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Review

Where do we stand on vascular calcification?

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ABSTRACT

Vascular disease, such as atherosclerosis and diabetic vasculopathy, is frequently complicated by vascular calcification. Previously believed to be an end-stage process of unregulated mineral precipitation, it is now well established to be a multi-faceted disease influenced by the characteristics of its vascular location, the origins of calcifying cells and numerous regulatory pathways. It reflects the fundamental plasticity of the vasculature that is gradually being revealed by progress in vascular and stem cell biology. This review provides a brief overview of where we stand in our understanding of vascular calcification, facing the challenge of translating this knowledge into viable preventive and therapeutic strategies.

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1. Introduction

We are approaching an understanding of vascular calcification, which was described in exquisite detail already in the late 19th and early 20th century [1–3]. Those early studies predicted and posed the questions that are still actively being studied today. Ectopic bone formation was commonly found in the vascular wall, and included the presence of osteoblasts- and osteoclast-like cells, osteoid, and fully formed bone with marrow spaces. Furthermore, the proximity of calcified areas to penetrating capillaries was noted as well as "metaplasia" of connective tissue into bone tissue, suggesting links to stem cells and a relationship between vasculature and bone. These findings posed questions on the origin of the calcifying cells, whether derived from the vascular wall itself or the circulation, cells that had according to Bunting [1] retained "into late life embryonic characteristics" and were "capable of a diverse development under appropriate stimuli".

Vascular calcification frequently emerges as a complication of disorders such as atherosclerosis and diabetic vasculopathy, indicating that an imbalance in the vascular wall is a prerequisite for triggering calcification. It also suggests that vascular calcification could be restricted by controlling the factors that provoke vascular disease, such as hyperlipidemia, diabetes and hyperphosphatemia. Most likely, preventive treatments would be aimed at the entire vasculature and promote the overall cardiovascular health. However, there would also be situations where a targeted approach might be of value, such as a simple reversal of vascular calcification in a particular segment of a vessel or a cardiac valve. The epitome of this would be the softening of aortic valves by non-surgical methods, which has the potential of improving the quality of life for numerous individuals, reducing health care costs, and in some cases saving lives. However, at this time, there is no effective preventive or targeted treatment for cardiovascular calcification.

Several things need to be considered when developing interventions aimed at vascular calcification, including the type of vascular calcification, the origins of the calcifying cells, and the characteristics of signaling pathways that regulate vascular calcification. Here, we provide a brief summary of the vascular calcification field, to serve as a primer for additional studies.

2. Diversity of vascular calcification and relationship to vascular disease

Initially, as vascular calcification became a topic of interest, all calcification was treated equally. However, it was soon recognized that some calcification existed in the form of remodeled ectopic bone, whereas other calcification consisted of mineralized matrix, still seemingly untouched by the remodeling forces of osteoblast- and osteoclast-like cells. Several patterns of calcification, which may exists in isolation or in combination, are currently known to exists and relate to various pathological conditions (Table 1). The calcification depends on the type of vessel, the disease that affects it, and what layer of the vascular wall is targeted by the disease. Basically all vascular layers can be affected by calcification, giving calcification a highly diverse face.

Table 1
Location of cardiovascular calcification.

Location	Disease	Reference
Systemic arteries: Intima	Atherosclerosis	[4,6]
Systemic arteries: Media	Media sclerosis (Mönckeberg's disease)	[8]
	Porcelain aorta	[12]
	Coral reef aorta	[14]
Internal elastic lamina	Variant of media sclerosis	[9]
Pulmonary arteries	Probable media calcification	[15]
Arterioles	Calcific uremic arteriolopathy (calciphylaxis)	[16]
Cardiac valves	Aortic stenosis, aortic sclerosis	[17,18]
Myocardium	Myocardial calcification	[19,20]

2.1. Systemic arteries

Most commonly, calcification affects thick-walled elastic arteries in the systemic circulation (Fig. 1), which are the targets of atherosclerosis and media sclerosis. Atherosclerosis is an inflammatory disorder promoted by a number of different risk factors, including hyperlipidemia, hypertension, diabetes, and tobacco use [4]. The atherosclerotic lesions develop in the arterial intima, often at specific locations that are subjected to disturbed flow such as branch points [5]. The calcification usually occurs at the base of the lesion, in proximity to the media. The lesions may show evidence of fully remodeled bone, cartilage metaplasia, adipose tissue, and bone marrow elements [6]. For example, cartilage metaplasia is a well-known phenomenon in the innominate arteries of apolipoprotein E (*Apoe*) null mice [7].

Media sclerosis, also referred to as Mönckeberg's disease, is classically associated with diabetes, chronic kidney disease and aging [8]. The calcification occurs along the elastic lamellae in the media, but may also involve the internal elastic lamina [9]. Signs of inflammation are rare in media sclerosis in contrast to atherosclerosis, although both frequently co-exist. How the absence versus the presence of inflammation influences calcification is poorly understood. Hyperphosphatemia, a hallmark of chronic kidney disease, is strongly associated with media sclerosis [8,10]. Pediatric patients with renal failure appear to be particularly sensitive to develop vascular calcification, possibly due to the still immature state of their vasculature. Systolic hypertension is usually worsened by the increased arterial stiffness associated with calcification, which in turn may further promote vascular osteogenesis. It has been shown that increased matrix rigidity can direct cells along the bone lineage [11], which would reinforce calcific and hypertensive changes.

Porcelain aorta is severe circumferential aortic calcification, which is limited to the ascending aorta and aortic arch and involves the aortic media [12]. It poses significant problems during cardiovascular interventions such as valve surgery by limiting cross-clamping of the ascending aorta. Interestingly, the location is similar to that of osteochondrogenesis observed in *Smad6* null mice [13]. Coral reef aorta is another rare type of calcification [14], where the calcifications protrude into the lumen, predominantly in the posterior thoracic and abdominal aorta.

2.2. Pulmonary arteries

The pulmonary arteries are less affected by vascular calcification than the systemic arteries, likely due to a variety of reasons, such as exposure to lower blood pressure in the pulmonary circulation. Indeed, calcification of the pulmonary artery is a known consequence of longstanding pulmonary artery hypertension [15].

2.3. Arterioles

Calcific uremic arteriolopathy, also referred to as calciphylaxis, is a rare but serious disease that occurs mainly in patients with end-stage renal disease. It obliterates the lumen of small arteries and arterioles, and may result in life-threatening soft tissue necrosis. Recent data suggest that it involves an osteogenic process driven by bone morphogenetic protein (BMP)2 signaling [16].

2.4. Cardiac valves

One of the clinically most significant types of calcification is aortic valve calcification associated with the development of aortic stenosis. It has many similarities to vascular calcification in regards to regulation [17], but may also exhibit features unique to the valves. Aortic valve