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Atherosclerotic calcification-back to oxidation hypothesis

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Atherosclerotic lesions are formed by deposition of lipids in the intima of arteries. Upon exposure to oxidative stresses, low-density lipoprotein (LDL) is converted to highly atherogenic oxidized LDL (ox-LDL) particles, contributing to disease development and progression. Advanced disease stages may result in calcification of lesions. This calcification process is important, as it has been shown to be associated with stable plaques that are less prone to rupture. Calcification is present in lipid rich domains of lesions and it is generally, it is assumed that calcium is present as calcium phosphate; however, neither the composition of the mineralized calcium deposits nor its relationship to lipid peroxidation is known. We hypothesized that lipid peroxide derived azelaic acid (AZA), a dicarboxylic acid formed from the oxidation of oxo-nonanoic acid, induces calcification in smooth muscle cells thereby providing the link between calcification and overall plaque burden, and association of calcification with the lipophilic region of the lesion. Accordingly, 13-hydroperoxylinoleic acid (HPODE) treatment resulted in the cellular conversion to 9-oxononanoic acid (ONA) and AZA as determined by mass spectrometry analysis. Delivery of AZA via lysophosphatidylcholine (lysoptdcho) micelles induced calcification of human aortic smooth muscle cells (HASMC). AZA was identified in the mineralized calcium deposits of human and APOE deficient mouse atherosclerotic plaques. These results demonstrate that DCA may contribute to atherosclerotic calcification thus accounting for the latter's relationship to plaque burden and association with lipids. This study also challenges the dogma that arterial calcification represents the deposition of calcium phosphate. In addition, the results also make a connection between the oxidation of LDL lipids with calcification.

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