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REVIEW

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Impact of inflammation and oxidative stress on vascular calcifications in chronic kidney disease

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Abstract Vascular and/or valvular calcifications in patients with chronic kidney disease (CKD) appear to indicate a poor prognosis in terms of overall survival and cardiovascular morbidity and mortality. Inflammation and oxidative stress represent new features of the arterial and/or valvular calcification process. However, only limited observational and epidemiological data are available in these areas. Therefore, the link between inflammation, oxidation and vascular and/or valvular calcifications deserves careful consideration in CKD patients, since they may become targets for the development of new therapeutic strategies.

Keywords Calcification · Chronic kidney disease · Dialysis · Inflammation · Oxidative stress

Vascular and/or valvular calcifications are frequent in the general population and are associated with high cardiovascular risk [1, 2, 3]. Calcifications of the thoracic and abdominal aorta are associated with an increased risk of cardiovascular morbidity and mortality [4, 5, 6]. Moreover, degenerative calcified aortic valve stenosis is currently the most frequent form of valvular heart disease in industrialized countries, with a prevalence of 2% in a North American population over the age of 65 years [7]. This valvular disease has various clinical presentations, ranging from benign asymptomatic aortic valve sclerosis to tight calcified aortic stenosis, which is often poorly tolerated and requires valve replacement. In 1999, the Cardiovascular Health Study prospectively followed 5,621 patients over the age of 65 years and demonstrated the negative prognostic value of aortic sclerosis [1]. With a follow-up of 5 years, patients with aortic sclerosis had nearly 50% higher risk of cardiovascular mortality and myocardial infarction, after adjustment for age, gender, other cardiovascular risk factors, and the presence of coronary heart disease [1].

The process of vascular and valvular calcification is accelerated and amplified in patients with chronic kidney disease (CKD) [8, 9]. As in the general population, the calcifications observed in CKD patients also appear to indicate a poor prognosis in terms of overall survival and cardiovascular morbidity [10, 11, 12]. Chronic micro-inflammation and oxidative stress are also commonly observed in patients with CKD [13, 14]. Inflammation and, to a lesser degree, oxidative stress have been shown to predict overall and cardiovascular mortality [13, 14]. Therefore, vascular or valvular calcifications might be one mechanism among several by which inflammation and oxidation influence the chance for survival in CKD patients (Fig. 1).

Cardiovascular calcifications are accompanied by mineralized protein matrix deposition in vessel walls or valves. These calcium-phosphate deposits are essentially localized in the media of vessel walls, but are also present on subintimal atherosclerotic plaques [15, 16]. Inflammation and oxidative stress are now recognized as integral components of subintimal atherosclerotic lesions. Moreover, recent data suggest an active cellular process leading to the deposition of an osteogenic type of extracellular matrix in the media of vessel walls [17]. Several experimental studies have demonstrated the capacity of arterial smooth muscle cells to dedifferentiate into an osteoblastic phenotype able to produce an extracellular matrix related to bone matrix [17]. It has been shown that inflammatory and/or oxidative stress molecules can amplify the smooth muscle cell dedifferentiation process. For example, in

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vitro studies have shown that oxidized low-density lipoproteins (LDL), certain pro-inflammatory cytokines [e.g., tumor necrosis factor-α (TNFα), and interleukin-1 (IL1)] stimulate dedifferentiation of smooth muscle cells into a bone phenotype [18, 19, 20, 21, 22, 23]. Parhami et al. [18] have shown a strong, dose-dependent positive effect of minimally modified oxidized LDL and different lipid peroxidation products on osteoblastic differentiation of vascular cells. It is possible that this effect is produced not only by lipid peroxidation products, but also by any oxidative stress. Mody et al. [22] found that hydrogen peroxide or xanthine/xanthine oxidase increased intracellular oxygen radicals and enhanced osteoblastic differentiation of vascular cells, and that this effect was blocked by exogenous antioxidants. Advanced glycation end products (glyco-oxidation markers) can induce osteoblastic differentiation of pericytes and could contribute to the development of vascular calcification [23]. Inversely, high-density lipoproteins (HDL) inhibit this dedifferentiation process [24]. The inhibitory effects of HDL were mimicked by lipids extracted from HDL but not by HDL-associated apolipoproteins or reconstituted HDL [24]. Interestingly, oxidation of HDL rendered them pro-osteogenic [24].

Monocytes/macrophages, which are inflammatory cells present in the calcified vascular wall, could accentuate stimulation of smooth muscle cell dedifferentiation to a bone phenotype via cell interaction and/or production of soluble factors such as TNFα [25, 26], thereby promoting vascular or valvular calcifications. Systemic inflammation may also be involved. Low concentrations of fetuin-A, a negative acute-phase protein, are associated with both an impaired capacity to inhibit calcium-phosphate precipitation in vitro and severe calcification of various organs in mice, which are fetuin-A deficient and on a mineral- and vitamin D-rich diet [27].

Conflicting data have been reported regarding the correlation between C-reactive protein (CRP) and coronary artery calcification in CKD patients [28, 29], as well as in the general population [30, 31, 32, 33, 34]. Serum CRP was inversely related to fetuin-A, and low fetuin-A concentrations in sera were associated with enhanced all-cause and cardiovascular mortality in chronic hemodialysis patients [35]. It is also possible that other inflammatory markers (e.g., TNFα, and IL1) might better correlate with coronary artery calcification than CRP. In a recent preliminary study, we observed that TNFα and IL1, but not CRP, are associated with the progression of coronary calcification in chronic hemodialysis patients (Drozdz et al., unpublished data). A direct effect of TNFα and IL1 on fetuin A production remains possible, since it has been shown that both cytokines decrease the rate of synthesis of phosphofetuin in adult rat hepatocytes in primary culture [36]. Therefore, fetuin-A, as an extracellular calcium regulatory protein, could play a role linking chronic inflammation and vascular calcification (Fig. 1).

The relationship between oxidative stress and cardiovascular calcification has not yet been firmly established

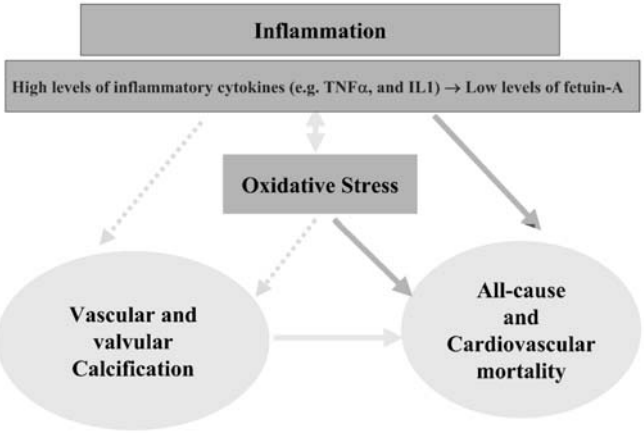

Fig. 1 Schematic link between inflammation and oxidation, vascular or valvular calcifications, and survival in patients with chronic kidney disease (*TNFα* tumor necrosis factor-α, *IL1* interleukin-1)

in CKD patients. Observational and epidemiological data are lacking. Recently we observed no relationship between lipid and protein oxidation products and the progression of coronary calcification in chronic hemodialysis patients (Drozdz et al., unpublished data). In a recent study, pentosidine (glycooxidation marker) staining and calcified deposits were co-localized in the media of cadaveric atherosclerosis-free aorta of non-diabetic hemodialysis patients [37]. Moreover, the mean medial contents of both elastin-associated pentosidine and calcium were significantly higher in hemodialysis patients than in controls [37].

In conclusion, inflammation and oxidative stress represent new features of the arterial and/or valvular calcification process. They deserve careful consideration in CKD patients, since they may become targets for the development of new therapeutic strategies.

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