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Editorial

Epicardial adipose tissue: A new cardiovascular risk marker?

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Over the last decade, the prevalence of obesity (body mass index; BMI ≥ 30 kg/m^2) and morbid obesity (BMI ≥ 40 kg/m^2) has been continuously increasing in the USA up to 30% and 6–8%, respectively [1]. This increase in obesity was also paralleled by an increase in cardiovascular morbidity and mortality issuing an intense public health debate [1]. Conversely, some studies have described that the presence of obesity was associated with a more favorable short- and long-term clinical outcome in individuals with coronary artery disease and heart failure [2]. In addition, reduced coronary atherosclerotic burden has been reported in individuals with morbid obesity in post-mortem analysis and in vivo cardiac computed tomography measured coronary artery calcifications [3,4]. The causes for this so called "obesity paradox" remain to be further elucidated but a heterogeneous manifestation and different entities of obesity may contribute to this [4–6]. It is also important to bear in mind that even differences in metabolic conditions and/or adipocytokine profile within an obesity disease entity may exist. For example, a dysbalance of various adipocytokines such as leptin, adiponectin, and/or endocannabinoids may be the critical determinant for cardiovascular risk rather than one hormonal and/or metabolic factor for itself [4,5,7,8]. More recently, the biological role of ectopic fat storages such as epicardial adipose tissue (EAT) has gained increasing attention in obesity. EAT has been realized not to be only a simple adipose tissue storage layer and to confer mechanistic protection to the heart vessels but rather to reflect a unique active endocrine organ that in the physiological setting provides important protective functions on the cardiovascular system, while these functions may turn detrimental under metabolic stress conditions affecting other tissues (Table 1) [9].

In this issue of *Int J Cardiol*, Ansaldo et al. [10] provide a unique and comprehensive report of the phenotypic shift of the EAT from its physiological towards a dysfunctional role promoting the initiation and/or progression of coronary artery disease (CAD), plaque vulnerability, and heart failure in obesity, metabolic syndrome, or type 2 diabetes mellitus, respectively. Recent research also outlines that EAT volume and thickness are influenced by genetic, epigenetic, and environmental factors [10]. In particular, EAT plays a key role in local lipid and glucose hemostasis. It functions as local storage for excess of free fatty acids in order to maintain myocardial energy supply and to prevent potential toxic effects of high levels of circulating free fatty acids on the myocardium and coronary vessels. Conversely, under metabolic stress conditions EAT releases free fatty acids in a much higher rate than other adipose tissue deposits and thereby enhancing metabolic abnormalities with its detrimental effects on cardiovascular health. EAT also exerts important homeostatic function by controlling the effects of insulin on the coronary microcirculation favoring insulin mediated vasodilation and glucose uptake. It is important to bear in mind that in the normal insulin-sensitive state of the arterial wall, insulin widely induces mitogen-activated protein kinase (MAPK) activation in the vascular endothelium, which confers endothelium-derived production and release of athero-protective nitric oxide with subsequent vasodilation. Conversely, in the insulin-resistant state, the insulin signaling cascade in the endothelium is geared more towards the phosphoinositide 3-kinase/Akt pathway leading to a coronary vasoconstrictor effect that, in conjunction with ET1-stimulated vascular smooth muscle cell contraction, overcomes the MAPK-mediated vasodilator and nitric oxide-mediated athero-protective effects. In the abnormal insulin-resistant state, therefore, EAT modulation of the net effect of insulin on the vascular endothelium may move the pendulum from athero-protection towards a paradoxical promotion of the CAD process. It would of further interest to investigate the role of EAT in influencing the adipocytokine and metabolic profile in different obesity disease entities such as standard obesity, morbid obesity, or visceral-inflammatory obesity in psoriasis [4–6]. For example, insulin resistance, insulin plasma levels and systemic inflammation commonly increases from obesity to morbid obesity, whereas there are no further decreases in high-density lipoprotein cholesterol and elevations in triglyceride plasma levels.

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Table 1
Studies investigating the relationship among EAT and cardiovascular outcome.

	Year	Numbers	Group characteristic	Cardiovascular outcome prediction
Britton KA et al. J Am Coll Cardiol	2013	3086	Framingham Heart Study Offspring and Third Generation Cohorts	Positive
Chen VY et al. J Am Coll Cardiol	2014	2751	Asymptomatic without known CAD	positive
Cheng VY et al. JACC Cardiovasc Imaging	2010	2751	Asymptomatic and intermediate pre-test probability for CAD	Positive
Ding J et al. Am J Clin Nutr	2009	6814	MESA Community-Based Prospective Cohort Study	Positive
D'Marco LG et al. Nephrol Dial Transplant	2013	109	Hemodialysis patients	Positive
Forouzandeh F et al. Circ Cardiovasc Imaging	2013	760	Acute chest pain admitted to the emergency department	Positive
Gitsioudis G et al. PLoS One	2016	177	Outpatients at intermediate risk for CAD	Positive
Greif M. et al. Cardiology	2012	145	Stable CAD	Positive
Hajsadeghi F et al. Atherosclerosis	2014	245	Suspicion for CAD	Positive
Kunita E et al. Atherosclerosis	2014	722	Atypical or non-cardiac chest pain and asymptomatic high risk individuals	Positive
Mahabadi AA et al. J Am Coll Cardiol	2013	4093	Population –based Heinz Nixdorf Recall cohort	Positive
Nakanishi K et al. Atherosclerosis	2014	517	Non-obese CAD patients with ACS	Positive
Possner M et al. Eur Heart J Cardivasc Imaging	2016	275	Known or suspected CAD	Negative
Shmilovich H et al. Am J Cardiol	2011	226	Asymptomatic and Healthy individuals with low Framingham Risk Score	Positive

Legend: CAD, coronary artery disease; ACS, acute coronary syndrome.

These differences in metabolic profile have been related to diverging adipose tissue distribution. Obesity is commonly characterized by increases in visceral adipose tissue that causes a higher fatty acid supply from the abdominal regions reinforcing the detrimental metabolic profile. This effect is lessened in morbid obesity with substantial increases in subcutaneous adipose tissue due to a lower lipolytic response to catecholamines, a higher antilipolytic sensitivity to insulin, and higher lipoprotein lipase activity. Such metabolic differences between obese and morbid obese individuals may also emerge in the adipocytokine profiles, such as endocannabinoids, leptin, and adiponectine, affecting coronary endothelial function that may favor or confer a certain protection against the initiation and/or progression of CAD [4,7]. For example, high plasma leptin levels, or yet unknown factors related to the effects of leptin, have been reported to contribute to maintain coronary endothelial function in morbid obesity [4]. On the other hand, this increase in high leptin plasma levels may play a central role in stimulating left ventricular hypertrophy, diastolic dysfunction, and heart failure manifestation. Contrasting effects of systemic micro-inflammation, as reflected by high levels of high-sensitive C-reactive protein, may also manifest in different obesity entities. While systemic micro-inflammation may contribute to cause coronary endothelial dysfunction as functional precursor of the CAD process in obesity, the inflammatory activation of the adipose tissue may not only lead to the release of inflammatory mediators such as adipocytokines but also endothelial progenitor cells involved in the protection and repair of the vascular endothelium in morbid obesity [4]. Overall, Ansaldo et al. [10] have to be complemented to provide such a unique and comprehensive review on the critical role of EAT in affecting cardiovascular health that should stimulate further investigations in the diverse entities of obesity.

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