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Commentary

Epicardial adipose tissue: An anatomic component of obesity & metabolic syndrome in close proximity to myocardium & coronary arteries

Epicardial adipose tissue (EAT) refers to a visceral fat depot located on the outer surface of myocardium and beneath the visceral pericardium. EAT should not be confused with pericardial adipose tissue which is located on the outer surface of pericardium and differs from EAT in terms of structure, embryonic origin, blood supply and biochemical profile. EAT also differs from myocardial fat which represents increased amounts of fat in myocardium in the form of fat droplets within cardiomyocytes, commonly associated with advanced adiposity. EAT is in direct contact with myocardium and epicardial coronary arteries without any separating anatomic structures such as fascias or aponeurotic tissues between EAT and these structures. It is supplied with blood from coronary circulation. These anatomic aspects are important because they allow a bilateral interaction (cross-talk) between EAT and myocardium or coronary artery wall *via* cells, metabolites or signalling molecules[1]. EAT originates from the splanchnopleuric mesoderm and has the same origin as mesenteric and omental fat deposits[2]. Post-mortem studies of individuals without clinically evident cardiovascular disease (CVD) or type 2 diabetes have shown that EAT constitutes up to 20 per cent of ventricular mass and covers up to 80 per cent of heart's surface[3]. On an average, EAT weights about 100 g and accounts for about one per cent of total body fat in healthy individuals[4]. In diabetic patients, EAT weight increases up to 400 g, occasionally reaching 800 g[4,5]. The EAT thickness varies from 5 to 7 mm over the right ventricular free wall and from 10 to 14 mm over the atrioventricular and interventricular grooves. In echocardiographic measurement, EAT represents an echo free space between the outer contour of myocardium and visceral layer of pericardium[2]. EAT is a tissue with mixed cellularity including smaller-size adipocytes, stromal cells, resident inflammatory cells such as $CD3^+$ lymphocytes, $CD68^+$ macrophages, mast cells and neural and ganglionic cells[6].

EAT is metabolically active and reveals a high lipolytic and lipogenic activity and serves as local energy store for myocardium and protects myocardium from lipotoxicity caused by a high influx of free fatty acids. Similar to brown fat tissue, EAT expresses thermogenin or uncoupling protein-1 (UCP-1), a transmembrane proton carrier localized in the inner mitochondrial membrane which is involved in heat generation potentially protecting the heart against hypothermia. Other putative EAT functions include regulation of coronary artery vascular tone, serving as platform for neural ganglia innervating the myocardium, immune barrier protecting the myocardium from inflammation and mechanical protection of the heart and coronary arteries[7,8]. EAT is an endocrine organ that produces and releases a large number of cytokines (called also adipocytokines) which play a protective role in cardiovascular physiology or a pathophysiological or detrimental role in CVD[6]. There are two ways of cross-talk between EAT and coronary arteries: paracrine transmission in which cytokines diffuse from EAT and reach arterial wall ('outside-to-inside' signalling) through interstitial space and vasocrine transmission in which cytokines reach arterial wall or atherosclerotic plaque *via* vasa vasorum. A modulation of EAT (cell differentiation, lipolysis, adipogenesis and secretome) by paracrine signalling from mediators generated by cardiomyocytes ('inside-to-outside' signalling) is also possible[8]. The complex EAT secretome is under genetic, epigenetic and environmental influences. Factors that lead to a shift from a physiological to a dysfunctional pro-inflammatory and pro-atherosclerotic secretome phenotype remain largely

unexplored. However, systemic conditions such as obesity, insulin resistance, diabetes and coronary atherosclerosis (in the setting of reverse causality) are suggested to contribute to this transition[6,8]. Numerous studies have implicated EAT in CVD including coronary artery disease (CAD), atrial fibrillation and heart failure as well as in metabolic syndrome and type 2 diabetes[6,9]. Patients with CAD have increased EAT amount (thickness and volume) and a dysfunctional EAT secretome characterized by secretion of various pro-inflammatory and pro-atherosclerotic adipokines. The close proximity and continuity of EAT with the myocardium and coronary arteries allow even small amounts of pro-inflammatory and pro-atherosclerotic cytokines released from EAT (maybe too small to impact on systemic levels of these mediators) to reach high local concentrations and exert important pathophysiological actions. It has been shown that coronary segments embedded in the EAT but not intra-myocardial segments (not in contact with EAT) develop atherosclerosis[1]. Studies have shown that EAT-generated pro-inflammatory and pro-atherosclerotic cytokines participate throughout the atherosclerotic process from endothelial dysfunction to plaque progression and instability. The majority of the studies have correlated EAT expansion, *i.e*., increased thickness (or volume) with the presence or severity of CAD[6]. Notwithstanding these findings, the place of EAT in the pathophysiology of CVD or risk-stratification of patients with CAD remains debatable.

In this issue Sahasrabuddhe *et al*[10] investigated EAT gene expression in patients with CAD undergoing coronary artery bypass surgery (CABG). By design, the study represents a case-control study: the group of cases comprised 27 patients with CAD undergoing CABG, whereas the group of controls comprised 16 patients undergoing heart surgery for valvular heart disease. From each patient, 0.5-1 g EAT tissue samples were obtained. The target genes were: adiponectin, *UCP-1*, monocyte chemoattractant protein-1 (*MCP-1*), vascular cell adhesion molecule-1 (*VCAM-1*), adenosine A1 receptor (*ADORA-1*) and tumour necrosis factor-alpha (*TNF-α*). Circulating leptin levels were significantly higher in CABG patients (*i.e*., with CAD) compared with control patients. Of note, the upregulation of *MCP-1*, *VCAM-1*, and *TNF-α* gene(s) in CABG patients compared with controls was found. Conversely, the expression of the adiponectin gene was downregulated in CABG patients. Finally, the study demonstrated an independent association between the upregulation of the *MCP-1* gene and the odds of being with CAD after adjustment for a number of covariates including clinical variables and gene expression patterns.

The authors should be congratulated for conducting this study. The study confirms and expands the findings from previous studies that have investigated the association between dysfunctional EAT secretome and the risk of CAD with the strength of assessing this association in well-characterized patients as are patients with CAD undergoing CABG and investigating some of the best-known genes with an established role in cardiovascular physiology or pathophysiology.

As the authors did well to emphasize, the study had limitations inherent to its case-control design, modest sample size, no matching of controls to cases at least in terms of age and sex and the possibility that patients with valvular diseases were not optimal controls because of eventual disease-related cardiac remodelling affecting EAT gene expression. Nonetheless, these limitations are unlikely to impact on the main study findings. However, some caveats remain. First, although the authors obtained EAT tissue, histological analysis of EAT specimens was not performed. Expanded and dysfunctional EAT shows signs of inflammation including infiltration with inflammatory and immune cells[1]. Moreover, the study showed upregulation of *MCP-1* gene whose protein product serves as chemoattractant for monocytes known to have a pivotal role in atherosclerosis. The histologic analysis could have provided important information linking gene expression with the cellular events directly involved in inflammation and atherogenesis. Second, the localization of EAT tissue obtained for analysis was not disclosed. It has been suggested that peri-coronary EAT expresses genes that are involved in cell proliferation and metabolism of sphingolipids which are constituents of atherosclerotic plaque involved in low-density lipoprotein oxidation and retention in subendothelial space, *i.e*., in atherosclerotic plaque formation. Conversely, peri-ventricular EAT shows upregulation of genes involved in energy metabolism, calcium signalling and contractility[11,12]. Third, the study offered no information on the obesity or severity of CAD. Ample evidence suggests that EAT volume and dysfunctional secretome correlate closely with these morbid conditions. Fourth, information on the nature of valvular disease and subsequent cardiac remodelling was not available. An increase in the EAT thickness

has been reported in aortic stenosis[13] and increased ventricular mass[14]. To what extent these conditions impact on EAT gene expression in controls remains unknown. Fifth, although an association between *MCP-1* upregulation and CAD is plausible, evidence offered is questionable due to the limited number of patients and suboptimal (case-control) study design. Finally, the study showed an association but not a causality relationship between the upregulation of several genes in EAT and the presence of CAD.

This study[10] may have implications for risk stratification and secondary prevention measures in patients with CAD and obesity. The study findings increase the awareness of healthcare providers to potential detrimental effects of EAT in cardiovascular health. These findings may be particularly important for India for at least two reasons: first, obesity and CAD are on the rise in this country and expected to reach epidemic proportions soon. Second, there may be some ethnic differences, with the Indian population having a greater amount of visceral fat for each body mass index value compared with Caucasians[15]. As a consequence, a large number of individuals in India, particularly those with obesity, are expected to have expanded and dysfunctional EAT and these individuals may be at a higher risk of developing CAD than those with physiological amounts of EAT. Although there is no clear recommendation to assess EAT in the setting of risk stratification for CVD or CAD, evidence is mounting that EAT is an anatomic component of obesity (probably most morbid variant), metabolic syndrome or diabetes close and continuous with coronary arteries and myocardium and thus, it may be considered a local risk factor for CAD. In clinical settings, EAT may be quantified anatomically by two-dimensional transthoracic echocardiography, cardiac magnetic resonance imaging or computed tomography. Echocardiography remains the most accessible, cheap and safe procedure for EAT quantification, even though it is limited to assessing EAT surrounding the right ventricle and to not being volumetric. A value of EAT thickness >5 mm has been defined as the threshold for increased EAT thickness in low-risk individuals[7]. No such a threshold has been defined as a metric of increased EAT dimensions in obese individuals. Although currently, there are no means to modulate EAT structure or function *in situ* (except surgery), but several interventions including low-calorie diet, statins (atorvastatin), bariatric surgery and antidiabetic drugs (pioglitazone) have been shown to reduce EAT thickness (or volume) or favourably modify its secretome. To what extent these interventions reduce CVD risk by impacting on the EAT volume or thickness or function (secretome profile) remains unknown.

***Conflicts of Interest*:** None.

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