Osteopontin, coronary calcification, and cardiovascular events: future diagnostic and therapeutic targets for disease prevention?

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This editorial refers to 'Prognostic significance of plasma osteopontin levels in patients with chronic stable angina'† by P. Minoretti et al., on page 802

Minoretti et al.1 describe the independent prognostic significance of plasma osteopontin (OPN). OPN was measured in baseline plasma samples from 799 patients with stable angina pectoris and angiographically documented coronary artery disease (CAD). Participants were prospectively followed for a median of 2.7 years. The primary study endpoint was a composite of non-fatal myocardial infarction and cardiovascular death. Age, number of diseased vessels, and treatment with statins were independent predictors of baseline plasma OPN levels. In univariate analysis, the log-transformed OPN level, levels of C-reactive protein, hypertension, and statin use were associated with future adverse events. Levels of OPN and C-reactive protein and hypertension remained independent predictors of adverse cardiovascular outcome in multivariable analysis. The study was limited to a patient population with angiographically documented stable CAD. Future studies in populations with subclinical disease (e.g. <50% angiographic stenosis or plaque by other imaging modalities) will be crucial to assess the prognostic value of OPN in primary disease prevention.

OPN is a calcium-binding, phosphorylated glycoprotein, which was originally identified as a mediator involved in bone remodelling. However, subsequent studies demonstrated that OPN exerts important cardiovascular effects. OPN is a component of human atherosclerotic lesions, where it is secreted by cells of the monocyte/macrophage lineage and to a lesser extent by endothelial and vascular smooth muscle cells. OPN is up regulated in calcified coronary plaques,2 and plasma OPN levels in patients with CAD correlate with angiographic disease severity, independent of conventional risk factors.3 Expanding these findings, the data by Minoretti et al.1 identify plasma OPN as a potential marker of atherosclerotic disease progression and future clinical events in patients with stable angina.

Importantly, beyond demonstrating the potential role as a disease marker, the findings suggest that OPN may be a window in the role of coronary calcification during progression and regression of atherosclerosis. Vascular calcification is a form of dystrophic calcification, which is a common response to injury in various soft tissues. In coronary arteries, calcification is an important manifestation of atherosclerosis. Imaging research has revised outdated concepts, which described calcification as a rare, end-stage, degenerative process of ageing. Intravascular ultrasound (IVUS) and, in particular, computed tomography have shown that coronary calcification occurs in the majority of patients with CAD, that its presence is related to lesion vulnerability, and that its extent is directly related to the overall burden of atherosclerotic disease.4,5 There are solid epidemiological data demonstrating that coronary calcification predicts future cardiovascular risk, independent of other risk factors.6

Many key regulators of bone formation and bone structural proteins are expressed in atherosclerotic plaques, including bone morphogenetic protein-2, matrix-carboxyglutamic acid protein, osteoprotegerin, and OPN.7 OPN was named for its function as a bridge between cells and minerals. Forming a proteinaceous coating over the solid crystal surface, OPN mediates attachment of both osteoblasts and osteoclasts to bone mineral through interaction with integrins. It appears to be induced in response to mineralization and is involved in the inhibition of vascular calcification.8 These studies provide evidence that vascular calcification is an active, regulated process with similarities to bone mineralization. A particular exciting hypothesis is that vascular calcification is related to lesion inflammation. Chronic inflammation is a unifying feature of all dystrophic soft tissue calcification including the response to foreign bodies, parasites, and infections. Chronic inflammation is a central characteristic of atherosclerosis, where oxidized lipids are considered important inflammatory stimuli. The inflammatory response is closely related to plaque stability/vulnerability, and systemic markers of inflammation including C-reactive protein and myeloperoxidase predict future cardiovascular events. It is not surprising...
that OPN, secreted from infiltrating macrophages that are intimately associated with calcified atherosclerotic plaque, influences the inflammatory processes that take place within the arterial wall. In summary, as also suggested for C-reactive protein, these data suggest that OPN is not only a marker of CAD activity but also actively involved in plaque progression, calcification, and stability.

The concept that vascular calcification is part of a dynamic process of vessel wall remodelling suggests that markers such as OPN and measurements of vascular calcification could become important diagnostic and therapeutic targets. A marker of calcification could be used to assess the efficacy of anti-atherosclerotic pharmacological interventions. Intriguingly, in the study by Minoretti et al., use of statins was associated with lower baseline plasma OPN concentration, potentially consistent with the established anti-inflammatory properties of statins. However, serial OPN measurements are not reported. Small, serial imaging studies suggest that pharmacological treatment with statins and the phosphate binder sevelamer affects the extent of calcification. Furthermore, previous studies, demonstrating the dose-dependent ability of OPN to inhibit vascular smooth muscle cell-mediated calcification in vitro, suggest that OPN might be useful in therapies aimed at preventing dystrophic calcification. However, despite the documented clinical relevance of vascular calcification, research on the mechanism of mineral deposition in arteries remains at an early scientific stage relative to other aspects of atherosclerosis, such as lipoprotein biochemistry and inflammation. It is incompletely understood how calcification of individual lesions and the entire arterial tree is related to disease progression and regression. It is unknown whether a potential therapeutic decrease in calcification is in fact associated with increased lesion stability and a reduced rate of cardiovascular events.

Our further understanding of these relationships could be significantly influenced by studies combining serum markers of disease, such as OPN, with in vivo atherosclerosis imaging. Such comparative studies, using IVUS, have recently described the complex relationship among atherosclerotic plaque burden, lipid metabolism, and inflammatory markers. This analytic approach allows insights into disease processes previously limited to histological studies. Importantly, it provides an in vivo understanding of the relationships among pathophysiology, clinical presentation, and disease prognosis and an opportunity to identify and evaluate novel therapeutic targets in the prevention of atherosclerotic disease progression.

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References