JOURNAL OF THE AMERICAN COLLEGE OF CARDIOLOGY
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PUBLISHED BY ELSEVIER

VOL. 67, NO. 1, 2016
ISSN 0735-1097/$36.00
http://dx.doi.org/10.1016/j.jacc.2015.11.014

EDITORIAL COMMENT

Calcification and Inflammation in Atherosclerosis

Which Is the Chicken, and Which Is the Egg?*

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In this issue of the *Journal,* Joshi et al. (1) ask the question, "Does vascular calcification accelerate inflammation?" To answer this question, the authors performed a substudy using data from the dal-PLAQUE trial (1), which was a phase 2 randomized trial to determine the vascular effects of the cholesterol ester transfer protein inhibitor dalcetrapib. As part of the trial, the investigators measured calcification and vascular inflammation. Calcification was measured in the ascending aorta, aortic arch, and carotid and coronary arteries on computed tomography (CT), with an attenuation threshold of 130 HU in 3 contiguous voxels on consecutive transaxial slices along the length of the arterial segment. The extent of calcification was expressed both in Agatston units and as a volume in cubic millimeters. Baseline and follow-up studies were compared to ensure that the same length of artery was analyzed on both scans.

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Vascular inflammation was measured with fluorodeoxyglucose (FDG) positron emission tomography (PET)-CT imaging in the aorta and carotid arteries. Arterial FDG uptake was quantified by delineating a region of interest on coregistered transaxial PET/CT images. The maximum arterial standardized uptake value (SUV) was determined in the aorta and carotid arteries from the ratio of SUV of the artery compared with background venous activity. They enrolled 130 patients with a median age of 65 years, 82% male, with previous known coronary heart disease or at high risk (diabetes or >20% risk by Framingham risk scoring). Two measurements of calcification (CT) and arterial inflammation (FDG-PET/CT) were performed—the first at the time of entry and the second 6 months later.

The investigators report 4 major observations on the basis of their analysis: 1) an association of age >65 years with higher baseline calcium scores; 2) a decrease in FDG uptake (inflammation) in the carotid arteries if carotid calcium was absent at baseline; 3) no change in carotid inflammation if calcification was present in the carotid arteries at baseline; and 4) no effect of the cholesteryl ester transfer protein inhibitor dalcetrapib.

The question raised by the authors is important. It is generally accepted that atheroma is initiated by lipoprotein cholesterol complexes trapped beneath the endothelium. The trapped lipoprotein causes an inflammatory response, resulting in the recruitment of phagocytic cells to the lesion. Depending on the amount of lipid and the effectiveness of the phagocytic cells, the lesion may resolve or progress. Progressive lesions develop a necrotic core with abundant macrophages, foam cells, cellular debris (from inefficient efferocytosis), and extravasation of erythrocytes from newly formed fragile capillaries (2). Lesions with an intense inflammatory response often have microcalcifications (3), likely due to a combination of necrotic cell debris serving as a nidus for calcification and a loss of calcification inhibitory factors (4,5). Although microcalcification of the lesions predisposes to plaque rupture, coalescence of calcification may result in sheets of calcium, effectively separating the residual inflammatory site from the

*Editorials published in the *Journal of the American College of Cardiology* reflect the views of the authors and do not necessarily represent the views of *JACC* or the American College of Cardiology.

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vascular lumen, making the lesion less likely to rupture.

Studies of vascular calcification and vascular inflammation (6,7) suggest that there is little overlap between vascular calcification seen on clinical CT and sites of vascular FDG uptake on FDG-PET/CT. Over short intervals, vascular inflammation, as measured on serial FDG-PET/CT studies, is stable (8), but on longer intervals, vascular FDG uptake often waxes and wanes (6). Meirelles et al. (6) found a change in vascular FDG uptake in 55% of patients between the baseline scan and rescan at a mean of 7 months. On the other hand, calcification tends to be stable or increase over time (6).

There is increasing recognition of the role of microcalcification early in the evolution of inflamed atheroma, but these microcalcifications are only visible at histopathology (9) or with high-resolution CT (3) of vascular specimens (e.g., carotid endarterectomy specimens). Recently, PET imaging with ionic F-18 fluoride has been proposed as the most sensitive marker of the active process of plaque calcification. However, dense vascular calcification as visible on clinical CT is often associated with plaque stabilization (10).

Abdelbaky et al. (11) evaluated 137 patients with serial FDG-PET/CT scans for locations that had FDG uptake at baseline without calcification (inflammation only) and that developed calcification on the follow-up scan. New vascular calcification developed in 9% of segments (with the highest SUV at baseline), suggesting that inflammation preceded calcification; these investigators also observed that the segments with stable calcium at baseline and follow-up scans had the lowest SUV.

If we accept the observations that: 1) vascular inflammation precedes calcification; 2) vascular inflammation waxes and wanes; 3) vascular calcification is stable or increases; and 4) vascular inflammation and calcification rarely co-localize, then it is also possible that new inflammation might appear at the pre-existing sites of calcification. Histopathological data (3,9) suggest that some lesions remain inflamed, even in the presence of calcium, particularly if the calcification is not very dense. In light of the pathophysiology of atheroma, it is less likely that calcification causes inflammation and more likely that new inflammation could occur at sites of calcified atheroma. It is unlikely that the chicken or egg dilemma can be answered by the serial PET/CT studies of atheroma; it may need more experimental data and a revisiting of the basic science of calcification.

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KEY WORDS atheroma, atherosclerosis, vascular calcification, vascular inflammation