EDITORIAL

Diabetes enhances epicardial fat dysfunction

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by Haberka et al, see p. 738

The association between obesity and cardiovascular (CV) diseases has been well established.[1] Obesity accelerates both the progression of atherosclerosis and cardiac remodeling and increases the risk of associated diseases such as stroke or heart failure. This is in part mediated by its effects on common risk factors, for instance, glucose intolerance, diabetes, hypertension, as well as dyslipidemia.[1,2] CV dysfunction in both obesity and diabetes is therefore multifactorial. Major mechanisms include insulin resistance, inflammation, and endothelial and cardiac dysfunction.[3]

In the present issue of *Polish Archives of Internal Medicine* (*Pol Arch Intern Med*), Haberka et al[4] present a cross-sectional study, in which the parameters of epicardial fat were studied in patients with multivessel coronary artery disease (CAD), comparing patients with and without concomitant diabetes mellitus (DM). They elegantly analyzed the volume of epicardial fat using magnetic resonance imaging and then defined epicardial fat dysfunction based on a comprehensive analysis of mRNA profiles for major factors linked to the inflammatory and metabolic dysregulation of fat. Despite similar clinical and anthropometric characteristics, the authors observed a higher deposition of epicardial fat in patients with diabetes, while other fat depots—such as paracardial or perivascular fat collected from the thorax or the internal mammary artery, respectively—remained unchanged. This observation may indicate the unique properties and specific importance of epicardial fat in the progression of CAD in patients with diabetes.

It has been well established that the adipose tissue, as an endocrine organ, plays an important role in homeostasis in the course of CV disease.[5,6] Epicardial fat, located between the heart and the pericardium, surrounds the coronary arteries. Physiologically, this unique fat depot is crucial for various functions such as thermoregulation, mechanical protection, metabolism of free fatty acid, and secretion of bioactive factors involved in endothelial function, coagulation, and protection against inflammation.[7] Yet in a pathological state, the epicardial fat releases various proinflammatory and proatherogenic mediators, which affects the function of the coronary artery, increases immune infiltrate, and contributes to inflammatory burden.[5,6] Interestingly, it has been observed that coronary atherosclerotic plaques originate mainly in arteries surrounded by epicardial fat[7] and that DM significantly increases plaque burden when compared with people without diabetes.[8]

In addition, epicardial fat in patients with CAD demonstrates higher mRNA expression of genes involved in the activation of inflammatory, immunological, and metabolic pathways.[7] Haberka et al[4] have found that among patients with CAD, DM was associated with a more dysfunctional profile of mRNA expression in the adipose tissue surrounding the myocardium, manifested by a downregulation of the fibroblast growth factor 21 (FGF21) and an upregulation of the receptor for advanced glycation end-products (RAGE).

FGF21 belongs to the FGF family of proteins and is mainly produced in the liver. The expression of this peptide hormone occurs in the adipose tissue where it plays a pivotal role in the regulation of glucose uptake. The serum level of FGF21 is elevated in many CV diseases and is believed to be protective in conditions associated with hyperlipidemia, obesity, and diabetes.[9] Haberka et al[4] have found that paracardial and epicardial fat collected from diabetic patients had lower mRNA expression of FGF21. This reduction may contribute to a decline in a local level of FGF21 and affect its cardioprotective role shown in many studies. The administration of FGF21 reduces plasma glucose levels and triglycerides in obese and diabetic animals,[10] suppresses the development of atherosclerosis in apolipoprotein E knockout ($apoE^{-/-}$) mice,[11] and protects the heart after myocardial ischemia-reperfusion injury.[12] In clinical trials, the administration of synthetically engineered FGF21 variants, such as LY2 405 319 and PF-05 231 023, resulted in beneficial changes in lipoprotein profile, body weight, lipid, insulin, and adiponectin levels in obese diabetic patients.[13]

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These studies support the observations made by Haberka et al[4] and may suggest that such therapies could be tested in vascular disease in diabetes and concomitant CAD. In contrast, the recent work by Shen et al[14] shows that an elevated serum FGF21 level in patients with CAD was associated with a greater risk for developing major adverse cardiovascular events, which clearly indicates that further clinical studies on larger populations are needed.

Interestingly, increased expression of RAGE in CAD patients with DM was observed only in epicardial fat and not in other fat depots. This could suggest an important role of this tissue in potentiating the progression of CAD in diabetic subjects, although it is surprising, considering the classic role of visceral fat in diabetes. Increased level of RAGE is associated with the worst prognosis in patients with CV disease. Experimental studies[15] show that RAGE is upregulated in key injuries to the heart, including ischemia-reperfusion injury, diabetes, and inflammation. Furthermore, in atherosclerosis, RAGE influences leukocyte recruitment into the intima to a great extent. In both diabetic and nondiabetic models of atherosclerosis, the role of RAGE has been well established. Increased mRNA expression of RAGE was found in streptozotocin-induced diabetic apoE$^{-/-}$ mice. This was accompanied by the progression of atherosclerotic lesions and sustainment of proinflammatory and prothrombotic pathways. In contrast, the knockout of RAGE was associated with reduction of atherosclerotic plaque, decreased accumulation of immune cells, and attenuated expression of inflammatory cytokines in apoE$^{-/-}$ mice. Similar effects were obtained after pharmacologic inhibition with anti-RAGE antibodies.[16]

Another interesting observation presented by Haberka et al[4] is that none of the adipose tissue mRNA expression levels correlated with circulating plasma protein levels. This emphasizes that in humans, a level of plasma inflammatory biomarkers might not reflect a local inflammation sufficiently well. Given the lack of a clear separation barrier between the epicardial fat and myocardium and, further, common vascularization from the coronary artery, the local interaction between these two tissues may be more important than suspected.

Taken together, the blockade of ligand–RAGE axis and / or exogenous FGF21 therapy could be a useful therapeutic approach, particularly for patients with DM. However, these findings raise further questions. Do the changes in gene expression levels correlate with their products in epicardial fat? And more importantly: do these changes in expression carry clinical significance for prognosis? To answer these, larger populations need to be studied, but it is essential to consider future therapeutic targeting of these processes.

ARTICLE INFORMATION

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