JACC: CARDIOVASCULAR IMAGING
VOL. 5, NO. 4, 2012

ISSN 1936-878X/$36.00
PUBLISHED BY ELSEVIER INC.
DOI:10.1016/j.jcmg.2012.02.006

EDITORIAL COMMENT

# Vascular Calcification, Diabetes, and Cardiovascular Disease

## Connecting the Dots*

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Vascular calcification has long been a major area of interest in cardiovascular medicine. A great deal of data has emerged, ranging from descriptions of the extent of vascular calcification in ancient Egyptian mummies to intricate dissections of complex molecular signaling pathways (1,2). Arguably, the strongest message to have arisen from the recent studies appears to be the sobering fact that vascular calcification is a complex pathobiological process about which we are only just beginning to gain a rudimentary understanding. As a prime example, although for a period, there was general agreement that there were 2 principal types of vascular calcification—intimal (associated with atherosclerosis) and medial (also known as Mönckeberg's sclerosis or arteriosclerosis) (3), even this long-standing classification has now come into question, with data from patients with renal failure suggesting that these distinct classifications should be considered as a continuum (4). Another important new paradigm to emerge is the so-called vascular calcification paradox, being a robust inverse association between the degree of bone mineralization and the degree of vascular calcification (3,5). However, at the present time, we are far from an adequate unifying explanation that might explain this reciprocal link between vascular and skeletal calcification, and a great deal of work remains to be undertaken. At the molecular level, unexpected complexities have arisen, such as the possibility that removal of lipid deposits by the use of statins may trigger macrophages, osteoclast-like cells, and vascular smooth muscle cells to generate extracellular matrix and cause vascular calcification (2,6). This may explain the paradox of an increase in calcium score as a parameter of disease, but during the process of vascular "healing" (6,7). In corroboration, meta-analysis data have shown that statin use to reduce or slow vascular calcification is ineffective (8).

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Amidst this flurry of activity, MESA (Multi-Ethnic Study of Atherosclerosis) has stood as a steadying reference beacon for almost a decade (9). In a series of seminal studies, the large and painstakingly collected MESA dataset has left an indelible impact on our understanding of coronary artery calcification (CAC), with a multitude of important factors shown to influence, or to at least be associated with, the incidence and progression of CAC (Fig. 1) (9–17). In the process, MESA has raised the bar for population-level cardiovascular observational studies, collecting a wealth of parameters with a large sample size, thus permitting this rich suite of publications. In this issue of *iJACC*, Wong et al. (17) add to this stable of MESA-derived papers, focusing on the role of the metabolic syndrome (MetS) and diabetes (DM) in CAC development and progression. Here, they solve several individually important pieces of the vascular calci-

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

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JACC: CARDIOVASCULAR IMAGING, VOL. 5, NO. 4, 2012
APRIL 2012:367–9

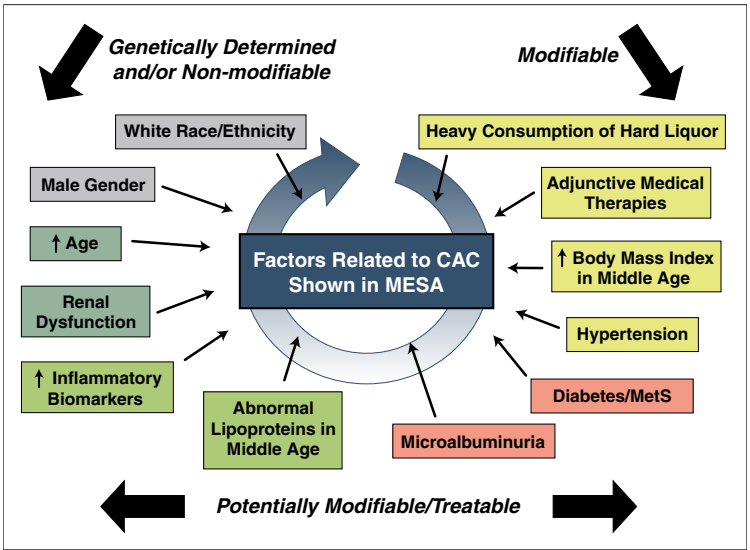


**Figure 1. Factors Shown to Be Associated With the Incidence and/or Progression of CAC From MESA**

What remains unclear is whether calcific deposition is a secondary phenomenon to coronary disease in some or all of the factors outlined in the figure. CAC = coronary artery calcification; MESA = Multi-Ethnic Study of Atherosclerosis; MetS = metabolic syndrome.

fication puzzle. First, for patients with no CAC at baseline (as assessed by computed tomography [CT] scanning), the relative risk of incident CAC at follow-up scanning (mean of 2.4 years later) was 1.7 to 1.9 for patients with MetS, DM, or both conditions compared with patients without DM or MetS. Second, and perhaps most interesting of their findings, in those with CAC at baseline, there was a dose-response effect for the progression of CAC, which in broad terms was least for those without MetS/DM, intermediate for those with either MetS or DM, and highest for those with both conditions. Third, although an association between CAC progression and clinical cardiovascular events is already known to exist across all-comers (DM and non-DM) (18), Wong et al. (17) extended these data by showing that CAC progression is associated with subsequent coronary heart disease events in patients with MetS and DM.

Inevitably, as with any study, there are limitations, one being the lack of consideration of renal function. Thus, as a possible confounding factor, patients with DM and/or MetS might be expected to have a greater prevalence of renal dysfunction, which may have increased the burden of CAC as a secondary rather than a primary effect. Also, patients who experienced a cardiac event before follow-up scanning were excluded; although their progression of CAC is unknown, these patients had more severe *clinical* progression of their coronary artery disease than others in the study and their exclusion is a potential source of selection bias; however, the number excluded was small (70 of 5,662). Finally, as pointed out, the use of statins may enhance vascular "healing" but with increased vascular calcification. The current study does not provide such therapeutic information (statin use); however, the relatively low and generally equivalent lipid levels across the patient groups might suggest similar use of these agents. Nevertheless, we believe that these caveats would appear unlikely to have made an appreciable impact on the overall results or conclusions.

What can we take away from this study? Certainly, the MESA investigators have now put the link between MetS, DM, and CAC beyond question. Also, they have demonstrated that even among patients with MetS/DM, who are already known to have an increased risk of coronary heart disease events, those with CAC progression are at even greater risk of these adverse outcomes. This begs the question of whether clinicians should be performing serial CT scans to identify patients with MetS/DM and significant CAC progression who may benefit from particularly aggressive medical therapy. Although interesting in theory, in the current climate of cost containment and clinical use appropriateness criteria, we believe that this use of resources would be unlikely to gain widespread acceptance. Indeed, current (2010) appropriate use criteria classify the repeat use of coronary CT scanning as "inappropriate" in asymptomatic patients with known coronary artery disease and previous CT scanning (19). Nevertheless, documentation of rampant progression of CAC in occasional selected patients with MetS/DM, renal dysfunction, or other comorbidities may be of assistance in tailoring individual therapeutic regimens, in effect, a form of personalized medicine.

Progress in understanding CAC at the basic and clinical levels has been moving forward at a steady pace. However, to put this in perspective, in the coming decades, we are potentially facing a worldwide cardiovascular health epidemic because it is predicted that the population will become significantly older, obesity will increase, and the prevalence of DM will increase significantly (20). Given this, in a small but important way, the data of Wong et al. (17) add to concerns of a looming cardiovascular health crisis, connecting the dots and highlighting that this growing number of people affected with MetS/DM will also be at increased

risk of CAC and coronary heart disease events. Averting this global health crisis has now become a priority agenda item at the highest levels, including the United Nations and the Institute of Medicine of the U.S. National Academy of Sciences (21,22). Among other things, we need to urgently engage in targeted research initiatives, to define novel therapies, and to implement global initiatives to combat obesity, DM, and other aspects of this major cardiovascular health concern (23).

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**Key Words:** atherosclerosis ■ calcium ■ diabetes mellitus ■ vasculature.