



Vascular Calcification in Chronic Kidney Disease: An Updated Physiopathology Approach

Valdeviño JO¹, Bellincanta GA¹, Soares MCP¹, Lara LM², Coelho GMM² and Sampaio MF*

¹Department of Cardiology, São Camilo University, Brazil

²Department of Cardiology, Dante Pazzanese Institute of Cardiology, Brazil

Abstract

Introduction: Vascular calcification (VC) is a physiopathological process of utmost importance at the clinic nowadays, being a cardiovascular risk factor and closely correlated with chronic kidney disease (CKD).

Objective: To describe the physiopathology of the vascular calcification involved in CKD, to expose the risk factors and disorders related to it and to correlate the function of the biomolecular markers involved in this process.

Methodology: Search publications indexed in the Lilacs, Scielo and Medline's databases (by PubMed), using Boolean operators 'and' and 'or'. Works selected from the last fifteen years in English, Spanish and Portuguese, involving adults, regardless the gender. Works regarding the treatment of the pathologies were excluded.

Results: A total of 567 scientific articles were found, whose summaries were appraised. After application of exclusion criteria, 74 articles were used to base introduction and discussion, and 18 of them referred specifically to markers related to VC and CKD. There were several markers and genetic loci identified, registered and correlated, as inducers or inhibitors of VC, in a clinical condition.

Conclusion: The several studies refer to specific markers separately, not establishing clear relation among them. Although some address the genetic subject of the process, they are limited to specific polymorphisms. The physiopathology of VC still presents several gaps; it is necessary new studies in order to correlate inducers and inhibitors of the process, as well as to explore its clinical application.

Keywords: Vascular calcification; Chronic renal disease; Chronic renal failure; Kidney failure

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*Correspondence:

Marcelo Ferraz Sampaio, Dante Pazzanese Institute of Cardiology, 500, São Paulo, SP, Brazil, Tel: (011) 5085-6122;

E-mail: msampaio@cardiol.br

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Introduction

The genetics, the habits and an individual's lifestyles are capable to predispose him to several non-transmissible chronic diseases. Among them, cardiovascular pathologies such as acute myocardial infarction (MI), stroke (CVA) and kidney lesions [1]. Besides that, the mortality for such diseases rises gradually due to the combined effect of the increase of the populations and its aging [2]. Only in Brazil, in 2009, 192.586 deaths happened for cardiovascular diseases (CVD) [3], while in the United States, in the same period, that number was of 610.000 deaths, representing 1 in 4 deaths in the country [4]. In that scenario, it must be pointed out the relevance of the risk factors for the vascular calcification (VC), key process in the genesis of these chronic diseases [2,5], as: age, vascular aging [6], diabetes mellitus (DM) [7], sedentary lifestyle [8], dyslipidemia [9], smoking [10,11], menopause [12], osteoporosis [12-16], and alcohol abuse. The calcification process is seen, still, as predictor of systemic arterial hypertension (SAH), ventricular hypertrophy, vascular rigidity and other cardiomyopathies [5,17,18]. The VC is a complex process, that it is characterized by the thickening and loss of elasticity of the arteries's muscular walls and it involves not only the simple precipitation of concentrations of supersaturated phosphate and calcium in the extracellular (mineral stage), but also a process strongly regulated and mediated by cells, including apoptosis, osteochondrogenic differentiation and elastin degradation (cell stage) [19]. Among the diseases that correlate to VC, it stands out the chronic kidney disease (CKD), defined as the presence of structural renal damages and deficit of renal function manifested in chronic way. Patients with CKD, frequently, present VC, considered a strong and independent cardiovascular risk factor, although its mechanisms are still incompletely understood. It is known that in the terminal phase,

Table 1: Markers related to vascular calcification.

Relation with calcification	Appraised Fator
Vascular calcification's potentializers / inducers	OPG [32], RANK [33], Wnt-beta-catenin [34], BMP [35], CD14 / IL-6 / TLR4/ INF gamma / TNF / IL-1 [36], IL-8, IL-13 [37], MSX2 [38], Kinase p38 [39], I-CAM [40], Osteocalcin [41], MMP2 [39,42], SM22a e SM-MHC [43]
Calcification's inhibitors	MGP [44], Fetuin [45], RANKL [46]
Induce osteoblast differentiation	BMP2 / BMP4 [35], Runx2 [47], CBFA [48]
Osteoblast precursors cells	NFk-beeta. [46]
Inconclusive markers	Dickkopf (DKK1) [49], Sclerostin [50]

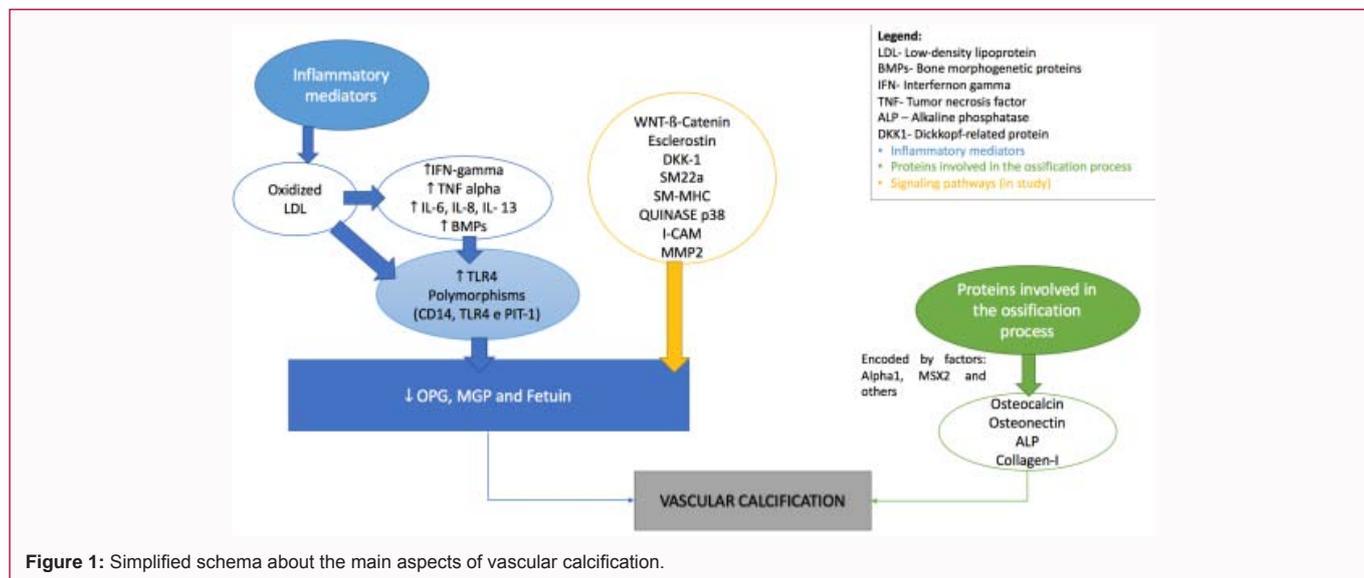


Figure 1: Simplified schema about the main aspects of vascular calcification.

the kidneys are not able to maintain the systemic metabolic normality [19], favoring processes as the calcification. Besides that, the CKD has its role in the VC's physiopathology. In Brazil and in the world, CKD is considerate as a public health problem. IT is spent, annually, about R\$ 1.4 billion on dialysis and kidney transplant programs in Brazil [20,21]. According to the Medicare Foundation, an American program, the number of patients in the end-stage-renal disease (ESRD) increased from about 10.000 patients in 1973, to 661.648 since 2013, increasing the expenses considerably in health, mainly with dialectic patients [22,23]. Nowadays VC in patients with CKD is not quantified routinely, so that the detection is, constantly, an image checking or because the manifestation of the disease. The guidelines (Global Kidney Disease Improving Outcomes - KDIGO 2012) recommend its tracking just in specific cases as patients with significant hyperphosphatemia or potential transplant recipients [24]. Several approaches, seeking the control of the calcification in the context of CKD, were already proposed, among them: the control of the hyperparathyroidism [25-27], the kidney transplant [28], the biophosphonates [29,30] and calcium channel blockers, the subtotal parathyroidectomy [31]. Thus, the present study aims to describe, shortly, the physiopathology of the vascular calcification involved in CKD, show the risk factors and disorders related to it, and write about the biomolecular markers's role involved in this process.

Methodology

The present study is about a literature revision accomplished by searching of publications indexed in the Lilacs, Scielo and Medical Literature and Retrieval System Online (MEDLINE), this last one by the PubMed's interface. Boolean operators "and" and "or" were used, and the following search descriptors: "vascular calcification", "chronic

renal disease", "chronic renal failure" and "kidney failure". Using the options of advanced search, works published in the last fifteen (15) years (2001 to 2016) were selected, in English, Spanish or Portuguese, regardless their country or origin place. Articles on treatment of the several pathologies related to VC were not included, only the ones which the samples involved adult patients, independent of gender or education, were accounted. Besides the articles, bibliographical references published in the last ten (10) years were also used.

Results

Starting from the established criteria, the bibliographical search resulted in 567 scientific articles, whose summaries were appraised by the authors. After application of exclusion criteria (articles were excluded because they did not match to the proposed subject and/or to the established inclusion criteria), 74 articles were used to base introduction and discussion, and 18 of them referred specifically to markers related to VC and CKD. The data obtained after analysis of the 18 selected articles are shown in Table 1. Several studies tried to establish better the components involved in the process of VC. Several markers and genetic loci related to the calcification and CKD were identified; however the signaling pathway that involves this process is still little explored and poorly defined. Among the markers described as inducers of VC, there were citations about: osteoprotegerin (OPG), receptor activator of nuclear factor kappa B (RANK), Wnt-beta-catenin, bone morphogenetic proteins (BMP), cluster of differentiation 14 (CD14), interleukins 1, 6, 8 and 13 (IL-1, IL-6, IL-8, IL-13), toll-like receptor 4 (TLR4), interferon gamma (IFN-gamma), tumor necrosis factor (TNF), MSX2 gene, kinase p38, ICAM, osteocalcin, matrix metalloproteinase 2 (MMP2), SM22a gene and "Smooth Muscle-Myosin Heavy Chain" (SM-MHC) (Table 1).

Other markers described in the studies were associated with the osteoblast differentiation induction and to precursor osteoblast cells: bone morphogenetic proteins 2 and 4 (BMP2 and BMP4), NF- κ B, runt-related transcription factor (Runx2) and CBFA1. Some markers in the study were, still, considered as inhibitors of VC: Gla proteins (MGP), fetuin and ligand of the receptor activator of nuclear factor kappa B (RANKL) (Table 1).

However, the works elaborated by Hampson et al. [49] and Kanbay et al. [50], evaluating, respectively, the Dickkopf (DKK1) and sclerostin markers, are inconclusive (Table 1).

Discussion

There are important components in CKD that, by themselves, they lead to favorable scenery to VC. Among them, the dialysis is an important contributing factor. It was demonstrated that 92% of the patients presented VC after doing dialysis about 16-year-time in average [51]. Besides that, changes related to calcification are detected by computed tomography (CT) in more than 80% of the dialytic patients [52-54]. The visceral calcification is present in about 79% of those patients, which 29% of them present heart calcifications [32]. Thus, the most common cause of death in dialysis is, exactly, the cardiovascular disease [17,33,55-57], that includes sudden deaths due to the calcification of coronary arteries.

Concerning the changes in the renal filtration, it is known that the small degrees of resulting hyperphosphatemia increase the secretion of fibroblastic growth factor, releasing the bone calcium stocks and accelerating the VC. The phosphorus stimulates the density lipoproteins (LDL) as well as the receptor PIT-1 of the vascular smooth muscle cells, making them to assume the osteoblast's functions [58].

In CKD, the process of VC happens in two different ways. About the calcification of the middle layer, it is known, partly, about its relation to serum vitamin D increases, phosphate and calcium. Rarely, it is also listed the inflammation or lipid deposition. It is like the membranous bone formation, in which mesenchymal cells differentiate directly into osteoblasts without an intermediate cartilaginous template. On the other hand, the calcification of the intima usually comes from an inflammatory process and it would correspond to an advanced atherosclerotic manifestation. Its process looks like the endochondral bone development, in which the mesenchymal cells, first become in chondrocytes and only later are calcified. Besides that, this kind of lesion reduces significantly the endothelial functions and it has a closer relation to cardiovascular mortality [16,59]. Although controversial, some scientists believe that the calcifications can serve, in fact, to stabilize atherosclerotic plaques and to reduce their rupture [60]. The VC, associated or not with CKD, has a complex physiopathology, corresponding, in short, to an active extra-endochondral ossification process [61]. Its main aspects can be observed in Figure 1.

The VC process looks like, in short, to the physiologic ossification process. The necessary stages for it happens involve proteins associated with the ossification process, such as osteocalcins, osteonectin and alkaline phosphatases (ALP), besides the significant increase of collagen-I in the vascular wall, that, later, differs in osteoblasts. Among the stimulants of the ossification process, Alpha-1 and MSX2 factors are mentioned, that allowed this transcription [62]. The calcification can be initiated by inflammatory mediators from oxidized LDL lesion responses. Mediators as TNF-alpha, IFN-gamma, IL-6, IL-8, IL-13, besides the polymorphisms in CD14, TLR4 [63] and

PIT-1 [40], which regulate in a positive way genes associated with the bone mineralization. Likewise, it was noticed that the increase of these factors would be responsible for the loss of inhibitors of bone matrix as osteoprotegerin (OPG), Gla proteins [64] and Fetuin, that would intensify the vascular calcification [49,65]. Besides that, the oxidized LDL lesion answer is capable, still, of amplifying the bone morphogenetic proteins (BMP), and they contribute with the oxidative stress, reducing the calcification inhibitors [66]. Another way of ossification induction, still in study, is the antagonist signaling pathway Wnt- β -catenin, Sclerostins and Dickkopf-1 (DKK-1), whose structures are secreted by osteocytes [67-69]. Wnt- β -catenin has a role in the regulation of the bone homeostase [70]. They are also considered inducers of vascular calcification: SM22a, SM-MHC [44], kinase p38 [39], ICAM [40] and MMP2 [39,42]. It is known that, among the biomolecular signalings, OPG competes against RANKL as ligand of receptor of NF- κ B and RANK, both of them found in the precursory osteoclasts cells. There is described, also, the necessary mechanisms to promote the appropriate cellular differentiation. Among them, it is important to point out the macrophage exposition to calcium phosphate crystals causing internalization in vacuoles [71,72]. Finally, it is possible that there is a stimulus to TNF-alpha [36], IL-1 and IL-8 [72], through dependent protein C, inducing the osteoblastic differentiation in smooth muscle cells. The osteoblastic differentiation of fibroblasts and macrophages could be made by the activation of RUNX2 [44]/CBFA1 [45] proteins receptors. In that interim, it is noticed that the pathways are still analyzed in an independent way, detaching inducers, inhibitors or inconclusive markers separately, however with detected action. A study that describes in detail such pathways is not found, in the same work.

Conclusion

Before the exposed, it is observed that there is little approach in the literature regarding the prevalence of the CKD problems and vascular calcification in inpatients at big hospitals, the relation of those problems amongst themselves, with socio-demographic variables, familiar and medical history.

Likewise, it is possible to point out that the genetics and the living habits evidence the appearance of CKD associated with VC by the inducer and inhibitor calcification agents. The several published studies deal on punctual markers separately of the vascular calcification process, without establishing clear direct relation among them. Some studies approach the genetic subjects related to the process, however, once again, choosing specific polymorphisms. Other studies deal just on the diagnoses and/or therapeutic aspects related to CKD and VC, without considering the biomolecular implications involved, though.

The VC process still presents a lot of gaps in its unfolding, being necessary new studies, more integrated among clinical, surgical and biomolecular aspects, seeking to correlate the vascular calcification inducers and inhibitors' action already described, as well as to identify other decisive factors of the process.

From such progresses, understanding better the VC process in CKD, it could open up field to work on/with the effective prevention, developing new therapeutic strategies and markers prognostics, and occasionally, to use minimally invasive interventions for reducing the number of chronic patients, reducing the public health costs related to the maintenance of CKD and comorbidities related to the VC process.

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