including coronary artery disease, heart failure, and stroke (4,14,17).

Dyslipidemia: Dyslipidemia is common in CKD and is characterized by elevated levels of triglycerides, reduced levels of high-density lipoprotein (HDL) cholesterol, and often normal to mildly elevated levels of low-density lipoprotein (LDL) cholesterol. Dyslipidemia in CKD is multifactorial and is influenced by factors such as inflammation, oxidative stress, insulin resistance, and altered lipid metabolism. Dyslipidemia contributes to the development and progression of atherosclerosis, increasing the risk of coronary artery disease and other cardiovascular events (4,6).

Diabetes Mellitus: Diabetes mellitus is a leading cause of CKD and is associated with a significantly increased risk of CVD. In individuals with both diabetes and CKD, the combination

of renal impairment and metabolic abnormalities further amplifies cardiovascular risk. Diabetes accelerates the progression of CKD through various mechanisms, including hyperglycemia-induced renal injury, activation of inflammatory pathways, and oxidative stress. Moreover, individuals with diabetes are prone to developing microvascular and macrovascular complications, including diabetic nephropathy and coronary artery disease (4,14,18).

Smoking: Smoking is a well-established cardiovascular risk factor and is particularly detrimental to individuals with CKD. Smoking not only increases the risk of atherosclerosis and cardiovascular events but also accelerates the decline in kidney function. Smoking cessation is therefore essential for reducing cardiovascular risk and slowing the progression of CKD (6).

Obesity: Obesity is prevalent in individuals with CKD and is associated with insulin resistance, dyslipidemia, hypertension, and chronic inflammation, all of which contribute to cardiovascular risk. Obesity-related metabolic abnormalities and systemic inflammation promote endothelial dysfunction, atherosclerosis, and left ventricular hypertrophy, further increasing the risk of CVD in CKD (4,14,18).
Management of traditional cardiovascular risk factors is essential in individuals with CKD to reduce the burden of CVD and improve outcomes. This includes lifestyle modifications (such as dietary changes, regular exercise, smoking cessation, and weight management) as well as pharmacological interventions (such as antihypertensive agents, lipid-lowering medications, and glucose-lowering therapies in individuals with diabetes). Additionally, close monitoring and early intervention for cardiovascular risk factors are crucial components of CKD care to optimize cardiovascular health and reduce the risk of adverse cardiovascular events (17,18).

Non-traditional cardiovascular risk factors

This article has focused attention on nontraditional cardiac risk factors that are particularly relevant to patients with CKD, including decreased hemoglobin levels, microalbuminuria, increased inflammation and oxidative stress, and abnormalities in bone and mineral metabolism. Moreover, the mechanisms by which these nontraditional risk factors contribute to cardiovascular disease are numerous. However, toxic metabolites produced by uremia in chronic kidney disease as well as conditions that alter the metabolism of chemical elements, such as calcium and phosphorus, account for the excess CVD in patients with CKD, and are known as non-traditional or new risk factors (19). These non-traditional risk factors play a significant role in the development and progression of CVD in CKD patients. We mention some of them:

Renal failure per se: Newly acquired evidence points to a strong, independent relationship between low eGFR and mortality risk, CV events and hospitalization (20). The mechanisms behind the process of progressive renal function deterioration's acceleration of the atherogenic process are not well known. However, the presence and severity of multiple novel CKD risk factors, including inflammation, oxidative stress, vascular calcification and accumulation of advanced glycation end products (AGEs) increases. Many other accumulating solutes for uremic retention, for example, ADMA, guanidine, homocysteine, indoxyl sulfate and p-cresol, could have a proatherogenic effect (21).

Inflammation: Inflammation is a key process observed in patients with CKD, and CKD is considered a systemic inflammatory disease with many causes (21, 22) and has been shown to predict the long-term risk of developing CKD (22).
Chronic inflammation is characterized by the persistent effect of a causative stimulus, destroying cells and tissue and having a deteriorating effect on the body. In later stages of CKD, the systemic concentrations of both pro- and anti-inflammatory cytokines are significantly higher as production has increased, coupled with decreased renal clearance (21). Inflammation, the effects of local inflammatory stimuli such as oxidation products, end advanced glycosylation products and chronic infective processes modify blood vessels in the sense of atherosclerosis development. These changes benefit proatherogenic adhesion molecule production, for example, intercellular adhesion molecule1 (ICAM-1) and vascular cell adhesion molecule 1 (VCAM-1), growth factor, as well as chemokine (such as IL-6, long pentraxin 3 (PTX3), S-albumin, TNF and white blood cell count). Such inflammatory intermediates encourage the synthesis of acute phase proteins such as C-reactive protein (CRP) (23), which leads to endothelial dysfunction, which is usually defined as reduced vasodilatation capability, which again creates early atherosclerosis occurrence predisposition. Aside from that, the proinflammatory IL-6 mark is increased in ESRD patients but is also an independent mortality predictor in patients on dialysis (24).

Endothelial dysfunction: There is evidence that suggests that the endogenic inhibitor of NO, ADMA, has a significant role in the origin and occurrence of CVD and mortality in dialysis patients. NO deficit and ADMA accumulation promote endothelial dysfunction, vasoconstriction, and arterial thrombosis (20, 22).

Malnutrition and protein-energy wasting (PEW): A marked connection between malnutrition, increased levels of CRP and atherosclerosis is well known, although the precise mechanisms of their synergistic effects on the organism are not known (25).
Oxidative stress: CKD patients experience increased oxidative stress due to reduced antioxidant defenses and accumulation of uremic toxins. Oxidative stress contributes to endothelial dysfunction, vascular inflammation, and accelerated atherosclerosis. CKD patients have a deficiency in the antioxidant defensive mechanism (because of e.g., reduced vitamin levels, or hypoalbuminemia) and increased pro-oxidant compound activity. One of the most important toxins connected to the uremic environment and connected to oxidative stress and inflammation stage and the presence of inflammation biomarkers is β2-microglobulin (16,24).
Hyperparathyroidism: PTH is considered a potent uremic toxin that has a detrimental effect on myocardial cells. The role of parathormone as a risk factor in the development of uremic cardiomyopathy is known. Important research results show in conclusion that a small level of vitamin D is associated with CVD in the general population and that a greater concentration of this vitamin may have a positive impact on survival (24).
Cardiovascular calcification: The calcification process frequently starts before the initiation of dialysis treatment. The arterial media, atherosclerotic plaques and heart valves are affected through this cardiovascular process. One of the main signs of medial calcification is arterial stiffness, which is shown clinically through an increased pulse pressure. It is now evident that the burden caused by atherosclerotic calcification is a suitable risk marker for cardiovascular events. In patients in dialysis, valvular calcification leads to a developing stenosis and morbidity that

goes with it, after targeting and affecting the aortic and mitral valves (26). CV calcification can be caused by abnormal calcium and phosphate metabolism and an enduring inflammation as it may by several mechanisms mediate untimely atherosclerosis and premature CVD.

Hyperhomocysteinemia: Homocysteine is a nonprotein sulfur-containing amino acid and may by several mechanisms mediate premature atherosclerosis and CVD. The prevalence of hyperhomocysteinemia in patients with advanced CKD is >90% (27).

Anemia: CKD often develops anemia due to decreased production of erythropoietin by the kidneys. Anemia leads to tissue hypoxia, cardiac remodeling, and an increased cardiac workload. Chronic anemia contributes to left ventricular hypertrophy, diastolic dysfunction, and myocardial ischemia, exacerbating cardiovascular risk (12, 13).

These non-traditional factors interact with conventional cardiovascular risk factors (e.g., hypertension, dyslipidemia) to amplify cardiovascular risk in CKD patients. Addressing these factors requires a comprehensive approach, including optimized CKD management, dietary interventions, control of inflammation and oxidative stress, and targeted therapies to mitigate vascular calcification and uremic toxin accumulation. By understanding and targeting both traditional and non-traditional risk factors, clinicians can improve cardiovascular outcomes and quality of life in CKD patients. Patients with CKD should be considered in the highest-risk group for development of cardiovascular disease (CVD), and aggressive treatment of traditional and nontraditional risk factors should be instituted.

Novel therapeutic approaches

Preventing cardiovascular risk in chronic kidney disease (CKD) requires a comprehensive approach that targets both traditional cardiovascular risk factors and CKD-specific factors. Several novel therapies and emerging strategies are being investigated to reduce cardiovascular risk and improve outcomes in CKD patients. Here are some promising therapies and interventions:

SGLT2 Inhibitors: Sodium-glucose cotransporter-2 (SGLT2) inhibitors, originally developed for the treatment of diabetes, have shown remarkable cardiovascular and renal protective effects in CKD patients with or without diabetes. These medications reduce cardiovascular events, slow the progression of CKD, reduce albuminuria progression, the preservation of eGFR, even in advanced CKD stages, and lower blood pressure through mechanisms independent of glucose lowering. Potential mechanisms explaining the beneficial effects of SGLT2 inhibitors in patients with HF or CKD include hemodynamic as well as metabolic effects (28). In addition, SGLT2 inhibitors may selectively reduce interstitial fluid, and this may limit the reflex neurohumoral stimulation that occurs in response to intravascular volume contraction with traditional diuretics (29).

MRAs: Nonsteroidal mineralocorticoid receptor antagonist reduce the aldosterone-mediated proinflammatory effects that are involved in the fibrotic remodeling processes. The new selective nonsteroidal MRA finerenone also blocks the damaging effects of the overactivated aldosterone system. Finerenone is equally distributed in myocardial and kidney tissue (30).

Novel Lipid-lowering Therapies: Beyond statins, newer lipid-lowering agents such as proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitors are being explored for their efficacy in reducing cardiovascular events in CKD patients with dyslipidemia (31).

Mineral and Bone Disorder (MBD) Management: Novel phosphate binders and calcimimetics are being developed to better manage mineral and bone disorders in CKD. These therapies aim to control serum phosphate levels, reduce secondary hyperparathyroidism, and mitigate vascular calcification, which is a major contributor to cardiovascular risk in CKD (26, 27).

Anti-inflammatory Therapies: Targeting inflammation is emerging as a promising approach to reduce cardiovascular risk in CKD. Novel anti-inflammatory agents, such as monoclonal antibodies against interleukin-1 beta (IL-1β) or interleukin-6 (IL-6), are being studied for their potential to lower systemic inflammation and improve cardiovascular outcomes. Omega-3 supplementation has shown anti-inflammatory effects and cardiovascular benefits in CKD populations (24, 25).

Novel Antihypertensive Agents: Agents targeting the renin-angiotensin-aldosterone system (RAAS), or novel mechanisms Endothelin receptor antagonists (ERAs) have been investigated for their potential role in chronic kidney disease (CKD), there is growing interest in their renal effects due to the involvement of endothelin in renal hemodynamics, fibrosis, and inflammation. Endothelin receptor antagonists, by blocking the action of endothelin, may promote renal vasodilation and improve renal blood flow, exert antifibrotic effects by inhibiting endothelin-induced fibroblast proliferation, extracellular matrix deposition, and myofibroblast activation, mitigate inflammation by blocking endothelin-mediated immune cell activation and cytokine release within the kidney, reduce proteinuria. ERAs may help preserve kidney function and delay CKD progression, may provide additional cardiovascular benefits beyond blood pressure control (29, 30, 31).

Precision Medicine: Personalized treatment approaches based on genetic and molecular profiling may help identify individuals at higher cardiovascular risk and tailor therapies accordingly. Biomarker-guided strategies can optimize cardiovascular risk management in CKD.

While these novel therapies hold promise for reducing cardiovascular risk in CKD, further research is needed to evaluate their efficacy, safety, and long-term benefits specifically in CKD populations. Comprehensive management strategies that address both traditional and CKD-specific cardiovascular risk factors remain essential for improving outcomes and quality of life in CKD patients at high risk for cardiovascular events.

Conclusion

CVD is very common in CKD, and vice versa. The presence of each condition promotes the incidence and progression of the other. Despite the high prevalence, morbidity, and mortality of these comorbid conditions, there are significant limitations to our current knowledge and management of this vulnerable group. As CKD progresses and the incidence of CVD rises, we have less knowledge and fewer management options. The complexity of these comorbid conditions necessitates a multidisciplinary approach to improve patient-centered care. It's important to note that while these novel therapies hold promise, further research and clinical trials are needed to establish their efficacy, safety, and long-term benefits specifically in CKD populations. Comprehensive management of cardiovascular risk in CKD requires a personalized approach that addresses individual patient factors and optimizes multifactorial interventions to improve outcomes and quality of life, requiring a multidisciplinary care model that includes nephrologists, cardiologists, internists, endocrinologists, dieticians, and other specialists.

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