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EDITORIAL COMMENT

Epicardial Adipose Tissue and Progression of Coronary Artery Calcium

Cause and Effect or Simple Association?*

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In this issue of *iJACC*, Mahabadi et al. (1) describe a parallel increase of subclinical atherosclerosis and epicardial adipose tissue (EAT). Two prior publications (2,3) reported a similar association, and together with experimental models, they support the role of EAT in atherosclerosis inception and progression. In an experimental porcine model, the investigators stripped the epicardial fat covering the middle section of the left anterior descending coronary artery and kept the animals alive for 3 more months on an atherosclerotic diet (4). They also performed intravascular ultrasound imaging before EAT stripping and just before sacrificing the

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animals. At the end of the experiment, they noted that atherosclerosis had progressed in the segments proximal and distal to the EAT resection, but not in the coronary artery segment underlying the area stripped of EAT. These observations contribute to an expanding body of evidence about the role of perivascular fat in atherosclerosis (5,6). EAT volume is increased in patients with plaques showing signs of vulnerability (7,8); in patients with intra-atherosclerotic plaque hemorrhage on post-mortem histology and in patients referred for coronary artery bypass surgery for progressive anginal symptoms, EAT is replete with inflammatory cells and serological mediators of inflammation (9,10). Several observations have demonstrated that EAT is associated with incident cardiovascular events (11–13). Of interest, controlling risk factors such as losing weight (14) or reducing low-density lipoprotein cholesterol with statins (15) reduced EAT volume. Hence, there seems to be consistent evidence suggesting a link between periarterial fat and arterial wall atherosclerosis. What separates the current report (1) from others is the unexpected association of progression of EAT and coronary artery calcium (CAC) in patients with a small burden of atherosclerosis at baseline (defined as a CAC score <100), but not in patients with more advanced disease. In addition, the association was stronger in younger subjects and patients with lower body mass index. The authors interpreted these apparently paradoxical results as an indication that epicardial fat may have an initial promoter effect on atherosclerosis rather than a sustained effect. The interesting suggestion here is that not all adipose tissue is the same and that an "aggressive behavior" can be found in the adipose tissue of lean patients and obese patients affected by the metabolic syndrome alike. Is this a proof of the "healthy obese subject" hypothesis? According to this hypothesis, some obese individuals have a metabolically benign profile and a lower risk of cardiovascular events than similarly obese patients with an adverse metabolic profile. Is this also a potential explanation for the occurrence of unexpected acute coronary events in lean subjects? Data from the Framingham study (16) showed that EAT is associated with coronary artery disease independent of body mass index and waist circumference, and Gorter et al. (17) reported a more pronounced association of EAT with coronary artery disease severity in leaner patients. De Larochellière et al. (18) showed that substantial amounts of visceral adipose tissue can be found even in nonobese individuals and are associated with an adverse cardiometabolic profile.

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Finally, Iwayama et al. (19) found larger amounts of EAT and a lower adiponectin concentration in the pericardial fluid of lean patients with CAD than lean patients without CAD. In essence, a lean phenotype is preferable, but not perfectly protective, in the presence of a relatively large volume of visceral fat. What is unclear, however, is why and how lean subjects would accumulate perivascular adipose tissue with proatherosclerotic activity, and why would EAT not (or not as effectively) promote progression of atherosclerosis in heavier patients and more advanced phases of disease (1). There are even more fundamental questions that need to be answered: is EAT truly promoting atherosclerosis, and if so, how does it do it? Or is it a bystander? EAT is in direct contact with the adventitia of the coronary arteries without the interposition of a fascia. Paracrine effects and a dense concentration of inflammatory cells in the milieu surrounding the adventitia may stimulate the proliferation of vasa vasorum (20). As they proliferate and expand, these vessels penetrate the vessel wall and cause a series of intramural hemorrhages. The cellular membrane of erythrocytes is rich in cholesterol, and cell death in the context of the vessel wall causes accumulation of a large amount of lipids promoting further inflammation. CAC accumulation is a very complex process resembling bone formation, and apoptosis of "procalcifying cells" in the vessel wall is 1 of the necessary stimuli for its accumulation (21). According to some researchers, the cell responsible for tissue calcification is a smooth muscle cell, and according to others, it is a pericyte (22). Pericytes are interspersed with endothelial cells in the vasa vasorum penetrating through the adventitia of vessels developing atherosclerosis and could thus promote some of the calcification occurring within the plaque. Of course, the mechanisms of calcification of the atherosclerotic plaque are much more complex than this brief summary suggests (23), although this explanation provides a glimpse of light on the potential link between EAT and CAC. However, as already mentioned, there is no obvious reason for the different behavior seen in leaner, younger individuals with a smaller atherosclerotic plaque load and other patients more likely to harbor a proatherosclerotic environment. It also remains unknown whether expansion of EAT and/or CAC can be inhibited or reversed and whether this will ultimately lead to a reduction in event rates. For the time being, the paper by Mahabadi et al. (1) adds another piece to the growing puzzle of the impact of visceral adipose tissue on atherosclerosis, a disease state that continues to fascinate us while a complete understanding of its pathogenesis continues to elude us.

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