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REVIEW

Mechanisms of cardiovascular complications in chronic kidney disease: research focus of the Transregional Research Consortium SFB TRR219 of the University Hospital Aachen (RWTH) and the Saarland University

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Abstract
Patients with chronic kidney disease (CKD) exhibit a massively increased risk for cardiovascular (CV) events, and traditional strategies to improve CV outcome have largely failed in the context of CKD. This review article summarizes the current understanding of the pathophysiology of CVD in patients with CKD, defines the gaps in knowledge and describes the structure of the German Transregional Research Consortium SFB TRR219 which addresses "Mechanisms of Cardiovascular Complications in Chronic Kidney Disease".

Keywords Cardiovascular disease · CKD · Heart · Vessel · Blood

Introduction

Patients with chronic kidney disease (CKD) exhibit a massively increased risk for cardiovascular (CV) events. About 50% of patients with CKD stage 4–5 suffer from cardiovascular disease (CVD) [1], and CV mortality accounts for ~40–50% of all deaths in patients with CKD stage 4 (eGFR of 16–29 ml/min) as well as in patients with end-stage renal disease (ESRD = CKD stage 5; need for dialysis or transplant, eGFR of 15 ml/min or less), compared with 26% in controls with normal kidney function [2, 3]. In addition to the high risk for fatal atherosclerosis-related complications such as ischemic heart disease and stroke, cardiac deaths also result from heart failure and arrhythmias [2, 4]. In more than 70 studies in non-dialysed subjects with CKD, correction for classical and even less classical CV risk factors, such as hypertension, diabetes mellitus and dyslipidemia, did not neutralize the impact of CKD on CV risk [5]. The underlying pathophysiological processes of CVD in CKD patients obviously differ from the CVD processes in the general population. This underlines the importance of non-traditional, CKD-specific CV risk factors [6] and that CKD itself is an independent risk factor for CV events [7]. This may explain at least in part why traditional strategies to improve CV outcome have largely failed in the context of CKD [6]. In addition, this emphasizes the need to identify pathological mechanisms adversely affecting the CV system in CKD, with the aim to reduce the increased CV mortality in CKD patients through novel therapeutic strategies.

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Cardiovascular disease in chronic kidney disease

Chronic kidney disease (CKD)

Via impaired regulation of the acid–base balance, the water and electrolyte balance, blood pressure and the bone

metabolism, CKD affects essentially all organs. CKD has developed into a serious health problem. In 2005, the incidence rate of CKD in Europe was 135 per million, the rate in the USA 336 per million [8]. In 2012, the overall prevalence of CKD exceeded 13% in the USA, which is a relative increase with ~12% compared to 1994 [4]. This worldwide rise in the prevalence of CKD is reflected in an increase of patients reaching CKD stage 5 (ESRD), necessitating renal replacement therapy. The prevalence of ESRD exceeded 635.000 people in the USA in 2012, which is more than a doubling compared to 1994 [4], and a similar development is seen in Europe. Key reasons are (1) the rapidly aging population with data from the National Health and Nutrition Examination Survey in the USA showing an increase in CKD prevalence to ~33% in elderly people, and (2) the rapidly increasing global prevalence of type 2 diabetes mellitus, an important risk factor for CKD [9]. In addition to age and diabetes, hypertension and higher body mass index are also associated with CKD. In these high-risk subpopulations, the prevalence of CKD is more than 50% [10].

Cardiovascular complications in CKD patients

CV death is responsible for ~40–50% of all deaths in patients with CKD stage 4–5 [2, 11, 12]. In addition to reduced glomerular filtration rate (GFR), proteinuria, even if mild, is a second key risk factor for CVD [13]. Vice versa, in patients with established CVD, the presence of CKD markedly worsens outcomes [14, 15], resulting in a vicious circle of increased CV injury and renal disease. CKD-related CV death is mostly caused by ischemic heart disease (myocardial infarction, angina pectoris and sudden cardiac death), accounting for ~55% of CV deaths in patients with CKD stage 2–4 [2] and up to 75% in patients with CKD stage 5 (ESRD) [4]. In patients with ESRD, there is an annual incidence of myocardial infarction of 10%; sudden cardiac death becomes dominant as CKD progresses and is responsible for 60% of all heart-associated deaths in dialysis patients [4, 16]. Other CV-related deaths in CKD patients are caused by cerebrovascular disease (14% in CDK stage 4), heart failure (including heart failure due to left ventricular hypertrophy; 14% in CKD stage 4) [17–19, Miro, 2018 #49] and arrhythmia (7% in CKD stage 4) [2].

The impact of typical CV risk factors such as gender, smoking or overweight is markedly reduced in CKD (stage 5) patients compared to the general population [20–22]. In more than 70 studies in non-dialysed subjects with CKD, correction for various CV risk factors did not neutralize the impact of CKD on CV risk [5]. Both, clinical as well as experimental data suggest that the underlying processes of CVD in patients suffering from CKD obviously differ from the process of non-CKD patients (reviewed in [23]). Thus, besides the traditional risk factors for CVD, integrated into the traditional Framingham risk score, non-traditional or novel CV risk factors exist in CKD patients [6, 24], and CKD was recently suggested as an independent risk factor for CV events [7], independent of geographic or ethnic factors [11].

The pathological mechanisms leading to CVD in CKD include hyperactivity of the renin–angiotensin–aldosterone system, sodium retention, volume overload, endothelial dysfunction, dyslipidemia, coagulopathy, inflammation, anemia, hyperparathyroidism, hypoalbuminemia, mineral–bone disorders, the uremic state and oxidative stress [25], each leading to histomorphological alterations of the heart, kidneys and vessels. Further pathologic features include reduced elasticity of large arteries [26–29]. Of course, risk factors for CVD in the general population also contribute to CV risk in CKD. These factors, for example, contribute to the progression of coronary heart disease via atherosclerotic plaques in CKD patients. The presence of coronary heart disease in turn accelerates the loss in kidney function resulting in further risk aggravation for cardiac events. This diversity of risk factors illustrates the complexity of the link between CKD and CVD and many underlying mechanisms are still unknown or poorly understood.

Sudden cardiac death in CKD

In the general population, the risk of sudden cardiac death (SCD) is 1 in 1000 patient-years. This risk increases in CKD patients up to 59 in 1000 patient-years. Conflicting data exist on the occurrence of SCD in relationship to the day and schedule of hemodialysis: some studies show an increased risk on the day after dialysis [30] suggesting that dialysis itself—in addition to the myocardial changes in uremia described above—may represent a risk factor for SCD. Other data point towards an increased mortality after a long interval between dialysis sessions [31, 32], suggesting that alterations in electrolyte levels as well as fluid changes favor the development of cardiac arrhythmias [33].

To date, no established risk score exists to predict cardiac arrhythmias in CKD patients and so far, successful therapeutic strategies to prevent SCD in these patients are lacking.

The circulation and myocardium as main components contributing to increased CV risk in CKD

Our current understanding of the increased CV risk in CKD (Fig. 1a) is based on the interaction of the kidney with the *circulation* (encompassing the *vascular system* and *blood*) and the *myocardium* (Fig. 1b). This increases CV risk by triggering pathological mechanisms (Fig. 1c).

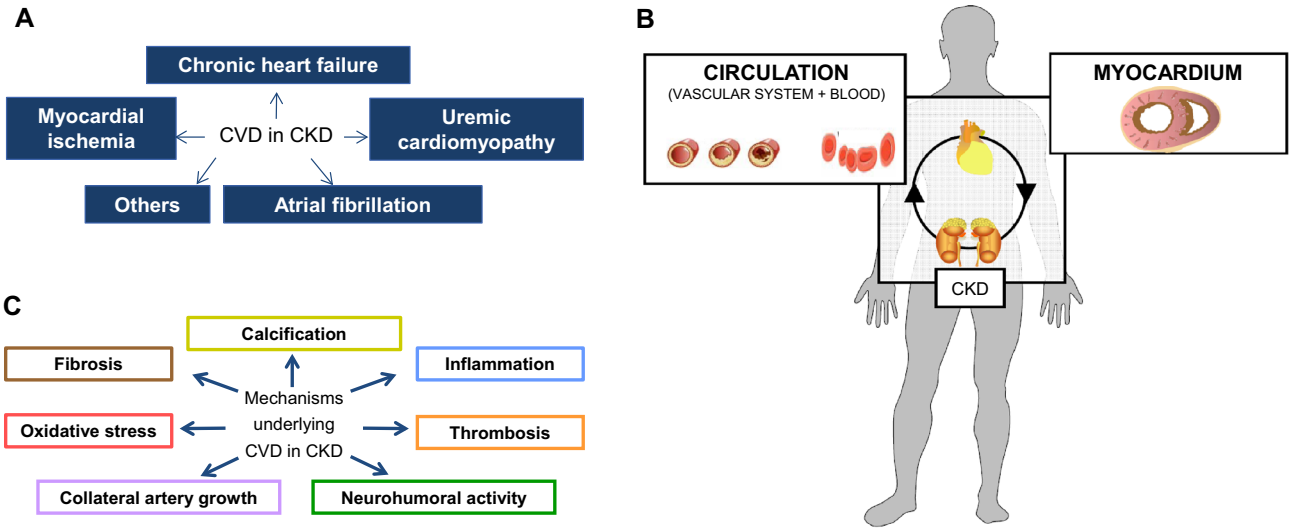

Fig. 1 CV complications in CKD are triggered by interactions of the kidney with the circulation and the myocardium. **a** Important CV pathologies in CKD patients. **b** Alterations in the circulation as well as in the myocardium crucially contribute to the increased CV risk in patients with CKD. **c** Pathological mechanisms underlying increased CVD risk in patients with CKD

Circulation

The vascular morphology in CKD exhibits two distinct characteristic but overlapping pathological features, namely accelerated atherosclerosis and arteriosclerosis (mediasclerosis). In contrast to non-CKD patients, most of the uremic vascular damage appears to be degenerative and thus has potential relevance to also understand processes in human aging. Atherosclerosis entails the formation of atherosclerotic lesions in the arterial intima driven by *endothelial dysfunction* and chronic *inflammation* of the vessel wall [34]. Upregulation of pro-inflammatory mediators in uremic vessels has been reported [35]. Dialysis patients also exhibit mostly *calcified* plaques in coronary arteries, whereas plaques of non-uremic patients were mostly fibroatheromatous [29, 36, 37]. Moreover, a lower estimated GFR (eGFR) was associated with increased numbers of newly formed intramural blood vessels and intraplaque hemorrhages [38]. Arteriosclerosis is characterized by *fibrosis* and thickening of the medial arterial layer. Whereas inflammation is not a major feature of arteriosclerosis, arterial wall *calcification* associated with an osteoblastic transformation of vascular smooth muscle cells (VSMCs), is an important characteristic of uremic damage [39]. Calcification is frequent in the general population and associated with high CV risk [5, 40, 41]. In patients with CKD calcification is accelerated and amplified, and heralds a poor prognosis in terms of CV morbidity [5, 40, 42, 43]. An important cause of increased calcification in CKD is the lack or dysfunction of calcification inhibitors, with one of the most important ones being the matrix gla protein (MGP), which is activated in the presence of vitamin K. CKD patients are vitamin K deficient [43], and a recent study by members of this Consortium showed that vitamin K2 supplementation in dialysis patients can improve the activation status of MGP [44]. Ongoing studies will determine whether clinically relevant parameters such as the progression of vascular calcification and CV mortality in dialysis patients are affected by vitamin K supplementation.

Besides vessel wall pathology, patients with CKD also exhibit alterations of the circulating blood that contribute to their increased CV risk. Thus, patients with CKD display a chronic *pro-inflammatory* state with increased levels of circulating pro-inflammatory and pro-atherogenic mediators. Furthermore, various studies document *altered platelet function* in CKD, and CKD patients exhibit a compact clot structure with an *impaired fibrinolysis*, which is associated with increased mortality [45, 46]. In addition, recent work to a large extent performed by our group, suggests that CKD leads to major *changes in lipoproteins*: high-density lipoprotein (HDL) is considered atheroprotective in non-renal populations through its anti-inflammatory properties and by promoting endothelial repair. However, independent of its concentration, the vasoprotective functions of HDL are severely reduced in patients with CKD and complex compositional and structural changes cause accumulation of dysfunctional HDL in these patients [47].

Finally, when kidney excretory function fails, a multitude of compounds accumulates in the blood, which under healthy conditions are excreted into the urine [48, 49]. Such *uremic toxins*, e.g., indoxyl sulfate and p-cresylsulfate, are the compounds that cause a gradual state of endogenous intoxication, termed uremia after the most abundant but relatively inert compound urea. Many uremic toxins have been associated with increased morbidity and mortality in CKD

patients, but the underlying pathological mechanisms are only partially understood. Uremic toxins alter platelet function, but also affect the function of other organs including the CV system [23]. Adverse effects of uremic toxins are at least partially mediated through DNA damage [50]. Furthermore, recent data revealed that increased plasma levels of the uremic toxin phenylacetic acid in ESRD inhibit the expression of the atheroprotective protein iNOS [51], and indoxyl sulfate contributes to oxidative stress and endothelial dysfunction in CKD [52]. Uremic toxins also promote phenotypic changes and damage of VSMCs. In addition, clinical and epidemiological data suggest an association of CKD with poor coronary collateral vessel development [53].

Some of the uremia-associated risk factors also seem to mediate CV mortality in aging persons with normal renal function, confirming the long-standing clinical observation that uremia is a state of accelerated (vascular) aging [50]. This suggests that findings and therapeutic strategies targeting increased CV risk in CKD could also be extrapolated to the aging population without CKD, which markedly strengthens the potential implications of our planned research.

Myocardium

Cardiac arrest is responsible for most CV deaths in patients with ESRD. Characteristic changes in the myocardium such as fibrosis and cardiac hypertrophy are of critical importance here and have been previously summarized under the not very well defined term “uremic cardiomyopathy”.

Extracellular matrix protein accumulation in the cardiac interstitium contributes to systolic and diastolic dysfunction in many cardiac pathophysiologic conditions. In addition to activated myofibroblasts, which are the main effector cells of the fibrotic heart, monocytes/macrophages, lymphocytes, mast cells, vascular cells and cardiomyocytes are involved in the fibrotic response by secreting key fibrogenic mediators. Inflammation, oxidative stress, the renin–angiotensin–aldosterone system, serum lipoproteins, mineral and iron homeostasis have all been recognized to influence cardiac fibrosis [54]. However, their specific role in the cardiorenal interaction, and their potential contribution to increased cardiac death in CKD patients, is poorly understood.

During the dialysis procedure, significant hypotensive phases occur in 25% of cases, which in combination with microvascular changes lead to local ischemia. Left ventricular dysfunction can persist after the return to normal perfusion, known as myocardial stunning [55], which is associated with an increased mortality [56]. A further risk factor of sudden cardiac death in CKD patients is left ventricular hypertrophy, resulting from hypertension, left ventricular dilatation, chronic inflammation and an activation of the renin–angiotensin–aldosterone system [57]. However, whereas the progress of left ventricular hypertrophy is prevented or even reversed in non-dialysis patients with strict anti-hypertensive therapy, this is not the case in dialysis patients, suggesting that CKD-associated risk factors contribute to a greater extent to left ventricular hypertrophy than hypertension itself.

A crucial interaction between the kidney, the circulation and the myocardium

The increasing incidence and prevalence as well as the high mortality of CVD require accurate identification and characterisation of involved signaling pathways and mechanisms. Numerous studies indicate a close interaction of the kidney, the heart and the circulation, influencing each other in their function. Worldwide researchers have identified important mediators that play relevant roles in renal, myocardial and vascular pathology. However, their functions regarding the complex interactions between kidney, heart and vessel are overall still poorly understood.

Transregional Research Consortium SFB TRR219

The Transregional Research Consortium SFB TRR219 is composed by two academic German centers with a strong scientific and clinical focus on CV diseases in CKD patients: the University Hospital Aachen (RWTH) and the Saarland University.

We assume that the increased CV risk of patients with CKD is determined by the circulation (blood and vessels) as well as the myocardium, both of which can contribute to cardiac and renal pathology. By collaborative and translational research based on existing interactions between groups of different clinical and methodological expertise, we pursue the overall long-term goal to gain understanding of the renal and CV interactions that may contribute to the development of novel treatment strategies to decrease CV risk in CKD patients. The following specific aims were defined:

- Characterisation of known and newly identified mediators relevant in CKD, and understanding of the mechanisms underlying their effect on heart and vessels causing CKD-related CVD.
- Identification of novel mediators relevant in CKD with a strong impact on CVD.
- Initiate clinical translation by investigating novel mediators as potential biomarkers of CKD-related CVD, by analyzing the effect of novel interventions on CKD-related CV pathology, and by optimizing diagnostic tests to aid its application into clinical practice. This should stimulate the development of novel pharmacological strategies in CKD-associated CVD to reduce CV morbidity and mortality in CKD in the long run.

We are focussing on ischemic heart disease (which includes myocardial infarction) and chronic heart failure, as they account for more than 70% of CV deaths in CKD patients (Fig. 1a). This includes analysis of uremic cardiomyopathy as well as atrial fibrillation, two common causes of heart failure in these patients.

Structure of the Transregional Research Consortium and research strategy to reach the consortium aims

Alterations in the circulation as well as in the myocardium crucially contribute to the increased CV risk in patients suffering from CKD, identifying these alterations as the main, critical components for their high CVD risk. However, the molecular mechanisms as well as the mediators involved are largely unexplored. Therefore, the aim of this Transregional Research Consortium is to analyze in experimental and clinical studies the multi-factorial aspects of CKD-related CV morbidity and mortality caused by:

(a) the *circulation*, here, we focus on (1) the pathological remodeling of the vessel wall and involved mediators and vascular cells, which results in inflammation, endothelial dysfunction, formation of vascular lesions and calcification; and on (2) components of the blood such as dyslipidemia, thrombogenicity, increased mineral load and uremic toxins, all contributing to CV damage;
(b) the *myocardium*, comprising pathological myocardial remodeling associated with deranged myocardial metabolism, altered oxidative stress, micro-angiopathy, autonomous neuropathy, and impaired cardiac function.

Future projects in this consortium will focus on the increased stroke risk in patients with CKD as well as changes in the brain vasculature in CKD.

In addition to examining pathological mechanisms affecting the CV system in CKD at the basic science level, we also study translational aspects by analyzing novel interventions and diagnostic tests in the context of CKD-related CV pathology. For example, we investigate in mouse models or/and small CKD patient cohorts whether interventions as renal denervation, vitamin K therapy or application of fibrinogen-binding peptides can modulate CVD (cardiac remodeling, calcification and thrombosis, respectively) in the context of CKD. Furthermore, we search for novel factors contributing to CVD in the context of CKD, to trigger the subsequent development of novel diagnostic and/or predictive tests. In addition, by optimizing a previously developed calcification blood test, we will actively contribute to the application of novel diagnostic tests into clinical practice.

In summary, a better understanding of the pathophysiology of CVD in CKD together with the development of novel diagnostic tests should pave the way for a better risk prediction in patients with CKD and facilitate the development of future therapeutic strategies to reduce CV morbidity and mortality in this high-risk population.

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