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Epicardial Adipose Tissue:

A Benign Consequence of Obesity?

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The obesity epidemic has emerged as one of the most critical public health problems worldwide that is closely associated with the development of metabolic and cardiovascular disease.[1] With increasing obesity, adipose tissue accumulates in multiple body compartments both within and surrounding internal organs with potential to negatively alter their biological function. In addition to increased fat mass, obesity is associated with functional abnormalities in adipose tissue that are linked to inflammation, metabolic dysregulation, vascular dysfunction, impaired angiogenesis, and insulin resistance.[2] These perturbations are particularly evident with visceral obesity, which has been most closely linked to cardiovascular risk.[3,4] Recently, interest has focused on the potential role of epicardial adipose tissue (EAT), which shares embryological origin with abdominal visceral fat, as a modulator of cardiovascular function, owing to its immediate anatomic proximity to the coronary vasculature and myocardium with shared microcirculation. Epicardial fat measured by different methods, including echocardiography, CT, and MRI, correlates with degree of intra-abdominal visceral adiposity. It has been suggested that EAT represents the visceral fat depot of the heart, displaying high metabolic activity and capacity for production of several mediators with paracrine effects that may regulate cardiovascular homeostasis.[5]

Several lines of evidence suggest that EAT could play a role in the pathogenesis of cardiovascular disease. Epicardial adipose tissue from patients with advanced coronary artery disease (CAD) is associated with higher chemokine and cytokine expression at the tissue level, including monocyte chemotactic protein-1, interleukin-6, and tumor necrosis factor-α that may support atherosclerosis while adiponectin is downregulated. [6–9] Epicardial fat in CAD patients displays greater infiltration of macrophages with M1 polarization consistent with a proinflammatory EAT phenotype compared with that in non-CAD patients.[10] Matrix metalloproteinase expression which modulates atherosclerotic plaque

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Disclosures

None.

stability is upregulated in EAT in CAD patients, and cardiac tissue incubated with epicardial fat–conditioned media displays fibrotic responses.[11] In line with these pathophysiological findings, clinical studies have reported close associations between degree of EAT thickness/volume and cardiovascular risk factors and prevalent CAD, although associations generally weaken or fall out after multivariable adjustment for abdominal visceral fat.[12] Increased EAT volume has been linked with metabolic syndrome, progression of coronary artery calcification,[13,14] and incident myocardial infarction.[15,16] Recently, in a sizeable study (n=970) of older individuals with chest pain and high CAD prevalence, EAT thickness correlated significantly with coronary artery calcification scores and severity of angiographic CAD.[17]

In this issue of *Circulation: Cardiovascular Imaging*, in contrast to previous studies, Tanami et al[18] report a resoundingly negative relationship between EAT volume, coronary calcium scores, and prevalent CAD in a medium-sized (n=380), cross-sectional study of intermediate-risk subjects with known or suspected CAD enrolled in the CORE320 multicenter study. Although not the largest publication to date examining the relation of EAT to CAD, this is the first study to have performed coronary calcium scoring, nuclear perfusion imaging, and quantitative coronary angiography by invasive cardiac catheterization in all subjects, thereby providing a fairly comprehensive anatomic and functional characterization of the coronary tree. The findings are some-what unexpected and contrast most published data, including a recent larger angiographic study[17] which found a strong association between EAT and CAD severity, but nevertheless methodologically quantified EAT as a linear thickness measure rather than volumetrically. Interestingly, the present report found no association between obesity and cardiovascular risk factors either, highlighting patient population differences as another possible explanation for discordant results across studies. Additionally, no measure of abdominal visceral adiposity was evaluated in multivariable modeling in these angiographic studies.

However, the present findings do not necessarily refute a potential role for epicardial fat in mechanisms of CAD events. Specifically, investigators did not examine clinical outcomes but rather prevalence of obstructive CAD. As such, the Heinz Nixdorf Recall Study[16] which examined 4093 participants longitudinally over 8 years demonstrated that epicardial fat volume predicted incident fatal and non-fatal coronary events, independent of traditional risk factors or extent of coronary calcification. It is thus plausible that EAT modulates distinct aspects of the atherosclerotic process influencing lesion composition or stability, including nonflow limiting, hemodynamically silent yet vulnerable coronary plaques that may rupture leading to clinical events. Although the current study by Tanami and colleagues[18] further adds to the controversy of whether EAT plays a direct role in the pathogenesis of CAD, it represents yet another cross-sectional report, adding to the myriad of observational studies most of which generally performed in patient subgroups for clinical reasons, prone to selection bias, largely descriptive in nature, and unadjusted for circulating inflammatory biomarkers or visceral fat volume that have been independently linked to cardiovascular risk. To date, there has not been a prospective study specifically designed to assess the role of EAT in the pathogenesis of cardiovascular disease, and a firm causal role of epicardial fat in atherosclerosis remains speculative.

Another issue to consider is the directionality of any potential relationship. For example, whether the proinflammatory milieu harbored within EAT mediates the development of coronary lesions or whether atherosclerosis induces reactive inflammation in adjacent fat remains unclear. In addition, consideration may be given to characterizing qualitative features of EAT, such as degree of inflammation, lipolysis, or oxidative stress that may provide mechanistic clues. Clinical data suggest that in addition to quantity, characterization of adipose tissue quality by histopathology or CT attenuation imaging techniques represents an emerging clinical paradigm in the assessment of adipose phenotypes in relation to cardio-metabolic risk.[19,20] Although compelling to speculate that epicardial fat with proinflammatory features may contribute to atherogenesis, lack of information regarding any temporal changes in EAT quality or quantity in response to pharmacological or therapeutic lifestyle intervention, correlating with any change in cardiovascular outcome, leaves us with little evidence for any causal pathophysiological relationships. Additional experimental models involving epicardial fat debridement or transplantation or re-examination of epicardial inflammatory profiles after coronary revascularization may provide interesting data. More basic and translational studies are needed to identify specific molecular mechanisms and determine whether epicardial adipose tissue is a benign consequence of obesity or should serve as a therapeutic target to modify cardiovascular risk.

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