Oxidative stress and atherosclerosis in chronic kidney disease

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Abstract

The rapid progression of atherosclerosis is a characteristic feature of cardiovascular abnormalities in the vast majority of chronic kidney disease (CKD) patients. The inflammatory network of numerous cytokines and pathological reactions underlying the primary kidney insult and progression to chronic disease accompanied by a loss of glomerular function is linked with the pathogenesis of enhanced oxidative stress in CKD. The generation of reactive oxygen species by endothelial nicotinamide adenine dinucleotide phosphate-oxidase (NADPH) oxidase (Nox) enzyme isoforms elicits activation of the nuclear transcription factor κB, and downstream signaling leading to inflammation, proliferation, accumulation of extracellular matrix, endothelial dysfunction, atherosclerosis and thrombosis. Chronic systemic and low-grade inflammation enhanced oxidative stress, retention of oxidized uremic toxins, depletion of antioxidant and buffering pools are unified mechanisms responsible for the enhanced atherosclerosis, contributing to the increased cardiovascular risk of all age groups of CKD patients.

Key words: atherosclerosis, chronic kidney disease, oxidative stress.

Introduction

The concept of accelerated atherosclerosis in chronic kidney disease (CKD) has been extensively studied fueled by the fact that the probability of death due to cardiovascular complications after 13 years of dialysis is as high as 90%. Furthermore, only 30 to 50% of the entire cardiovascular mortality is a result of myocardial infarction due to coronary atherosclerosis [1]. Chronic kidney disease is characterized by glomerulosclerosis, interstitial infiltration of leukocytes, tubular atrophy and tubulointerstitial fibrosis [2]. Structural abnormalities of blood vessels are detectable at a predialysis stage of CKD [2]. Chronic kidney disease and the progressive loss of renal function are associated with the increased risk of cardiovascular sudden incidents that cannot be explained solely by established abnormalities in vascular regulation, accelerated atherosclerosis or conventional risk factors [3]. The plethora of cardiovascular biomarkers that correlate with functional indices of left ventricular dysfunction and decreased glomerular filtration rate (GFR) or predict final fatal outcomes of cardiovascular mortality in end-stage renal disease (ESRD) patients include: (i) markers of endothelial dysfunction: asymmetric dimethyl-L-arginine (ADMA), homocysteine; (ii) inflammatory markers: CRP (C-reactive protein), TNF-α (tumor necrosis

factor-α), TNF-α receptors p55 and p75, IL-6 (interleukin-6), fibrinogen, serum amyloid A; (iii) fetuin A as a blood serum inhibitor of vascular calcification (α2-Heremans Schmid glycoprotein – AHSG); (iv) markers of endothelial monocyte recruitment: ICAM-1 (inter-cellular adhesion molecule 1), VCAM-1 (vascular cell adhesion molecule-1), selectins, MCP-1 (monocyte chemoattractant protein-1); (v) indices of oxidative stress: malonyldialdehyde and isoprostanes as markers of lipid peroxidation, hydrogen peroxide as a relatively stable oxidative end-product, reduced glutathione, protein thiols, advanced oxidation protein products; (vi) markers of enhanced sympathetic activity including catecholamines, neuropeptide Y and renalase in addition to indices of bone marrow function, platelet activation, natriuretic peptides related with left ventricular stain, especially NT-proBNP (N-terminal pro-B-type natriuretic peptide) and urotensin II, in addition to a number of indices of myocardial necrosis [4]. The excess cardiovascular risk related to renal damage was even more specifically linked to malnutrition-inflammation-atherosclerosis (MIA) syndrome [5]. Progression of CKD coincides with an atherogenic lipid profile, typically with low high-density lipoprotein (HDL) cholesterol, high triglycerides and increased small dense low-density lipoprotein (LDL), which appears comparable to the metabolic syndrome [6]. Also, increased blood serum homocysteine is an independent, graded risk factor for the development of atherosclerosis and thrombosis in CKD, despite current evidence suggests that elevated homocysteine levels are not an independent cardiovascular disease (CVD) risk factor and that there is no need for routine measurement of its levels [6-8]. One should also remember about the well-known risk factors, such as: smoking and insulin resistance [9]. All of theses factors contribute to the alarming observation that CKD patients on adequate renal replacement therapy are facing a high mortality due to cardiovascular complications.

Oxidative stress and endothelial dysfunction

The term oxidative stress was coined to characterize the increased reactive oxygen species (ROS) production in numerous human diseases, although ROS plays a physiological role in the normal regulatory mechanisms of endothelial function [9]. The enhanced oxidative stress is characteristic of the uremic milieu [9, 10]. The retention of both large molecular weight inflammatory mediators and small molecular weight oxidized uremic toxins; oxidized thiols, lipid peroxides and reactive aldehydes are specific abnormality in the course of chronic kidney failure (CKF) [3]. The typical end-stage renal failure atherosclerosis, β2-microglobulin amyloidosis, malnutrition and anemia are apparently related to increased oxidative stress and depletion of antioxidant enzyme pools in peripheral blood and tissues [3, 9].

In addition to the conventional role of renin angiotensin aldosterone system (RAAS) abnormal activation on water and electrolyte balance, overactivity of the RAAS is mechanistically linked to increased ROS (reactive oxygen species) generation within the endothelium [6-9]. Non-phagocytic NAD(P)H (endothelial nicotinamide adenine dinucleotide phosphate) oxidase (Nox) includes the prototypic Nox2 homolog-based, nicotinamide adenine dinucleotide phosphate NAD(P)H oxidase- a major source of ROS in endothelial and renal cells [6]. Reactive oxygen species, including superoxide anion of the highest oxidation potential, hydroxyl radical, hydrogen peroxide as a relatively stable peroxidation product are also generated by other NAD(P)H oxidases, such as Nox1 and Nox4 [6]. Reactive oxygen species may be generated not only by NAD(P)H oxidase but also by xanthine oxidase, cyclooxygenase, lipoxygenase, mitochondrial electron transport enzymes and inducible nitric oxide synthase (iNOS) [6]. NAD(P)H oxidase, or Nox, is a enzyme complex activated by angiotensin II acting via angiotensin receptor 1 (AT1R) and protein kinase C to stimulate Nox, mediating the vascular remodeling signaling in chronic cardiovascular upregulation of angiotensin II and the renin-angiotensin system [6-9]. Located predominantly in vascular adventitia, Nox4 promotes angiotensin II-induced myofibroblasts migration through H_2O_2 mediated signaling [7]. Low molecular weight specific Nox inhibitors were found to reduce vascular oxidative stress, decrease neointimal hyperplasia related to endothelial injury and limit excess platelet activation associated with atherosclerosis and endothelial dysfunction, consequently contributing to the control of formation of thrombi [11]. The common nongenomic abnormalities linking the cardiovascular system with failing kidneys do include increased serum aldosterone, associated with inflammation, proliferation, fibrosis and vascular remodeling. Mineralocorticoid receptor inhibition was shown to counteract these effects and improve insulin sensitivity in addition to well-known benefits of blockade of the renin-angiotensin-aldosterone system in CKD patients [11]. Therefore, oxidative stress was proposed as a unifying pathogenesis mechanism of RAAS-related and aldosterone-mediated chronic cardiovascular and renal injury, underlying basic abnormalities leading to cardiac arrhythmias and conduction disturbances [12].

Superoxide dismutase, glutathione peroxidase, myeloperoxidase (MPO), catalase, reduced intracellular glutathione and plasma thiol constitute antioxidant defense system that is almost uniformly altered, depleted or of decreased activity in a number of chronic diseases in addition to CKD [13]. Although the enzymatic activity does appear altered in CKD, it is related to a number of genetic polymorphisms whose predictive value for cardiovascular disease is quite murky at different stages of CKD, with various levels of eGFR. The more comprehensive alternation of antioxidant defense system is identified in the form of depleted blood serum pools of thiol redox potential, contributing to accelerated atherosclerosis [13].

Nitric oxide (NO) is a biologically active gas product of the complex enzymatic reaction catalyzed by 3 different nitric oxidase synthetase (NOS) isoforms of the diverse localization, regulation of expression, calcium signaling sensitivity relevant for the biological effects in the course of inflammation and the regulatory mechanism of vascular dilation. The endothelial isoform present generates nanomolar concentrations of NO in response to Ca^{2+} transients due to endothelial cell surface binding of agonist or increased shear stress produced by increased blood flow. Nitric oxide readily diffuses into all directions, where its is rapidly scavenged in the blood vessel lumen in a high-affinity reaction with hemoglobin or it diffuses to adjacent smooth muscle cells and binds with heme moiety of guanyl cyclase catalyzing the conversion of GMP into cGMP, ultimately leading to the dilation of blood vessel smooth muscle cells [14]. The impairment of this mechanism is apparently termed the endothelial dysfunction or inability to dilate the blood vessels via increased NO production in response to agonist or blood flow stimulation. The iNOS is responsible for high output, micromolar range of NO synthesis, that is calcium independent and it is not occurring under normal, constitutive conditions but in response to the stimulation of predominantly phagocyte cell with bacterial lipopolysaccharide or endotoxin, interleukin 1β, tumor necrosis factor-β or interferon γ, which are all proinflammatory cytokines [15]. The activity of constitutive endothelial isoform is related with endothelial dysfunction due to limited NO bioavailability, which may be engaged in the reaction with reactive oxygen leading to the synthesis of a number of reactive nitrogen species (RNS) [15]. Conversely, iNOS activity is typically related with cytotoxicity due to the interaction of high levels of NO with superoxide anion released by adjacent Nox isoforms [15]. The product of superoxide and NO reaction is peroxynitrite of the highest oxidizing potential among reactive species in human body, which is responsible for the majority of noxious effects related with oxidative stress [15]. The interaction between high concentrations of superoxide generated by Nox and iNOS-produced NO, yielding powerful peroxynitrite, are thought to constitute final effector pathways for inflammatory mediators, vascular remodeling and fibrosis [15]. Moreover, endogenous NO is able to inhibit its own synthesis to a limited extent due to its free diffusion, whereas asymmetric dimethyl-L-arginine (ADMA) and monomethyl arginine (L-NMMA) are endogenous inhibitors of all 3 types of NO synthase isoforms. Increased ADMA levels or decreased activity of ADMA degradation enzyme – dimethylarginine dimethylaminohydrolase (DDAH-1) may be linked with decreased NO mediated vasorelaxation and increased in the course of atherosclerosis and CKD [16].

Chronic inflammation and remodeling of extracellular matrix

Considering whether pathophysiological mechanisms translate into the clinically relevant associations, it is noteworthy that the majority of inflammatory parameters were altered in CKD patient populations. Plasma concentrations of high-sensitivity C-reactive protein were increased and related to left ventricular mass in CKD patients with left ventricular hypertrophy [16]. In a prospective studies, circulating ICAM-1 and VCAM-1 levels were identified as relevant predictors of cardiovascular mortality and morbidity in non-diabetic hemodialysis (HD) patients [17,18]. The entire variety of blood serum markers including MMP-9 (matrix metalloproteinase-9), t-PAI-1 (tissue plasminogen activator inhibitor-1), IL-6, NT-proBNP, IL-8 and VEGF (vascular endothelial growth factor) were demonstrated to relate with carotid atherosclerosis in CKD patients but, interestingly only IL-6 was able to significantly predict the severity of atherosclerosis [19]. Also, the significant correlation between C-reactive protein, interleukin-6, tumor necrosis factor-α soluble receptor 1, intercellular adhesion molecule-1 and decreased eGFR have been shown recently in a large cohort of ethically diverse CKD patients with eGFR < 60 ml/min/1.73 m^2 [20]. Noteworthy, tumor necrosis factor-α soluble receptors, intercellular adhesion molecule-1 and vascular cell adhesion molecule-1 demonstrated an increase in the setting of maintenance hemodialysis [18].

Recently, a novel proinflammatory atherosclerosis mediator, high mobility group box protein-1 (HMGB-1), a 30-kDa transcription and growth nuclear and cytosolic protein factor, was found increased and correlated with eGFR in CKD patients, while its usefulness as a predictor of outcome in

CKD is still being evaluated [21]. More solid research data point currently to urotensin II, originally envisaged as a potent vasopressor is an undecapeptide expressed in kidney, heart and nervous system, has been recently implicated in myocardial and renal dysfunction and found to play a cardioprotective role in coronary heart disease and chronic renal failure [22]. Its precursor is highly expressed in many human tissues including blood vessels and the kidney [23]. Urotensin II, which is a potent NO-dependent vasodilator in pulmonary vasculature, was found increased in both non-dialyzed CKD, precisely twice above the normal level, and in hemodialyzed patients, correlating inversely with sympathetic activity, neuropeptide Y and ADMA levels [22]. Urotensin II, released into peripheral blood predominantly by cardiomyocytes proportionally to the degree of ventricular systolic dysfunction, appeared to trigger cardiac hypertrophy and fibrosis [24]. Its role is assumed to counteract the increased sympathetic activity and down regulation of NO activity in ESRD. The clinical value of the malnutrition-inflammation-atherosclerosis (MIA) syndrome for long-term prediction of cardiovascular mortality was confirmed with the parameters of increased carotid intima-media thickness, CRP > 1 mg/dl and serum albumin < 3.5 g/dl, which combined predicted 5-year mortality in ESRD patients [5].

The turnover of extracellular matrix is regulated by a local and systemic recruitment of a number of metalloproteinases and tissue inhibitors of metalloproteinases (TIMPs) that combined are responsible for degradation, rebuilding and ultimately remodeling of extracellular matrix of blood vessels, heart and renal tissue [25]. Increased serum levels of MMP-2 were recently demonstrated to coincide with increased proteinuria and increased risk of atherosclerosis in patients with CKD [26]. Remarkably, the increased left atrial volume, a predictor cardiovascular events in general population, indeed appeared an independent index of inflammation, atherosclerosis and cardiovascular events also in CKD patients [27]. Progression of atherosclerosis, as evidenced with increased carotid intima-media area during the course of dialysis treatment, was associated with the accumulation of AGEs (advanced glycation end-products) in CKD patients may have a role in the pathogenesis of CVD in the HD patients [28].

At least some complex interactions between bone and vascular disease in renal failure could be explained with the abnormalities of mineral metabolism, bone matrix turnover and the apoptosis of vascular smooth muscle is involved in the ossification of the arterial wall in CDK [29]. As it is assumed currently, one of the most crucial pathophysiological events in CKD associated with acceleration of atherosclerosis involves transformation of smooth muscle and endothelial cells into an osteoblast phenotype cell. The key role is attributed to the reduced activity of blood serum fetuin A, an acute phase glycoprotein, also termed an inhibitor of vascular calcification or α2-Heremans Schmid glycoprotein. Although a decrease of blood serum fetuin A concentration by 0.1 g/l correlated with increased all-cause mortality by 13% in dialyzed patients, its predictive value in case of cardiovascular death was not that apparent [30]. Among CKD patients with GFR 33 ml/min, 40% have coronary artery calcification compared with 13% in subjects with no renal impairment [31]. Nevertheless, the mechanism of osteogenic transformation involves fetuin-A action as an antagonist of transforming growth factor-β via tyrosine kinase pathway and autophosphorylation of insulin receptor [32]. The phenotypic transformation of endothelial cells into an osteogenic phenotype is induced by bone morphogenetic proteins [33]. Bone morphogenetic proteins (BMPs) belong to the transforming growth factor-β superfamily and their increased expression was found in calcified sites within atherosclerotic plaques [34]. The serum complex of fetuin-A and matrix Gla protein (MGP) forms calciprotein particles with ionized calcium and phosphates. Matrix Gla protein is a protein inhibitor of interaction between BMP-2 and BMP-2 receptor. Matrix Gla protein, by preventing from BMP-2 binding with its receptor, acts as an osteogenic inhibitor. Increased MGP expression was characterized in endothelial cells surrounding atherosclerotic plaques [35]. Osteoprotegerin is another osteogenic inhibitor and a regulator of osteoclast activation found increased in ESRD in parallel with high CRP levels [36]. Osteoprotegerin-α appeared to be involved in the pathogenesis of atherosclerosis: stimulation of osteoclast maturation occurs due to binding of receptor activator of nuclear factor κB (RANK) with its ligand (RANKL) [29]. Osteoprotegerin-α prevents from this interaction after its binding of RANKL and it expression is regulated by several cytokines. Uremia-associated hyperphosphatemia (> 2.5 mM) was able to elicit reactive oxygen production, mitochondrial membrane damage, caspase activation and subsequent apoptosis in endothelial cell within hours [37]. Interestingly, the inhibition of the phosphate transporter on endothelial cell surface completely prevented endothelial apoptosis. Further, osteogenic processes are inhibited by increased concentrations of pyrophosphate (PPi) synthesized by enzyme nucleotide pyrophosphatase phospho-diesterase-1, which activity is crucial for PPi serum levels [38]. Also, the tissue-nonspecific activity of membrane bound alkaline phosphatase

may decrease PPi levels allowing for hydroxyappatite formation, especially in hemodialysis, which is a rapid washout of PPi and is considered specifically responsible for HD accelerated vascular calcification. BMP-2 and BMP-4 are both able to induce metastatic calcification and osteogenic differentiation of endothelial cells at the transcriptional level by the induction of transcription factors termed as msh homeobox homolog (MSX-2), Cbfa1 (core binding factor α1) and osterix in parallel with the ability of BMP-4 to induce generation of ROS and enhance oxidative stress. Expressed mainly in kidney BMP-7, in contrast to the action of BMP-2 and BMP-4, acts as osteogenic inhibitor due to its ability to increase actin expression and was found to decrease in the course of CKD [38]. The deficiency of BMP-7 is associated with elevated blood serum levels of phosphates and increased product of calcium and phosphate concentrations, ultimately leading to osteogenic transformation of endothelial cells and allows metastatic calcification to occur [38, 39]. Additionally, decreased clearance of leptin in CKD and its increased binding with hypothalamus receptors leads to the increased release of catecholamines and the stimulation of both adrenergic osteoblast receptors and osteoprogenitor bone marrow cells, which in turn stimulate ROS generation in endothelial cells and induce BMP-2 expression [40-43].

Conclusions

Chronic kidney disease and CRF provides multiple abnormalities at diverse levels spanning from blood serum biochemistry to transcription that accelerate atherogenesis including those quite specific for this disease, as it is in case of disturbed regulation of phosphorus-calcium metabolism, increased activities of retained large molecular weight proinflammatory cytokines, compounds regulating osteogenic transformation of endothelium and kidney specific proteins affecting cardiac performance [44-46].

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