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EDITORIAL

Receptor activator of nuclear factor κB ligand/osteoprotegerin axis and vascular calcifications in patients with chronic kidney disease

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Abstract

Vascular calcifications are commonly observed in patients with chronic kidney disease (CKD) and contribute to the excessive cardiovascular morbidity and mortality rates observed in these patients populations. Although the pathogenetic mechanisms are not yet fully elucidated, recent evidence suggests a link between bone metabolism and the development and progression of vascular calcifications. Moreover, accumulating data indicate that receptor activator of nuclear factor κB ligand/osteoprotegerin axis which plays essential roles in the regulation of bone metabolism is also involved in extra-osseous bone formation. Further studies are required to establish the prognostic significance of the above biomarkers as predictors of the presence and severity of vascular calcifications in CKD patients and of cardiovascular morbidity and mortality. Moreover, randomized clinical trials are needed to clarify whether inhibition of osteoclast activity will protect from vascular calcifications.

Key words: Arterial stiffness; Bone turnover; Chronic kidney disease; Osteoprotegerin; RANK ligand; Receptor activator nuclear factor κB; Vascular calcifications

Core tip: Vascular calcifications are commonly observed in chronic kidney disease patients and recently mounting evidence suggest that Receptor activator of nuclear factor κB ligand/osteoprotegerin axis controls both bone metabolism and extra-osseous bone formation. Further studies are required to establish the role of these biomarkers as predictors of the presence and severity of vascular calcifications and of cardiovascular morbidity and mortality. Moreover, randomized clinical trials are needed to clarify whether inhibition of osteoclast activity will protect from vascular calcifications.

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INTRODUCTION

Cardiovascular disease (CVD) remains the leading cause of excessive morbidity and mortality for patients with chronic kidney disease (CKD) and particularly those with end-stage renal disease (ESRD) on renal replacement therapy with either hemodialysis or peritoneal dialysis[1]. Vascular calcifications are also commonly observed in CKD and are now considered part of the syndrome chronic kidney disease-mineral and bone disorder (CKD-MBD), the pathogenesis of which has accumulated great research interest the last years. In CKD patients calcifications in both intimal (atherosclerotic) and medial lamina (arteriosclerotic) often coexist, appear early and follow an accelerated course. Particularly the latter is an almost ubiquitous feature of arterial tree in chronic uremia and a major contributor to the accelerated arteriosclerosis and to the increased all-cause and CVD mortality in these patients populations[2].

The presence of vascular calcifications in CKD has been associated with a number of traditional risk factors including older age, hypertension, dyslipidemia and diabetes mellitus which are highly prevalent in this population, as well as uremia-related risk factors including chronic inflammation, oxidative stress and mineral and bone disorders which are currently under investigation. Of note, mineral alterations (hypercalcemia, hyperphosphatemia) and disorders of bone metabolism (both secondary hyperparathyroidism and adynamic bone disease) are mainly associated with the development and progression of medial but not intimal calcifications[3].

It is now well recognized that vascular calcification is not simply a passive physicochemical process of calcium phosphate deposition but a highly regulated active process similar to normal bone modeling. Moreover, recent evidence suggests that the phenotypic transdifferentiation of vascular smooth muscle cells (VSMCs) into osteoblast-like cells is a key pathogenetic event in the osteogenesis of the vascular wall. A variety of regulatory factors and molecular pathways of this process which regulate bone turnover and/or mineralization have been identified[3]. Although their relative importance in different disease states appear still incompletely understood emerging evidence suggest that the receptor activator of nuclear factor κB (RANK)/RANK Ligand (RANKL)/osteoprotegerin (OPG) system that plays essential roles in the regulation of bone metabolism is also involved in extra-osseous bone formation[4].

RANK/RANKL/OPG PATHWAY

RANK, RANKL and OPG are members of the tumor necrosis factor (TNF) superfamily which were originally studied as factors involved in bone tissue and immune system physiology. However, recent studies revealed that they also constitute a link between bone metabolism and vascular pathophysiology by controlling simultaneously bone remodeling and vascular calcification mechanisms[5].

RANK/RANKL/OPG signaling pathway regulates osteoclast differentiation and activation. RANKL is a transmembrane protein consisted of 316 aminoacids, which is expressed on osteoblasts, stromal and T cells in areas of bone remodeling. RANKL binds to its receptor RANK, a 616 amino acid type Ⅰ transmembrane protein which is expressed on the surface of myeloid cell lineages like osteoclasts, monocytic and dendritic cells. The above activates multiple intracellular signals, including activation of the c-jun N-terminal kinase and nuclear factor κB pathways that regulate the differentiation, function and survival of these cells. A variety of factors including hormones, cytokines and growth factors regulate its expression. Thus, parathormone (PTH), TNF-α, calcium, corticosteroids and several interleukins (IL-6,-11,-17) increase RANKL expression on osteoblasts, whereas transforming growth factor-β (TGF-β) decreases it[3,5]. OPG is a soluble glycoprotein widely expressed in most human tissues including bone (osteoblests, mesenchymal stem cells), immune cells (T and B cells) and vessels (endothelial and VSMCs). It acts as a decoy receptor and binds to RANKL, thereby not allowing the activation of RANK and inhibits its regulatory effects on inflammation, skeletal and vascular systems[5]. OPG also has anti-apoptotic actions, as it binds and deactivates the TNF related apoptosis-inducing ligand (TRAIL), which is expressed by many cell types, including VSMCs, and can also lead to ectopic mineralization[5]. OPG's expression is increased by vitamin D, TNF-α, IL-1α, IL-6, IL-11 and IL-17, bone morphogenic protein-2, TGF-β and estrogens, whereas it is reduced by PTH, corticosteroids and prostaglandin E2[5].

Mounting evidence suggests that the RANK/RANKL/OPG axis exerts actions simultaneously on endothelial cells and VSMCs and participate in multiple processes that regulate vascular calcification. The implication of this system in vascular pathophysiology is supported by the expression of these molecules in the normal cardiovascular system (heart, arteries and veins). Both endothelial cells and VSMCs constitutively express OPG, and their levels are particularly high in aortic and renal arteries. Furthermore, OPG is physically associated with factor Ⅷ-von Willebrand factor complex localized in the Weibel–Palade bodies of endothelial cells, it is rapidly secreted in response to inflammatory stimuli and inhibits osteoclastogenesis and promotes endothelial cell survival[6] through neutralization of pro-apoptotic TRAIL[5]. In contrast, RANKL and RANK are frequently undetectable in normal vessels and non-calcified arteries or valves[5]. However, osteoclast-like RANK(+) cells were found close to VSMCs on calcified vascular walls and

expression of both RANK and RANKL was reported on the vascular wall, in calcified areas[7].

Several studies suggested that OPG's expression might reflect a protective mechanism against the vascular calcifications. Thus, over-expression of OPG leads to osteopetrosis, while its gene deletion, increases bone metabolism and leads to osteoporosis and medial calcifications in the aorta and the renal arteries[8,9]. Moreover, OPG administration in laboratory animals, was reported to potently reduce both bone resorption activity and medial arterial calcifications induced by administration of toxic doses of vitamin D or warfarin[10]. These findings, together with the fact that OPG is expressed in the vascular wall under normal circumstances, indicate that the endogenous production of OPG prevents the ossification of the vascular wall and favors bone mineralization. In accordance with the above, OPG was detected in matrix vesicles, nanoparticles that are released from VSMCs with the capacity to nucleate mineral, which directly inhibited deposition of hydroxyapatite in the vascular wall[11].

OPG AND VASCULAR CALCIFICATIONS IN CKD PATIENTS

In the general population, studies have demonstrated that high levels of OPG are correlated with cardiovascular risk[12]. In CKD patients, it has been shown that OPG levels significantly increase along with the decline in GFR and are reduced after a successful renal transplantation[13]. However, studies examining the association of OPG levels with the presence and extent of cardiovascular calcifications are relatively limited and their results were sometimes inconsistent. Thus, in non-dialyzed CKD patients a cut-off value of OPG level was found to predict the presence of coronary artery calcifications (CAC) assessed by chest multidetector computed tomography[14]. In addition, a very recent study in CKD patients reported a significant association between high OPG levels and CAC independently of other risk factors including age, gender, diabetes, body mass index and smoking habits[15]. In transplanted patients CAC at baseline, but not 1 year after renal transplantation, was found to be independently associated with baseline OPG whereas post-transplant CAC progression was predicted by baseline CAC score[16]. In contrast, another study in transplanted patients reported that OPG levels were significantly and independently associated with the progression of aortic calcification index (ACI) assessed by lateral lumbar x-ray during a two-year follow-up period[17]. In adults and children with ESRD on hemodialysis, studies demonstrated a significant independent correlation between OPG levels and CAC[18,19]. Similarly, another study showed an association between OPG and ACI assessed by computed tomography scans independently of traditional and uremia-related risk factors[20]. In addition, high OPG levels have been found to correlate with faster progression of aortic calcifications during a 5-year follow-up[21]. Finally, several studies in patients with various CKD stages as well as in renal transplant recipients demonstrated that OPG levels were a significant independent predictor of all-cause and cardiovascular mortality during the follow-up period[22-26]. However, one study in ESRD and pre-dialysis CKD patients showed that renal function rather than OPG levels were mostly associated with the progression of aortic and coronary calcifications[27], whereas another one correlated elevated OPG levels only with moderate CAC[28].

Regarding the association of OPG with markers of medial calcifications such as arterial stiffness and pulse wave velocity (PWV), the results are also sometimes controversial. A study in non-dialyzed CKD patients demonstrated a strong relationship between serum OPG and arterial stiffness independent of many potential confounders including traditional cardiovascular risk factors, abnormal bone and mineral metabolism, and inflammation[29]. Similarly, in hemodialysis patients OPG levels were found to be strongly associated with aortic or carotid-to-femoral PWV independently of traditional and uremia-related risk factors including markers of inflammation[25,26,30]. However, other studies in adults and children on hemodialysis treatment were unable to confirm the above findings[19,31].

As it was previously noted, the exact role of OPG in the VC process remains unclear. Since OPG inhibits osteoclast activity and OPG knockout mice develop arterial calcifications, it appears reasonable to assume that it plays some regulatory and/or inhibitory role against ectopic calcifications and thus its increased levels could be interpreted as an attempt to compensate for the ongoing calcification process[9-11]. The above speculation contradicts the reported association of high OPG levels with cardiovascular mortality[22,23,25,26] and moreover, increase of OPG levels could be due to its production by calcified vascular cells in conditions of diffuse calcification. Thus, it remains to be clarified whether the elevated OPG levels induce arterial wall sclerosis or represent a compensatory mechanism to prevent further arterial damage or are just a marker of initiation of vascular calcification process[4].

RANKL AND VASCULAR CALCIFICATIONS IN CKD PATIENTS

The exact role of RANKL in the development of cardiovascular calcifications and CVD remains to be identified. Some studies showed a correlation of RANKL levels with future cardiovascular events[32], but the probable association between vascular calcifications and RANKL levels has been scarcely investigated so far. A prospective study in 3250 Framingham Study participants reported that RANKL concentrations were inversely associated with multiple cardiovascular risk factors, including smoking, diabetes, and antihypertensive treatment, but that were not related with CAC or incident CVD or mortality during

a mean follow-up of 4.6 years[33]. However, a study in hemodialysis patients found that change in OPG levels after 1-year were an independent predictor of CAC score progression during the same period[34]. Of note, RANKL levels, in contrast with OPG, are low in CKD patients[35]. Considering the fact that OPG and RANKL have opposite functions in bone resorption, OPG/RANKL ratio could be considered a better biomarker of bone metabolism and consequently a better predictor of the presence and severity of vascular calcifications[35]. In agreement with the above hypothesis, the aforementioned study in hemodialysis patients, showed that baseline OPG/RANKL ratio was significantly higher in patients whose coronary calcifications progressed during the one year follow up period[34].

CONCLUSION

Despite the progress and the knowledge acquired within the previous years, the pathogenesis of vascular calcifications remains to be fully elucidated. Recently, mounting evidence suggest that RANKL/RANK/OPG system which controls bone metabolism plays a significant role in this process. Alterations of RANKL/OPG axis appear a promising prognostic biomarker of the initiation and progression of vascular calcifications in CKD patients and of cardiovascular morbidity and mortality. Further studies are required to establish this theory and to identify the exact role of these two biomarkers in CKD patients. Moreover, randomized clinical trials are needed to clarify whether inhibition of osteoclast activity will protect from vascular calcifications.

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