Letter to the Editor

Pyrophosphate, Alkaline Phosphatase, and Vascular Calcification

To the Editor:

In their editorial on vascular calcification, Demer and Tintut[1] incorrectly state that pyrophosphate reduces calcification by inhibiting alkaline phosphatase. Actually, the opposite is true. Alkaline phosphatase promotes calcification by reducing pyrophosphate levels. Pyrophosphate is a substrate for alkaline phosphatase,[2] and this enzyme regulates pyrophosphate levels in vivo as shown by the increased pyrophosphate levels in humans deficient in alkaline phosphatase.[3] Pyrophosphate is a potent inhibitor of medial vascular calcification in vitro[4] and in vivo,[5] and this occurs through a direct physiochemical inhibition of hydroxyapatite formation at concentrations normally present in plasma.[6] Also, the concept that alkaline phosphatase promotes calcification by providing inorganic phosphate is outdated. Substantial data over the past 5 years have shown that the principal role of alkaline phosphatase in mineralization is to remove inhibitory pyrophosphate.[7–9] The mineralization defect in mice lacking alkaline phosphatase can be ameliorated by crossing the mice with mice lacking the ectopyrophosphorylase that synthesizes extracellular pyrophosphate[7] or with mice lacking the protein responsible for transporting pyrophosphate out of cells.[8] Thus defective mineralization in alkaline phosphatase deficiency can be corrected solely by reducing pyrophosphate levels. The same is probably true in vascular calcification because the medial calcification induced in aortas in culture by alkaline phosphatase can be prevented with bisphosphonates, nonhydrolyzable pyrophosphate analogs.[10]

Disclosures

None.

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(*Circ Res*. 2006;99:e2.)

Circulation Research is available at http://circres.ahajournals.org
DOI: 10.1161/01.RES.0000234909.24367.a9