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State of Central Hemodynamics in Patients with Coronary Heart Disease and Diabetic Nephropathy

Karimov S. B., Jabbarov O. O., Alyavi A. L., Umarova Z. F., Tursunova L. D., Xodjanova Sh. I.
Tashkent Medical Academy

Abstract: This article highlights the role of diabetic nephropathy in the origin and course of ischemic heart disease.

Keywords: coronary heart disease, central hemodynamics, EchoKG, diabetic nephropathy, GFR.

Coronary heart disease is a disease that has taken the form of a pandemic, causes disability of a large number of people, and is considered as a medical and economic problem.

In most developed countries, coronary artery disease (CAD), mostly caused by atherosclerosis of coronary arteries, is one of the primary causes of death. From 1990s to 2000s, mortality caused by acute MI declined up to 50%. The incidence of CAD is related with age, gender, economic, etc. Atherosclerosis contains some highly correlative processes such as lipid disturbances, thrombosis, inflammation, vascular smooth cell activation, remodeling, platelet activation, endothelial dysfunction, oxidative stress, altered matrix metabolism, and genetic factors. Risk factors of CAD exist among many individuals of the general population, which includes hypertension, lipids and lipoproteins metabolism disturbances, diabetes mellitus, chronic kidney disease, age, genders, lifestyle, cigarette smoking, diet, obesity, and family history [1-4].

Type 2 diabetes (T2D) affects over 382 million adults globally and is one of the most common causes of chronic kidney disease (CKD) and cardiovascular (CV) disease.

Patients with chronic kidney disease (CKD) exhibit an elevated cardiovascular risk manifesting as coronary artery disease, heart failure, arrhythmias, and sudden cardiac death. Although the incidence and prevalence of cardiovascular events is already significantly higher in patients with early CKD stages (CKD stages 1–3) compared with the general population, patients with advanced CKD stages (CKD stages 4–5) exhibit a markedly elevated risk. Cardiovascular rather than end-stage kidney disease (CKD stage 5) is the leading cause of death in this high-risk population. CKD causes a systemic, chronic proinflammatory state contributing to vascular and myocardial remodelling processes resulting in atherosclerotic lesions, vascular calcification, and vascular senescence as well as myocardial fibrosis and calcification of cardiac valves. In this respect, CKD mimics an accelerated aging of the cardiovascular system [5-7].

Richard Bright, a British physician, was the first to report the association of chronic kidney disease (CKD) with cardiovascular disease (CVD). Patients with CKD exhibit a pronounced risk for cardiovascular events: 50% of all patients with CKD stage 4 to 5 have CVD, and cardiovascular mortality accounts for ≈40% to 50% of all deaths in patients with advanced CKD (stage 4) as well as end-stage kidney disease (stage 5), compared with 26% in controls with normal kidney function. In addition to the high risk for fatal atherosclerosis-related complications such as myocardial infarction and stroke, cardiovascular death also results from heart failure (HF) and fatal arrhythmias, particularly in advanced CKD stages. In >70 studies in nondialyzed subjects with CKD, correction for classical and even less classical cardiovascular risk factors, such as hypertension, diabetes, and dyslipidemia, did not neutralize the impact of CKD on cardiovascular risk. This review summarizes the current knowledge of CVD in patients with CKD, clinical consequences, and treatment options of CVD in CKD. Given space limitations, we will not cover special situations such as extrarenal involvement in vasculitides or the association of autosomal dominant polycystic kidney disease with vascular

abnormalities such as intracranial, aortic, or coronary artery aneurysms as well as aortic dissection [8-10].

Molecular mechanisms involved in cardio-renal-metabolic disease include hyperglycaemia, insulin resistance, hyperactivity of the renin-angiotensin-aldosterone system, production of advanced glycation end-products, oxidative stress, lipotoxicity, endoplasmic reticulum stress, calcium-handling abnormalities, mitochondrial malfunction and deficient energy production, and chronic inflammation [11-14]. Pathophysiological manifestations of these processes include diabetic cardiomyopathy, vascular endothelial dysfunction, cardiac and renal fibrosis, glomerular hyperfiltration, renal hypoperfusion and venous congestion, reduced exercise tolerance leading to metabolic dysfunction, and calcification of atherosclerotic plaque. Importantly, recognition of the interaction between cardio-renal-metabolic diseases would enable a more holistic approach to cardio-renal-metabolic care, rather than isolated treatment of individual conditions, which may improve patient outcomes.

Pathophysiology of CVD in CKD. In general, in addition to traditional risk factors, 2 major mechanisms are thought to contribute to the development of CVD in CKD. On the one hand, the kidney can release hormones, enzymes, and cytokines 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, as discussed in the following sections [15-16].

Traditional Risk Factors of Vascular Disease in CKD. 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. 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 (eg, kidney artery stenosis) and smaller (eg, nephrosclerosis) kidney vessels. In addition, some of these effects also seem to contribute to the recently described association of CKD with abdominal aortic aneurysms [16-18].

Traditional and Nontraditional Risk Factors for CVD in CKD

Risk factors for CVD in CKD	Specific aspects/treatment options compared with the non-CKD population
Hypertension	Optimal target blood pressure has not yet been established
Dyslipidemia	Characteristic lipid pattern of hypertriglyceridemia and HDL cholesterol levels
Smoking	—
Hyperglycemia	Intensive glucose control beneficial to avoid microvascular complications
Vascular calcifications	Treatment of electrolyte imbalances with magnesium
	Vitamin K administration might be beneficial
Inflammation	Inhibition of proinflammatory effector molecule interleukin-1ß (IL-1ß) with canakinumab after myocardial infarction
Increased proteinuria	RAS blockade

CKD indicates chronic kidney disease; CVD, cardiovascular disease; HDL, high-density lipoprotein; and RAS, renin-angiotensin system.

Hypertension. The elevated cardiovascular risk in CKD cannot solely be explained by the presence of traditional risk factors as shown by data from the ARIC (Atherosclerosis Risk In Communities) and CHS (Cardiovascular Health Study) trials.[52] In addition, the specific aspects of CKD have not fully been addressed in studies targeting the modification of these risk factors. However, treatment of hypertension is beneficial in CKD, as recently corroborated by results of the SPRINT trial (Systolic Blood Pressure Intervention Trial), but the optimal target blood pressure in patients with CKD has not yet been established.

Diabetes. Hyperglycemia is strongly associated with the development of both CKD and CVD. However, improvement in glycemic control in type 2 diabetes mainly contributes to a reduction in microvascular events such as nephropathy, although various studies failed to show a significant effect on macrovascular events; for example, the ADVANCE trial (Action in Diabetes and Vascular Disease: Preterax and Diamicron Modified Release Controlled Evaluation") demonstrated in ≈11 000 patients with type 2 diabetes that intensive glucose control compared with standard therapy leads to a reduction in the combined outcome of major macrovascular and microvascular events, but this effect was mainly driven by a reduction in nephropathy with no significant effect on macrovascular events; the ACCORD trial (Action to Control Cardiovascular Risk in Diabetes) was not able to demonstrate that treatment targeting nearly normal glycemic control reduces the risk of cardiovascular events in ≈10 000 patients with type 2 diabetes, and intensive versus standard glucose control in patients with poorly controlled type 2 diabetes had no significant effect on the rates of major cardiovascular events, death, or microvascular complications in VADT (Veterans Affairs Diabetes Trial), including 1791 patients [18-20].

Moreover, data for lifestyle modifications are mostly observational and extrapolated from non-CKD trials. This fact has been clearly exposed by a recent meta-analysis reporting that randomized trials conducted between 2006 to 2014 were less likely to exclude patients with CKD than those between 1985 to 2005 (46% versus 56%). However, this apparently encouraging trend is not sufficient to close the gap of evidence in patients with CKD.

Dyslipidemia. In addition, patients with CKD exhibit a characteristic lipid pattern of hypertriglyceridemia and low high-density lipoprotein (HDL) cholesterol levels, but mostly normal low-density lipoprotein cholesterol levels. Recent clinical evidence suggests that vascular effects of HDL can be heterogeneous in different conditions, and that progressive kidney dysfunction dramatically changes the composition and quality of blood lipids, particularly HDL and triglyceride-rich lipoproteins, in favor of a more atherogenic profile. Adverse endothelial effects of HDL are also detectable in children with CKD, in whom cardiovascular risk factors such as smoking, hypertension, diabetes, and dyslipidemia were not yet present. Several factors modify the composition of the HDL particle in CKD, including uremic toxins, increased oxidative stress, and the proinflammatory microenvironment. These factors contribute to a pronounced remodeling of HDL particles, altering the proteome and lipidome composition of HDL and inducing posttranslational modifications of HDL's protein cargo. Furthermore, the accumulation of uremic toxins such as symmetrical dimethylarginine in advancing CKD plays a key role in the functional changes of HDL.

Last, increased albuminuria or proteinuria is a potent risk factor for CVD in both diabetic and nondiabetic patients with CKD, and the incidence of cardiovascular events decreases with the institution of antiproteinuric measures, in particular renin-angiotensin system (RAS) blockade. However, the pathomechanistic link between albuminuria and CVD may not be a direct one, as systemic but particularly intrarenal hemodynamic effects of RAS blockers affect progression of CKD and thus indirectly of CVD. Therefore, the data in support of RAS blockers in albuminuric patients are reasonably strong for preventing progression of CKD and less so for CVD protection.

Nontraditional Risk Factors of Vascular Disease in CKD

Vascular Calcification. Vascular smooth muscle cells are the cellular components of the medial layer of the vessels, which can switch from a contractile phenotype to a more synthetic phenotype caused by hemodynamic changes observed in CKD. Resulting cardiovascular calcifications are markedly accelerated in patients with CKD, and even children with advanced CKD frequently exhibit vascular calcifications. The histological prevalence of vascular calcifications in radial arteries was 45-fold greater in patients with CKD compared with those without CKD. In addition to CKD, several common comorbidities, in particular diabetes, further enhance the progression of calcification.

Calcification of central arterial vessels contributes to increased pulse wave velocity, earlier reflection of the pulse wave, increased cardiac afterload, and thus HF. Resulting hemodynamic alterations induce left ventricular hypertrophy associated with a decrease in coronary perfusion. A particularly severe

form of vascular calcification is uremic calcific arteriolopathy (calciphylaxis), which is caused by calcium deposition in the media of the dermo-hypodermic arterioles leading to skin necrosis and carries a high mortality rate. The exact mechanism of uremic calcific arteriolopathy is unclear: previously, an increase in the calcium-phosphorus product was thought to cause calcification leading to uremic calcific arteriolopathy, but it becomes increasingly clear that calcification involves active cellular processes, not just passive mineralization, because of an increase in calcium-phosphorus concentrations. However, hemodynamic consequences of medial calcification seem to have an exacerbated risk for left ventricular hypertrophy.

Calcification of cardiac valves, in particular the aortic valve, is a frequent cause of valvular stenosis requiring intervention. The extent and progression rate of vascular calcifications in CKD herald a poor prognosis. However, the first data raise the hypothesis that repleting patients with vitamin K can retard the progression of valvular calcification; still, negative trials have also been published on this topic.

In addition, electrolyte imbalances like dysmagnesemia are common in patients with CKD and contribute to poor patient outcome, and therefore, electrolyte imbalances are potential targets for managing coronary artery calcification. In particular, magnesium, frequently reduced in serum in CKD, has recently gained interest because of the inhibitory effect on vascular calcification: magnesium interferes with hydroxyapatite crystal formation and can halt vascular calcification progress in advanced CKD.

Inflammation. Inflammation is a key process observed in patients with CKD, and CKD is considered a systemic inflammatory disease with many causes and has been shown to predict the long-term risk of developing CKD. Proinflammatory circulatory mediators progressively increase as kidney function declines. Proinflammatory processes in CKD patients comprise, among others, a variety of infections including periodontal disease, oxidative stress caused by accumulation of advanced glycation end products, metabolic acidosis, reduced cytokine clearance, insulin resistance, posttranslational modifications of blood-borne molecules such as lipoproteins, and epigenetic factors.

In accordance, the CANTOS trial (Canakinumab Anti-Inflammatory Thrombosis Outcome Study) focusing on ≈10 000 stable postmyocardial infarction patients with high-sensitivity C-reactive protein demonstrated a benefit of inhibition of proinflammatory effector molecule interleukin-1β (IL-1β) with the antibody canakinumab, which was larger in patients with eGFR <60 mL/min/1.73 m^2 than in those with eGFR >60 mL/min/1.73 m^2.However, further studies are needed to firmly establish the pathophysiological mechanisms and potential treatment options for inflammation in patients with CKD.

Myocardial Alterations in CKD. Patients with CKD exhibit characteristic changes in the myocardium with pathological myocardial fibrosis with collagen deposition between capillaries and cardiomyocytes and cardiac hypertrophy the hallmarks of uremic cardiomyopathy.Left ventricular hypertrophy (LVH) is present in about one-third of all patients with CKD, increasing up to 70% to 80% in patients with end-stage kidney disease. The presence of LVH is an independent predictor of survival in patients with CKD, even in those with early-stage CKD. Three main mechanisms are considered to contribute to LVH in CKD: (1) afterload- and (2) preload-related factors as well as (3) nonafterload, nonpreload-related factors. Afterload-related factors include abnormal arterial stiffness, increased systemic arterial resistance, and systolic hypertension, leading to an initial concentric LVH. Continuous left ventricular overload subsequently leads to maladaptive changes and cardiomyocyte death, which in turn result in an eccentric hypertrophy and subsequent left ventricular dilatation, systolic dysfunction, and reduced ejection fraction (EF). Preload-related factors in the pathophysiology of LVH comprise the expansion of intravascular volume in CKD leading to volume overload, length extension of myocardial cells, and eccentric or asymmetrical left ventricular remodeling. Nonafterload, nonpreload-related factors include intracellular mediators and pathways contributing to progressive LVH. Essential mechanisms in this context are activation of peroxisome proliferator-activated receptors, stimulation of small G-proteins or the mechanistic target of rapamycin pathway, as well as metabolic changes such as decreased fatty acid oxidation. The second hallmark of

uremic cardiomyopathy besides LVH is the development of myocardial fibrosis occurring independently of LVH itself. Cardiac fibrosis in patients with CKD is characterized by diffuse collagen deposition between capillaries and cardiomyocytes funneling into the maladaptive ventricular hypertrophy with subsequent dilatation of the heart.

Furthermore, there is an epidemiological collinearity of the prevalence and incidence of CKD with aortic and mitral valve disease. Valve disease has a strong impact on the outcome in patients with CKD. Early CKD stages 1 to 3 are associated with enhanced calcifications of valves and coronary arteries. Heart valve calcification occurs in stage 5 CKD in up to 88% to 99% of patients, increasing from 40% of patients in CKD stage 3, and the final destruction of valves occurs at a 10-fold higher rate in patients with CKD compared with patients without CKD. Valvular disease in patients with CKD is accelerated by comorbidities like diabetes, arterial hypertension, hyperlipidemia, anemia and ongoing infections of valves, and malnutrition, as well as hypercalcemia, hyperphosphatemia, and hyperparathyroidism.

Conclusions. Patients with CKD have high cardiovascular risk, with cardiovascular death being the leading cause of death. Several novel therapies to decrease the risk of cardiovascular diseases in CKD are in clinical development or have been already established, raising the hope that cardiovascular risk in patients with CKD may be modifiable in the future. Still, the lack of data from large cardiovascular outcome trials in the high-risk group of patients with CKD should be a call for action to ensure that novel therapeutic options are assessed in dedicated trials in the CKD population, in particular in those with advanced CKD, thus paving the way toward a more evidence-based approach to reduce cardiovascular risk in CKD.

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