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FULL REVIEW

The vulnerable patient with chronic kidney disease

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ABSTRACT

Patients with chronic kidney disease (CKD) exhibit an increased cardiovascular risk. The high susceptibility to cardiovascular disease renders CKD patients 'vulnerable patients'. The overall cardiovascular risk of a vulnerable patient with CKD is determined by the components of the vulnerable myocardium, the vulnerable vessel and the vulnerable blood which in sum contribute to the increased morbidity and mortality risk in CKD patients. Future therapeutic strategies to reduce cardiovascular morbidity and mortality in this high-risk population should address all three aspects of vulnerability in CKD patients.

INTRODUCTION

Patients with chronic kidney disease (CKD) exhibit an increased propensity to develop cardiovascular events, and cardiovascular mortality accounts for 50% of all deaths in patients with end-stage renal disease (ESRD) on dialysis. In addition, data from the United States Renal Data System (USRDS) database suggest that up to two-thirds of cardiac deaths are attributable to sudden cardiac death and arrhythmias. The high susceptibility to cardiovascular disease renders CKD patients 'vulnerable', thus the term 'vulnerable patients', which is a new concept in cardiology [1]. The overall cardiovascular risk of the vulnerable patient with CKD is determined by the components of the vulnerable myocardium, the vulnerable vessel and the vulnerable blood which in sum contribute to the increased morbidity and mortality in CKD patients. Vulnerability is linked to the concept of 'frailty'. The present article will give an overview of the various aspects of vulnerability and summarize our current understanding of cardiovascular disease in the high-risk CKD population.

THE VULNERABLE MYOCARDIUM

In contrast to the general population, in which coronary artery disease is the most prevalent cause of mortality, patients with CKD, in particular those on haemodialysis, mainly die of

sudden cardiac death (SCD). Characteristic changes in the myocardium, such as pathological cardiac hypertrophy and fibrosis, are of critical importance here and have been summarized under the term 'uraemic cardiomyopathy'.

Left ventricular hypertrophy

In CKD, left ventricular hypertrophy (Figure 1) is present in ∼30% of all patients, increasing up to 70–80% in patients with ESRD [2, 3]. Even in patients with moderate CKD, left ventricular hypertrophy has been shown to be a strong independent predictor of survival [2, 4]. Current data suggest that three main mechanisms contribute to left ventricular hypertrophy in CKD: afterload- and preload-related factors, as well as non-after- or preload-related factors. Afterload-related factors include abnormal arterial stiffness, increased systemic arterial resistance and systolic hypertension [5], which initially lead to concentric left ventricular hypertrophy. Early on, ventricular hypertrophy with enlargement of myocardial cells is an attempt to maintain the wall stress and may be seen as a beneficial adaptive response, allowing the maintenance of systolic function and cardiac output. Continuous left ventricular overload subsequently leads to maladaptive changes and cardiomyocyte death with eccentric hypertrophy, consecutive left ventricular dilatation, systolic dysfunction and reduced ejection fraction. Concentric left ventricular hypertrophy is present in 40% and eccentric hypertrophy in 28% of patients at initiation of haemodialysis [6, 7]. Activation of the renin–angiotensin system in the heart [8], non-angiotensin II-dependent pathways after mechanical stress, oxidative stress as well as xanthine oxidase activation are also thought to play an important role in this context [9].

Preload-related factors. The preload-related factors in the pathophysiology of left ventricular hypertrophy include the expansion of intravascular volume in CKD leading to a volume overload, length extension of myocardial cells and eccentric or asymmetric left ventricular modelling.

Non-after- or preload-related factors. The non-after-or preload-related factors contributing to cardiac hypertrophy in CKD patients, involve various potential intracellular mediators and pathways (reviewed in [8]) that translate the above haemodynamic and circulatory changes into a progressive left ventricular hypertrophy. Among the crucial mechanisms are, activation of peroxisome proliferator-activated receptors (PPARs), stimulation of small G-proteins and the mammalian/mechanistic target of rapamycin (mTOR) pathway, as

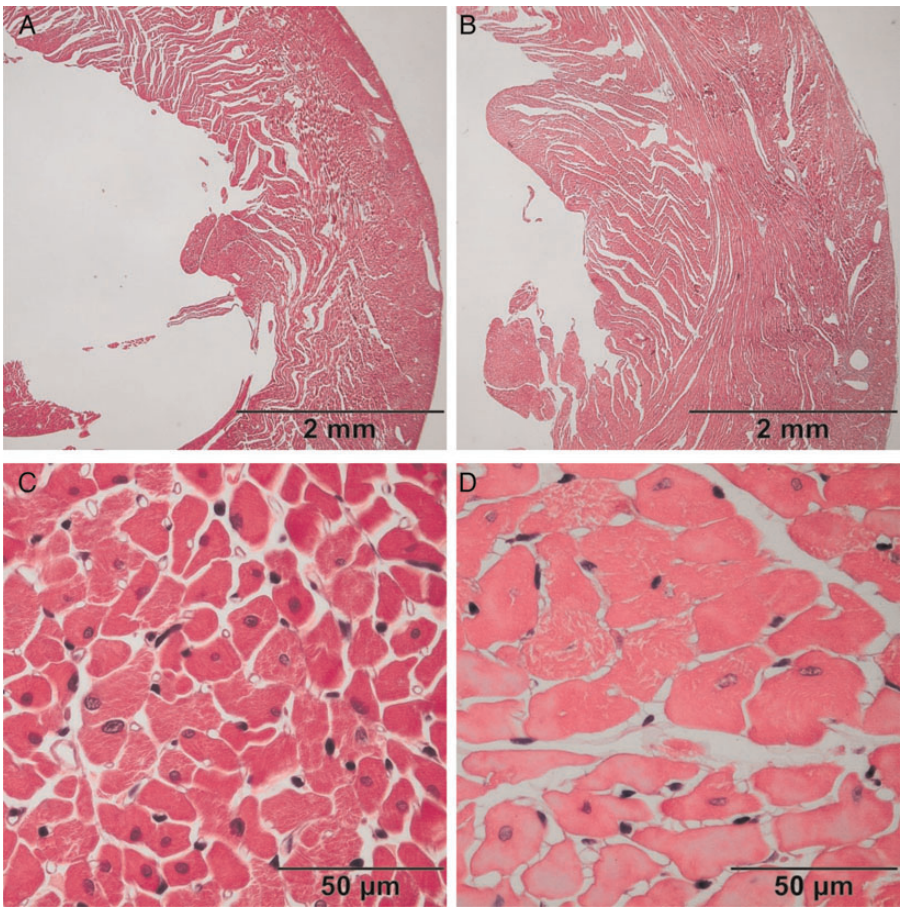

FIGURE 1: Experimental uraemia induces cardiac hypertrophy [(**A**) sham control, (**B**) uraemia induced by subtotal nephrectomy]. High magnification reveals hypertrophic cardiomyocytes, interstitial expansion and a reduced number of capillaries in uraemic (**D**) versus control (**C**) animals. Courtesy of Kerstin Amann, Erlangen, Germany.

well as metabolic changes, e.g. a decrease in fatty acid oxidation. Accumulation of hypertrophy-inducing factors in uraemia, such as endothelin 1, parathyroid hormone, tumour necrosis factor α (TNFα) and certain interleukins, also seem to be of importance [8, 10]. In addition to these mechanisms, a special focus in research has been placed on Na-K inhibitors as well as insulin resistance which lead to changes in the AKT (a serine/threonine-protein kinase) pathways and also contribute to uraemic cardiomyopathy and hypertrophy.

Recently, the term 'heart failure with preserved ejection fraction' (HFpEF) has been introduced [11], of which diastolic dysfunction (relaxation and/or stiffness) and other pathophysiologies (including sodium and fluid retention, anaemia, inflammation and activation of the sympathetic and renin–angiotensin–aldosterone systems) are contributing factors [12]. In CKD patients, HFpEF seems to be highly prevalent (30–60%) [13]. Registry data reported a similar prevalence of renal disease (~50%) in HFpEF patients and patients with reduced ejection fraction [12].

Fibrosis

Besides left ventricular hypertrophy, uraemic cardiomyopathy is characterized by myocardial fibrosis, occurring independently of blood pressure and left ventricular hypertrophy itself [14]. Typically, CKD patients exhibit diffuse myocardial fibrosis with collagen deposition between capillaries and cardiomyocytes, which in turn contributes to the maladaptive ventricular hypertrophy with subsequent dilatation of the heart. Relative oxygen starvation of cardiomyocytes due to myocardial fibrosis renders the myocardium more susceptible to ischaemia and ventricular arrhythmias [9]. Recently, strain parameters assessed by echocardiography have been used to detect uraemic fibrosis in early CKD stages, and these parameters were predictive for mortality in dialysis patients [15].

Sudden cardiac death

In the general population, the risk of SCD is 1 in 1000 patient-years. This risk increases to 59 in 1000 patient-years in CKD patients (USRDS). Conflicting data exist on the occurrence of SCD in relationship to the day and schedule of haemodialysis: some studies show an increased risk on the day after dialysis [16] suggesting that dialysis itself—in addition to the myocardial changes in uraemia described above—may represent a risk factor for SCD. Other data point towards an increased mortality after a long interval between dialysis sessions [17, 18], suggesting that alterations in electrolyte levels as well as fluid changes favour the development of cardiac arrhythmias.

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 [19].

THE VULNERABLE VESSEL

Histological changes of the vascular wall in CKD

The vascular morphology in CKD exhibits a number of particular features. It is characterized by two distinct but overlapping pathological processes, namely accelerated atherosclerosis and arteriosclerosis (mediasclerosis) involving fibrosis and thickening of the medial arterial layer. Autopsy studies comparing the coronary and arterial plaque area between CKD patients and non-renal controls found either no difference or significantly more and larger plaques in the CKD group and more signs of inflammation [20, 21]. However, compared with non-renal patients, dialysis patients exhibited significantly more calcified plaques in the coronary arteries, whereas plaques of non-uraemic patients were mostly fibroatheromatous [20–22]. In addition, a lower estimated glomerular filtration rate (eGFR) was associated with increased numbers of newly formed intramural blood vessels and intraplaque haemorrhages [23]. Intima thickness did not differ significantly from non-renal patients but media thickness of coronary arteries was 30–40% higher in dialysis patients [20]. This resulted in a significantly lower lumen area in the end-stage renal patients. Intima media thickness of the carotid artery is a predictor for increased risk in dialysis and CKD patients.

In contrast to non-CKD patients, inflammation is not a major feature of uraemic vascular damage, in particular that of the arterial media. Thus, arterial medial calcification in CKD patients was not associated with macrophage infiltration [22]. Findings in the intima are more variable with one study describing no difference in the cellular infiltrate in coronary arteries in advanced plaques of uraemic and non-uraemic subjects [20], whereas others noted more macrophages in calcified arterial intima of CKD patients [22]. In addition, some upregulation of pro-inflammatory mediators such as tumour necrosis factor-alpha has been noted in uraemic vessels [24]. Another pro-inflammatory mechanism may involve angiopoietin-2, whose levels correlated independently with the severity of arterial stiffness in CKD patients and blockade of angiopoietin-2 in experimental CKD reduced vascular damage and stiffness [25].

Most of the uraemic vascular damage appears to be degenerative. Uraemic toxins, such as increased oxidized low-density lipoprotein in CKD vessels [23], indoxyl sulfate [26], *p*-cresyl-sulphate [27] or circulatory translocation of gut bacterial endotoxin [28], but in particular dysregulated mineral metabolism, promote phenotypic changes and damage of vascular smooth muscle cells (VSMC). Some of these risk factors also seem to mediate cardiovascular mortality in ageing persons with normal renal function, confirming the long-standing clinical observation that uraemia is a state of accelerated (vascular) ageing [29]. Mechanistically, uraemic toxins promote DNA damage, and this key factor driving cellular ageing, seems to involve similar mechanisms as observed, for example, in progeria syndrome—a rare genetic disorder with accelerated ageing—caused by nuclear lamina disruption [29].

A particular feature of uraemic damage is arterial wall calcification [24, 30, 31]. Advanced CKD is associated with an osteoblastic VSMC transformation, indicated by the *de novo* expression of Cbfa1/Runx2 in VSMC of dialysis patients [22, 24, 32]. The origin of calcifying VSMC is at present uncertain. Calcifying VSMC may derive from local VSMC following phenotypic transformation (from contractile to synthetic phenotype) or they may derive from smooth muscle progenitor

cells in the circulation, which increase with declining kidney function [33]. Alternatively, invading mesenchymal stem cells, i.e. perivascular VSMC precursors, might differentiate into osteoblast-like cells in a uraemic milieu [34].

Vascular calcification is a complex consequence of pro-calcific stress (e.g. via disturbed mineral homeostasis [35] and impaired defenses in CKD (e.g. inactive matrix gla protein [36] or reduced vascular wall pyrophosphate levels [37]), which may act differently on different parts of the arterial tree [38, 39]. In experimental CKD, arterial medial calcification was associated with *de novo* expression of osteocalcin and decreased levels of alpha-smooth muscle actin, a marker of normal VSMC [40]. The calcium-sensing receptor is expressed in VSMC of normal arteries. Its expression decreases markedly in atherosclerotic, calcified arteries, and such reduced receptor expression contributes to mineralization [41]. Vice versa, stimulation of the receptor with calcimimetics prevented experimental medial calcification [42]. In addition, factors that regulate bone resorption, such as osteoprotegerin, may also contribute to vascular stiffness in CKD patients [43]. The role of other factors, such as transglutaminase-2, in mediating calcification is less well established with experimental studies describing an important pro-calcific role [44] but other studies documenting reduced expression of this enzyme in CKD vessels [24]. In addition, disruption of the elastic lamella, possibly due to increased activity of matrix-degading enzymes [45], occurs in CKD [40], and this is a known nidus for calcium-phosphate precipitation [46]. Another nidus for calcification of the media may be apoptotic bodies of VSMC, which are markedly increased in uraemia [47, 48]. This mechanism is probably the best available illustration of the concept of a 'vulnerable patient' (Figure 2): thus, in an *ex vivo* model of arterial vessel rings, those from children on dialysis avidly accumulated calcium and calcified in contrast to rings from non-renal children, and this was ameliorated by a pan-caspase inhibitor [48]. In agreement with this, paediatric pre-dialysis vessels appeared histologically intact, whereas dialysis vessels exhibited evidence of extensive VSMC loss owing to apoptosis [32]. Of particular note, most of this occurred in vessels before any overt calcification was detectable by radiology.

Uraemia also increases the propensity of the arterial (neo-) intima to undergo hyperplasia, as shown experimentally after AV fistula creation in mice with or without CKD [49, 50]. This is related to the CKD-associated greater migratory capacity of aortic VSMC and was prevented by treatment with bone morphogenic protein-7, which promotes VSMC differentiation before creation of the AV fistula [49]. In addition, already in early CKD, bone marrow-derived endothelial progenitor cells in the circulation decrease, impairing endogenous vascular regeneration [33].

Functional changes of the arterial intima and endothelium

Late stages of CKD, but not the milder stages, are associated with endothelial dysfunction, as detected by an altered flow-mediated vasodilation, in patients without significant cardiovascular or diabetic comorbidity [51, 52]. Like pulse-wave velocity (see below), flow-mediated vasodilation in dialysis

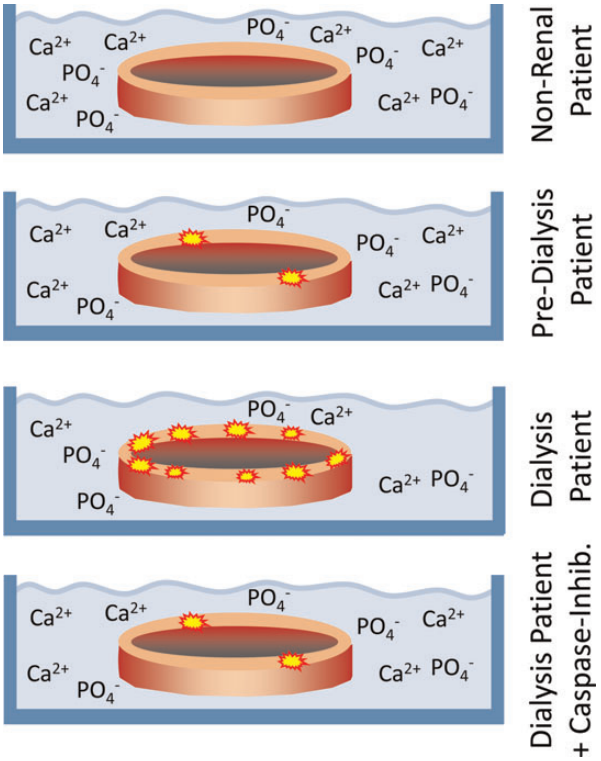

FIGURE 2: Longterm *ex vivo* exposure of arterial vessel rings to elevated calcium and/or phosphate induces no calcification in tissue of non-renal children, whereas in arterial rings from children prior to dialysis, but particularly those on dialysis, massive calcium uptake into the vessel wall was noted and associated with calcification (yellow stars). In the latter, calcification was markedly reduced by addition of a pan-caspase inhibitor that prevented VSMC apoptosis. Adapted from [48].

patients also correlated with markers of inflammation [52]. One common confounder in assessing functional vascular changes in early CKD is the very common occurrence of components of the metabolic syndrome in such patients. Indeed in early CKD stages, these components better predicted endothelial dysfunction and arterial stiffness than the degree of CKD [53, 54]. If such components are excluded as far as possible, endothelial dysfunction manifests only in stage 4–5 CKD. Possibly, studies in kidney donors may help to better elucidate the relationship between CKD and vascular dysfunction [55]. In this context, it is important to stress that elderly or obese kidney donors do not exhibit higher mortality or higher risk of cardiovascular disease [56–58].

Experimentally, the induction of CKD is also associated with impaired flow-mediated vasodilation. Thus, after creation of an arteriovenous fistula in rats with CKD, afferent arterial dilatation was markedly impaired and the downstream fistula vein had delayed dilation as well [50].

One of the key pathways impairing arterial vasodilation in CKD may be reduced endothelial nitric oxide availability. Recent data suggest that symmetric dimethylarginine in uraemic high-density lipoprotein (HDL) particles transforms the physiological HDL into an abnormal lipoprotein with pro-inflammatory activity and nitric oxide-reducing activity [59].

Functional changes in the arterial media

One of the key consequences of the vascular changes in CKD described above is augmented vascular stiffness and loss of elasticity in particular of the aorta [60–65]. Experimentally, CKD with arterial media calcification induced a significant increase in pulse pressure and pulse-wave velocity, and this correlated with the reduction in vascular wall alpha-smooth muscle actin and elastin expression and with the deposition of collagen [40]. In humans, this was reflected by an increase in the aortic pulse-wave velocity, which can already be documented in children on dialysis for 6 months or more [66]. This study is of particular importance, since children usually exhibit little confounding comorbidity. In adult CKD patients without clinically established cardiovascular disease or diabetes, pulse-wave velocity was also increased and correlated with the loss of renal function and blood pressure and, to a lesser degree, with inflammation markers, oxidative stress and the endothelin-nitric oxide balance [51]. Association studies have identified increased arterial stiffness as a very powerful predictor of mortality in advanced CKD [67, 68] whereas the predictive power of increased arterial stiffness in earlier CKD stages is not that well established [69, 70].

Increased arterial stiffness imposes high pressures and pressure changes on vulnerable vascular beds in the brain and kidney in addition to the heart, which in turn aggravates microvascular damage [71]. High pulse pressures in CKD also lead to increased left ventricular afterload in systole and reduced coronary perfusion in diastole [72]. All of this contributes to the known clinical cardiovascular complications in CKD, such as heart failure, myocardial ischaemia, increased risk of arrhythmias, stroke and accelerated progression of renal failure.

THE VULNERABLE BLOOD

Alterations of the blood emerge as additional risk factors in patients with CKD. Platelet dysfunction and alteration of the coagulation in CKD place these patients at increased risk for thrombosis but also for bleeding events.

Uraemic thrombocytopathy

One example for altered coagulation in uraemia is the observation that patients with ESRD and atrial fibrillation do not necessarily profit from warfarin and may even be exposed to an increased risk of both thrombo-embolic events as well as bleeding [73].

Several platelet or vessel wall-derived factors (and others) have been considered to contribute to platelet dysfunction in CKD patients. Among them, prostacyclin and altered von Willebrand factor may contribute to platelet dysfunction. A qualitative defect of thrombocytes in uraemia leading to disturbed aggregation could be corrected in two patients by dialysis treatment [74]. In addition, platelet numbers in patients with CKD are somewhat lower in comparison to healthy controls. In haemodialysis patients, an additional slight reduction in thrombocyte numbers occurs within the first 15–30 min of the dialysis treatment.

Platelets of uraemic patients often show an acquired storage pool defect as well as an activation defect with imbalance of agonists and inhibitors of platelet function such as ADP or cAMP [75, 76]. Interestingly, platelet responses to agonists such as ADP are decreased in uraemia, and actin shows a decreased binding to other cytoskeletal proteins in platelets. Furthermore, the interaction of platelets with the vasculature is impaired in CKD patients and a decreased binding of both von Willebrand factor and fibrinogen to glycoprotein GPIIb/IIIa have been described in uraemia [75, 76].

Uraemic toxins and renal anaemia also contribute to platelet dysfunction. However, urea itself does not impair thrombocyte function [74, 77] thus other uremic toxins seem to be responsible. Both dialysis and correction of anaemia by erythropoietin treatment can improve platelet dysfunction. Still, contact with artificial materials in haemodialysis patients has been shown to trigger coagulation, and several surface markers of platelets show activation in the outflow of dialysers (albeit with differences among dialysis membrane types) [78]. Changes are also dependent on the time points during the haemodialysis session: for example, ADP-induced P-selectin (CD62P, a marker for the degranulated platelet) expression was impaired at the end of dialysis [79], which may be due to impaired platelet function at the end of a dialysis session or the consumption of activated platelets. In addition, heparin also influences not only coagulation but also thrombocyte function potentially by interaction with integrins.

Altered gene and/or protein expression may also contribute to dysfunction of platelets in uraemia. Platelets from CKD patients exhibit an altered transcriptome [80] with, for example, a reduced phosphatidylcholine transfer protein regulated by microRNAs. Proteome analysis confirmed a different protein expression profile in normal and dysfunctional platelets from uraemic patients [81]. However, a direct link between differentially regulated genes or proteins with uraemic platelet dysfunction has not been established.

Finally, dialysis patients seem to exhibit higher levels of circulating procoagulant microvesicles than healthy controls [82], a finding that may also explain alterations of blood coagulation in these patients.

Uraemic coagulopathy

The development of an occlusive vascular thrombus represents the final step in the atherothrombotic process and is a critical step in the development of cardiovascular events. Fibrin clot structure is crucial in determining the predisposition to atherothrombotic events with compact fibrin clot structure and impaired fibrinolysis being associated with more severe cardiovascular disease [83, 84]. In contrast to patients with diabetes, little is known about alterations of clot structure in patients with CKD. In 60 patients with acute coronary syndrome (ACS) a lower eGFR was independently associated with unfavourable changes in clot structure including an earlier onset of clot formation, less porous fibrin clots, thicker fibres and prolongation of clot lysis [85]. Despite there being no other data investigating clot structure in CKD, several studies point towards a prothrombotic profile in CKD (Figure 3).

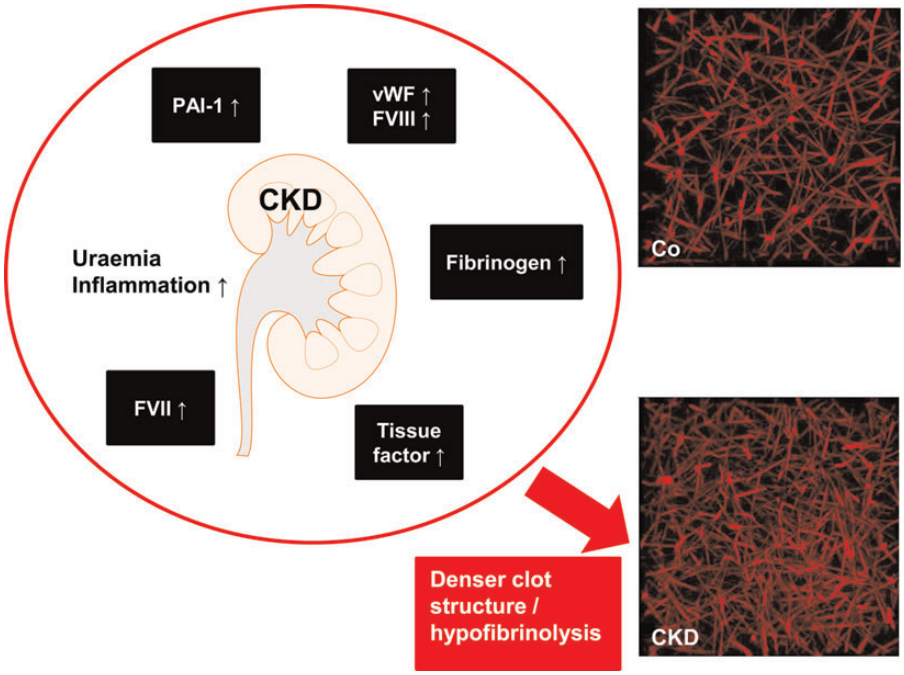

FIGURE 3: Alterations of the blood in CKD [compared with control (co)]. Uraemia and inflammation induce alterations of clot structure including earlier onset of clot formation, less porous fibrin clots, thicker fibres and prolongation of clot lysis. This is due to the elevation of several coagulation components in CKD. PAI-1, plasminogen activator inhibitor-1; VIII, factor VIII; vWF, von Willebrandt factor; FVII, factor VII.

Tissue factor (TF), the key initiator of the coagulation cascade, is produced by different cell types, including endothelial cells, VSMCs, monocytes/macrophages and platelets. Plasma levels are elevated in CKD and further increase in dialysis [86–89]. While TF expression is very low under basal conditions, in CKD monocytes display elevated expression of TF thereby contributing to the prothrombotic profile [90]. TF activates factor VII consecutively leading to the activation of factor X and the prothrombinase complex. Similar to TF, plasma levels of FVII are elevated in CKD with a further increase in dialysis [89]. FX can also be activated by von Willebrandt factor (vWF) and factor VIII (FVIII). vWF is selectively expressed on endothelial cells and platelets and has two major functions: it promotes platelet adhesion and serves as a carrier for factor VIII thereby increasing its half-life. In CKD, plasma levels of factor VIII are increased [91], which has been associated with an increased cardiovascular risk. The latter is mainly thought to occur in concert with other risk factors as the effect was lost after adjusting for common cardiovascular risk factors [92]. Besides uraemia, low-grade inflammation may also contribute to altered coagulation factors in CKD. This leads to the increased expression of several cytokines including interleukin (IL)-1β, IL-6, and TNFα, which all increase fibrinogen plasma levels [93, 94]. Accordingly, in a large cohort of CKD patients, fibrinogen plasma levels strongly correlated with eGFR [94], and fibrinogen plasma levels have been shown to independently predict all-cause mortality and cardiac events in stage III–IV CKD [95, 96], highlighting the importance of alterations of the coagulation cascade. In addition, other factors such as microvesicles may also contribute to altered coagulation.

Clot formation is accompanied by fibrinolysis, a key process in homeostasis of coagulation. Activated by tissue plasminogen activator (t-PA) or urokinase, plasminogen is transformed to plasmin, which cleaves fibrinogen in its degradation products. PAI-1 is thought to be the main inhibitor of fibrinolysis [97]. To prevent plasmin generation, PAI-1 rapidly forms inactive complexes with t-PA and urokinase. Several studies demonstrate PAI-1 to be elevated in CKD [85, 91], thereby further enhancing the prothrombotic profile of these patients. Altogether, these data underline the impact of CKD on alterations of coagulation factors thereby enhancing the prothrombotic risk of these patients.

Inflammation

Dialysis patients often present a state of chronic inflammation as shown by biomarkers such as hsCRP or IL-6. Many studies have shown that these biomarkers are independent predictors of survival in patients with CKD. The underlying pathomechanisms leading to subclinical, chronic inflammation may not be obvious in each case and are often multifactorial. Inflammation may trigger cardiovascular disease and oxidative stress, and in this context inflammation may be accompanied by malnutrition which further contributes to the poor prognosis of CKD patients. In addition, aggregates of leucocytes with thrombocytes are formed and may subsequently contribute to altered coagulation in patients with CKD. In this context, it is important to note that uraemia impairs the anti-inflammatory properties of HDL [98], thereby likely contributing to dysfunctional cholesterol transport.

Oxidative stress and uraemic toxins

Many factors can contribute to increased oxidative stress in patients with CKD. Among these factors are uraemia,

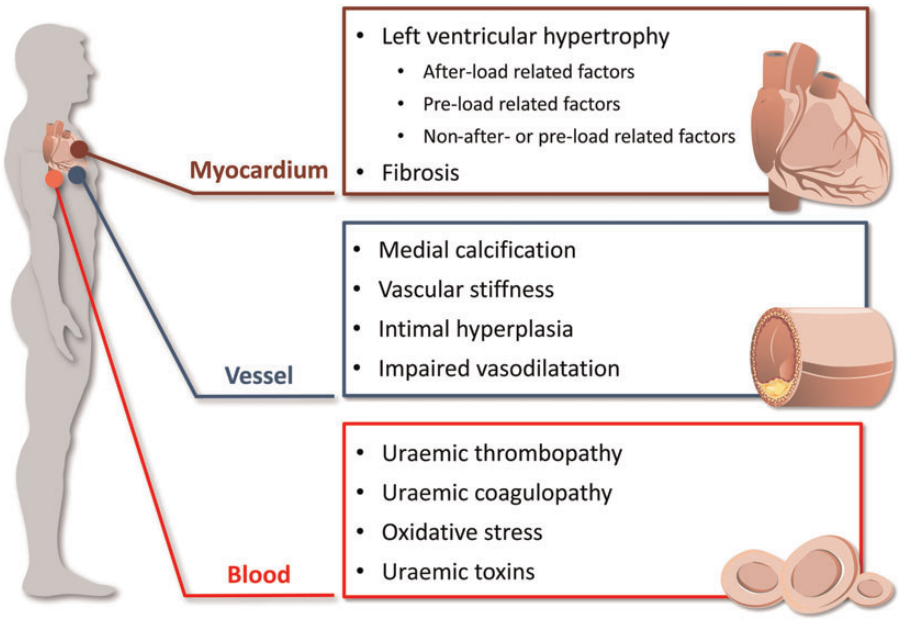

FIGURE 4: The vulnerable patient with CKD. Patients with CKD exhibit components of the vulnerable myocardium, the vulnerable vessel and the vulnerable blood, all of which contribute to the increased cardiovascular risk of these patients.

loss of antioxidants, malnutrition and dialysis-associated factors (e.g. blood-membrane interaction, dialysate). In terms of function, reactive oxygen species contributes to cardiovascular disease, and nitric oxide can inhibit platelet-platelet interactions.

In terms of vulnerable blood, uraemic toxins not only contribute to dysfunction of the coagulation system but also alter the function of other organs including the cardiovascular system. Among the uraemic toxins, b2-microglobulin, indoxyl sulphate, uric acid and parathyroid hormone were often mentioned as 'classic toxins' whereas more recent studies reported higher uraemic concentrations of solutes such as carboxymethyllysine, cystatin C, methyguanidine or guanidine succinic acid [99]. Despite the fact that the exact role of the uraemic milieu is still only partially understood, many uraemic toxins have been reported to be associated with increased morbidity and mortality in CKD patients. Some of these toxins have been shown to exert direct toxic effects in experiments. For example, increased levels of plasma phenylacetic acid in dialysis patients inhibit iNOS expression [100] which in turn may affect vascular and/or myocardial function.

Taken together, patients with CKD are vulnerable patients because they exhibit all of these features, the vulnerable myocardium, the vulnerable vessel, as well as the vulnerable blood (Figure 4). To date, the interaction of these different aspects of vulnerability in CKD is relatively unexplored, and further research is mandatory to better understand the pathophysiology of cardiovascular events in this high-risk population. In addition, diagnostic approaches to predict cardiovascular events, and in particular the risk of SCD, need to be developed. Finally, future therapeutic strategies to reduce cardiovascular morbidity and mortality in this high-risk population should address all three aspects of vulnerability in CKD patients.

CONFLICT OF INTEREST STATEMENT

None declared.

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