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Editorial

Is epicardial fat attenuation a novel marker of coronary inflammation?

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Epicardial adipose tissue (EAT) plays an important role in the development and progression of atherosclerosis, as emerged only in the past decade [1,2]. Remarkably, the atherogenicity of EAT could be linked to its imaging appearance, as suggested by the paper published by Liu et al. in this issue of *Atherosclerosis* [3].

Excessive and abnormal EAT increases the risk of coronary artery disease (CAD), myocardial infarction, and non-calcified and calcified coronary plaque burden [4,5]. The atherogenicity of EAT is multifactorial, but is mostly related to the unique anatomy and pro-inflammatory transcriptome and secretosome [6–8]. Microscopically, EAT cellularity is composed by small white and beige adipocytes and pre-adipocytes, but also inflammatory, stromovascular and immune cells, ganglia and interconnecting nerves [6,7]. EAT has a dense intrinsic inflammatory infiltrate, mainly composed by macrophages [9]. EAT pro-inflammatory M1 macrophages and anti-inflammatory M2 macrophages are unbalanced in patients with coronary artery disease (CAD) [10]. Macro-anatomy is also unique, as EAT is the only visceral depot in direct contiguity with its target organ. It lies between the myocardium and visceral layer of the pericardium, with no muscle fascia separating the two tissues that share the same microcirculation. This anatomical vicinity translates into peculiar physiological and pathophysiological properties, as EAT provides energy and heat to the myocardium whereas, under pathological conditions, its anatomical cross-talk with the heart allows the paracrine release of pro-inflammatory and pro-atherogenic adipokines that directly reach the coronary lumen. This intense pro-atherogenic activity is regulated by a peculiar transcriptome, highly enriched in genes encoding for transcriptional factors and inflammatory cytokines [8]. Adaptive and maladaptive mechanisms differently modulates EAT gene expression in unfavorable hemodynamic and metabolic conditions, such as in CAD and diabetes [11]. One of the most appealing aspects of the EAT is its measurability and modifiability. EAT can be clinically detected by ultrasound and computed tomography (CT). If EAT thickness can be easily measured with standard echocardiography [1,12], cardiac CT undoubtedly provides a more accurate and deeper quantification of its volume. Due to its intrinsic fast metabolism, organ-specificity and expression of specific targeting receptors, EAT has recently shown to significantly respond and shrink under the effects of drugs modulating the adipose tissue [13–15].

The article by Liu *et* al. addresses the importance of a qualitative, rather than simply quantitative, assessment of EAT in the setting of CAD risk stratification [3]. The authors report that CT-derived EAT attenuation was associated with EAT volume and higher CAD risk, but not with severe coronary artery lesions.

Potential imaging-based markers of local inflammation within the EAT depot have gained specific interest. Echocardiography and nuclear medicine could indirectly detect signs of inflammation, such as increased echogenicity and signal-intensity, but no reliable methods have been developed yet. CT-measured EAT volume has been largely associated with higher risk of CAD and myocardial infarction [4,5,16]. However, the role and importance of CT-derived EAT attenuation, in addition to volume, has been recently evaluated [17]. Radiodensity around the right coronary artery as measure of coronary inflammation was found to improve prediction of cardiovascular and all-cause mortality in patients undergoing CT angiography [18]. In the general population cohort of the SWAN study, the association of radiodensity with cardiovascular risk burden was described [19]. Radiographic fat density is determined by adipocyte hypertrophy and/or hyperplasia and fibrosis that oppositely influence CT-derived fat attenuation. The paper by Liu and colleagues suggests that EAT density may reflect fibrotic and inflammatory changes within the fat depot itself, and then provide additional information to EAT volume alone [3]. Interestingly, a reduced expression of EAT genes regulating cellular processes such as intracellular trafficking, proliferation and transcription regulation, and protein catabolism has been reported in subjects with severe CAD and attributed to the chronic ischemic insult and poor metabolic milieu [8]. Whether EAT gene down-regulation could be associated to its fibrosis is unknown, but plausible. Liu *et* al. implies that EAT fibrosis can alleviate

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the expected decrease in fat density and therefore explain the unsynchronized correlation between CT-derived EAT attenuation and volume in advanced CAD. The authors suggest that the increased EAT attenuation could be due to the intrinsic inflammatory infiltrates that mitigate the effect of hypertrophic and/or hyperplasic fat cells on fat attenuation. Notably, hypertrophic EAT adipocytes can drive higher inflammation throughout the infiltration of M1-polarized macrophages [20]. We can therefore postulate that fat density reflects the higher inflammatory status rather than an inactive tissue fibrosis. Together with the existing literature, the present findings by Liu and colleagues direct towards the hypothesis that quantification of coronary inflammation by assessment of EAT attenuation could improve CAD prediction.

The need for simple and reliable imaging marker of cardiac inflammation is compelling. CT-derived EAT attenuation provides promising results. Once CT angiography is performed, assessment of EAT attenuation may improve its prognostic value.

Conflict of interest

The authors declared they do not have anything to disclose regarding conflict of interest with respect to this manuscript.

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Gianluca Iacobellis*

Division of Diabetes, Endocrinology and Metabolism, Department of Medicine, University of Miami, Miller School of Medicine, Miami, FL, USA

E-mail address: giacobellis@med.miami.edu.

Amir A. Mahabadi

Department of Cardiology and Vascular Medicine, West German Heart and Vascular Center Essen, University Hospital Essen, Essen, Germany

* Corresponding author. University of Miami Hospital Diabetes Service, Division of Diabetes, Endocrinology and Metabolism, University of Miami, 1400 NW 10th Ave, Dominion Tower suite 805-807, Miami, FL, 33136, USA.