

The Predictive Value of Circulating Osteopontin in Vascular Calcification and Cardiovascular Risk

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Abstract

Vascular Calcification (VC) is the major contributors of Cardiovascular (CV) morbidity and mortality in patients with established Coronary Artery Disease (CAD), diabetes mellitus and Chronic Kidney Disease (CKD). Amongst several factors in abundant involved in the molecular mechanisms of regulation of ectopic calcification, Osteopontin (OPN) appears to be promised, while its role in the VC is controversial. OPN is chemokine-like matricellular phosphor glycol proteins with abilities to regulate inflammation, bone formation, hematopoiesis, and angiogenesis. It is known that the elevated circulating level of OPN may independently predict VC in subjects with established CAD, diabetes mellitus and CKD. The peak concentration of OPN in peripheral blood used to assay aimed to assume the risk of the CV-related clinical outcomes. The editorial recaps our knowledge regarding OPN as a biological marker of VC with possible predictive value.

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Vascular Calcification (VC) remains a leading Cardiovascular (CV) risk factor in patients with established Chronic Kidney Disease (CKD) and diabetes linking CV death, accelerated atherosclerosis and dysregulated ectopic bone remodeling [1, 2]. The basic underlying mechanism of VC development affect phenotypic transformation of Vascular Smooth Muscle Cells (VSMCs) into osteoblastic-like cells through excessive oxidative stress, high phosphate-induced α -actin protein content and core-binding factor alpha-1 mRNA

expression, imbalance between fibroblast growth factor 23 and Klotho, transforming growth factor-beta-induced phosphorylation of Smad2/3 gene expression, bone morphogenetic protein 2-induced VSMC apoptosis and autophagy, etc. [3-6]. Whatever initiated stimuli of the development of osteoblastic-like cells including inflammatory activation, high phosphate level, impaired glucose level, the final result is calcium deposition in vascular media enhancing bone mineralization key gene expression in phenotypic changed VSMCs [7].

The one of the factor, which plays a crucial role in the calcium deposition in VSMCs and VC through a mechanism involving the Wnt/ β -catenin pathway and fibroblast growth factor 23, is Osteopontin (OPN). OPN as a member of a chemokine-like, matricellular phosphoglycoproteins belongs to the small integrin binding ligand N-linked glycoprotein superfamily, which is involved in bone formation, hematopoiesis, vascularization and neo angiogenesis [2]. The role of OPN in VC is uncertain and controversial. On the one hand, it is well known that OPN is upregulated in endothelium in senescence, atherosclerosis, and vasculopathies various origin. OPN may induce autophagy via binding with its receptor integrin $\alpha\beta3$ and sustaining FoxO3a stability [8] sustaining osteogenic gene expression [9]. OPN may modulate angiotensin II-induced inflammation, oxidative stress, and fibrosis of the kidney [10]. Finally, there is a large body of evidence from several genetic animal studies that OPN is an enhancer of atherosclerosis due to enhance inflammatory changes in the plaques [11]. On the other hand, OPN counteracts osteogenic conversion of VSMCs as a part of a compensatory mechanism to mitigate VC [2, 12], prevent endothelial dysfunction [13], protects against inflammation [14] and improved endothelial repair [15]. Moreover, OPN is able to

regulate the VSMC survival signals via the binding of growth arrest-specific gene 6 to its cognate receptor Axl and further Akt activation, resulting in attenuated survival and suppressed apoptosis [16]. Overall, the expression of OPN in the vessel wall as well as in other ectopic sites of calcification may occur prior to deposition of calcium/phosphate precipitation that optionally confirms the regulatory role of OPN in this process [17].

Recent clinical studies have shown that the elevated circulating level of OPN independently predicts VC in subjects with established coronary artery disease [18], diabetics [19], patients with CKD [20] and also associates with increased risk for major adverse cardiovascular events [21, 22]. Interestingly, OPN may elevate in a course of a calcification processes affected valves and their roots beyond traditional CV risk factors [23] and even established CV disease [24]. However, everything is not uniquely identified for OPN. Gluba-Brzózka et al., (2016) have reported that at the early stage of the CKD the CV risk has not associated with OPN concentration even when contractile cardiac dysfunction, mitral and aortic valve calcification were determined [25]. In contrast, Sponder et al., (2016) [26] found that lower levels of OPN in physically active patients with angiographically established CAD might be a sign of attenuated angiogenesis and decreased inflammation and VC. Therefore, there is evidence that the over expression of OPN in endothelium has strongly associated with parameters that are characteristic of unstable and inflammatory atherosclerotic plaques in diabetics with critical limb ischemia [27]. Thus, the predictive value of elevated OPN in different patients' cohorts has not guessed equal and requires more investigations in future. Whether circulating OPN level could serve as a marker for monitoring VC and atherosclerosis severity is not fully clear, because of the predictive value of dynamic of its concentration for a while is uncertain and peak concentration of OPN does not well associate with CV outcomes and prognosis [28, 29].

In conclusion, the role of OPN as a marker of CV event and disease in general population is not still understood. Additionally, elevated level of OPN might be used as predictor of asymptomatic atherosclerosis and VC as well as future CV outcomes amongst individuals at higher CV risk. The continuous monitoring of circulating level of OPN does not met strong scientific evidence and probably might postpone in a while till large clinical studies regarding this issue would be completed.

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