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Review

Epicardial adipose tissue in the pathogenesis and progression of coronary artery disease

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Coronary artery disease (CAD) represents one of the most important causes of morbility, hospitalization and death, and its incidence greatly increases in the elderly population. In the last decades, several pieces of evidence have suggested a pathogenetic role of systemic and visceral fat inflammation in the development and progression of CAD. The epicardial adipose tissue (EAT), the visceral fat depot of heart, produces and secretes numerous pro-inflammatory mediators that could be involved in the pathogenesis of coronary atherosclerosis. Furthermore, age-related low-grade inflammation leads to the accumulation and inflammation of EAT. Therefore, this review aims to explore the potential implication of EAT in the pathogenesis of CAD, the link between systemic inflammation and an EAT pro-inflammatory phenotype, and, finally the perspectives for novel therapeutic strategies targeting the cardiac visceral fat.

Key words: Epicardial adipose tissue, Coronary artery disease, Elderly

INTRODUCTION

Coronary artery disease (CAD) represents one of the most important causes of morbility, hospitalization and death worldwide. In the elders, the incidence of cardiovascular disease is greatly increased. In particular, advanced age is associated with higher incidence of myocardial infarction, cardiovascular and extracardiac comorbidities [1-5]. Furthermore, elderly subjects form the largest and fastest growing part of the population, accounting for one-third of hospitalization for acute cardiovascular events and for most of all cardiac deaths [6-8]. Age has been reported as an important risk predictor in patients admitted in hospital with non-ST elevation myocardial infarction (NSTE-ACS) [9] and some studies have shown poor outcomes and high age-related mortality rates, after primary percutaneous coronary interventions in the elderly [10 11].

The causes of cardiovascular diseases are complex, but increasing evidence suggests a pathogenetic role of inflammation in the development and progression of CAD. The epicardial adipose tissue (EAT), the visceral fat depot of heart, produces and secretes numerous inflammatory mediators that could be involved in the pathogenesis of coronary atherosclerosis.

Inflammation and CAD

A correlation between inflammation and CAD has been initially hypothesized since autopsy studies, conducted in patients died for acute coronary syndrome, showed the presence of rich inflammatory infiltrates, consisting of lymphocytes, monocytes, and macrophages, in the adventitia of coronary arteries. In these studies, the degree of coronary narrowing correlated with the number of inflammatory cells in the coronary adventitia [12].

In the last decades, several pieces of evidence have supported the association between inflammation and CAD, identifying many inflammatory mediators involved in the atherosclerotic process. In particular, it has been demonstrated that, following an atherogenic stimulus, vascular cells adhesion molecule-1 binds monocytes and T lymphocytes [13]. Once adherent to

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the endothelium, the leukocytes penetrate the intima. Some chemoattractant molecules, such as monocyte chemoattractant protein-1 (MCP-1), are responsible for this transmigration at sites of lesion formation [14 15]. The recruited macrophages ingest lipids and become foam cells [16]. Afterwards, blood-derived inflammatory cells trigger and perpetuate a local inflammatory response, also through the release of numerous inflammatory and fibrogenic mediators, as tumor necrosis factor-α (TNF-α) and interleukins (IL) [17]. Interestingly, in the atherosclerotic plaque, activated macrophages and T cells can release hydrolytic enzymes, cytokines, chemokines and growth factors, leading to a focal necrosis of the fibrous cap, that becomes thin, weak, and susceptible to rupture [18 19]. Macrophages also produce tissue factor, the major procoagulant mediator, triggering thrombosis found in the plaques [20]. Thus, inflammation is responsible for the onset and progression of atherosclerotic process and plaques rupture.

The pathogenetic role of inflammation in the atherosclerotic process is also confirmed by high circulating levels of acute phase proteins. In clinical studies, elevated serum levels of C-reactive protein (CRP), IL-6 and TNF-α represent an important prognostic factor of atherosclerosis development both in patients with known CAD and in healthy population [21 22]. There is also a direct correlation between the level of CRP in the serum and the severity of atherosclerosis in patients with stable CAD [23]. In apparently healthy men, elevated levels of IL-6 are associated with increased risk of future myocardial infarction [24].

Of note, aging is characterized by the presence of chronic low-grade inflammation. This condition can contribute to the recruitment of inflammatory cells, damage and impairment of endothelial function, migration and proliferation of smooth muscle cells to the site of injury, resulting in the formation of early atherosclerotic lesions and higher susceptibility to CAD [19].

VISCERAL ADIPOSE TISSUE AND CAD

In the literature, visceral adipose tissue (VAT) is usually defined as an intra-abdominal accumulation of adiposity, predominantly localized at the omental and mesenteric level. The adipose tissue is composed of 50% of adipocytes and 50% of other cells, such as stromal vasculature fraction of fibroblasts, endothelial cells, macrophages and preadipocytes [25]. It has been demonstrated that persistent positive caloric balance, as occurs in obesity, induces excessive fat cell enlargement with consequent adipocyte metabolic and immune dysfunction [26-29]. These alterations lead to the activation of lipolysis, increased formation of free fatty acids (FFA), oxidative stress, hypoxia, and increased apoptosis of adipocytes [30]. Moreover, infiltrated monocytes generate M1 macrophages, increasing the total secretion of pro-inflammatory cytokines, such as TNF-a, IL-1β, and IL-6. Through these mediators, the increase of VAT mass can also contribute to systemic inflammation [31 32]. Several studies have confirmed the central role of this pro-inflammatory state in endothelial dysfunction and cardiovascular disease [33-35]. Of note, clinical data initially suggested the association between VAT and CAD. In one of the first observations, non-obese men with CAD showed larger VAT deposits than age- and BMI-matched controls [36]. The association with CAD remained significant even after adjustment for risk factors [37]. In a small study population with known CAD, it has been reported that increased VAT volume correlates with the presence of multivessel rather than single vessel disease [38]. In a recent study, VAT was associated with the risk of progression of non-calcified coronary artery plaques in patients with CAD [39]. Interestingly, in obese people, cardiovascular risk is predominantly associated with visceral than with subcutaneous adiposity [40 41].

EPICARDIAL ADIPOSE TISSUE AND CORONARY ARTERY DISEASE (FIG. 1)

EAT is the visceral fat depot of the heart, principally distributed in atrio-ventricular and interventricular grooves, between the myocardium and the visceral layer of pericardium. The absence of fascial boundaries permits a direct influence of EAT on surrounding tissues and coronary arterial vessels [42 43]. The increase of EAT mass is associated to production of several pro-inflammatory and pro-atherogenic mediators [44-47]. Interestingly, subjects with angiographically significant CAD show higher EAT thickness than patients without CAD. EAT thickness increases as the number of vessels with > 50% stenosis increase. On multiple logistic analysis including various CAD risk factors, EAT results an independent predictor of CAD [48 49]. A prospective study, exploring the metabolic activity of EAT measured by positron emission tomography (PET)/CT, has demonstrated that patients with NSTE-ACS show maximum fludeoxyglucose uptake (SUV) in fat surrounding coronary arteries. Additionally, the inflammatory activity of EAT was greater than in subcutaneous, visceral or thoracic adipose tissue, and correlated with plaque burden and with the necrotic core component, assessed by virtual histology intravascular ultrasound [50 51]. These clinical observations have been also supported by a positive correlation between density of macrophage infiltrates and SUV, in an experimental model of atherosclerosis [52].

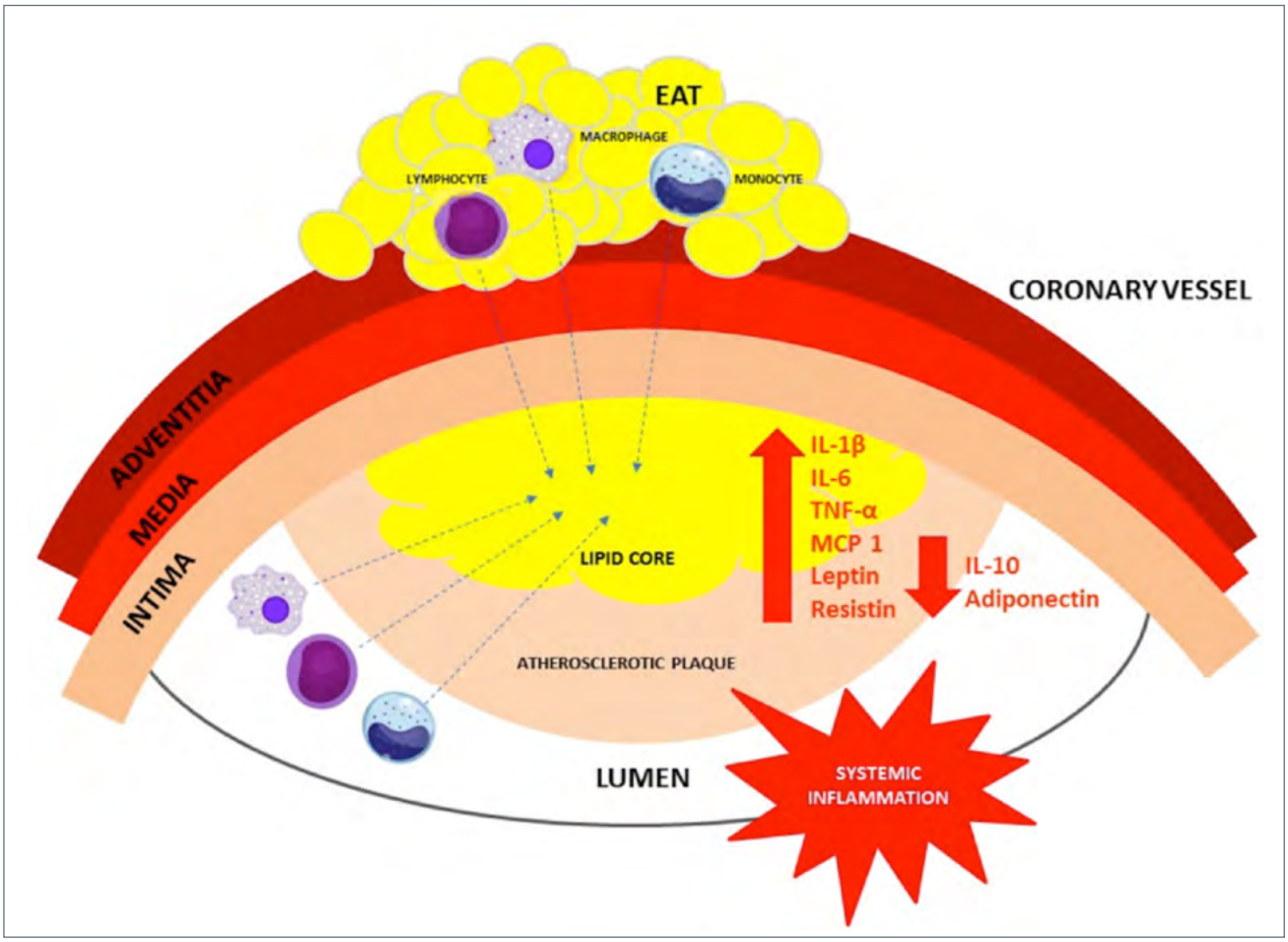

Figure 1. Involvement of epicardial adipose tissue in the pathogenesis of atherosclerotic plaque. The figure illustrates the intercorrelation between Epicardial Adipose Tissue (EAT) and systemic inflammation through a bidirectional continuum. Inflammatory cells from systemic circulation and from EAT penetrate the lipid core of the atherosclerotic plaque. The imbalance between production of pro-inflammatory and anti-inflammatory molecules promotes plaque progression and contributes to plaque instability and rupture.

Other studies, conducted in patients with established CAD, have demonstrated a pathological increase of EAT-derived inflammatory mediators and their messenger RNA, with a dense infiltration of inflammatory cells observed in EAT but not in the subcutaneous adipose tissue [45]. The inflammatory proatherogenic stimulus results more evident in patients with acute coronary syndromes than in patients with stable CAD [53].

In patients undergoing coronary artery bypass graft (CABG) surgery, it has been reported an increased EAT expression of interleukin (IL)-1β, IL-6, TNF-α, and MCP-1 compared to that observed in the subcutaneous adipose tissue [45 46]. In order to investigate the underlying mechanism of pro-inflammatory cytokines levels in EAT of CAD patients, Bourlier et al., performed immunohistochemistry against CD68, marker for all types of macrophages, CD11c, marker for inflammatory M1 macrophages, and CD206, marker for anti-inflammatory M2 macrophage. CD68 positive macrophages were significantly increased in the EAT of the CAD group. The ratio of CD11c/CD68-positive cells was significantly increased, while the ratio of CD206/CD68-positive cells was significantly decreased in the EAT of the CAD group [54]. This result demonstrates a relative increase of M1 macrophages and a relative decrease of M2 macrophages in the EAT of the CAD group. Furthermore, the ratio of M1/M2 macrophages showed a positive correlation with the severity of CAD. Overall, these results suggest that the macrophage polarization in EAT would play a central pathological role in the coronary atherosclerotic process [55-57].

Other studies have demonstrated that patients with acute coronary syndrome present with a higher expression and secretion of resistin in the EAT, compared to patients with stable CAD or subjects without CAD [58]. The exact role of resistin is currently unclear. It is

probably involved in the processes of inflammation and atherogenesis through increasing expression of adhesion molecules on endothelial cells and impairing vasodilation [59 60]. Resistin has been recently linked to the incidence of acute coronary syndromes and stroke [61]. In humans, resistin is produced by macrophages [62] and correlates with markers of inflammation, as well as with coronary atherosclerosis [63]. Plasma resistin levels have been also recently shown to be predictive of mortality in patients with acute myocardial infarction [64]. Similar clinical evidence has been reported for Leptin [65].

Several studies have identified adiponectin as the principal antiatherogenic protein detected in EAT in physiologic conditions. Adiponectin inhibits the expression of IL-8 by endothelial cells, increases the production of anti-inflammatory IL-10 and tissue inhibitor of metalloproteinase-1 in macrophages. Finally, this cytokine exerts vasodilatory properties on small arteries [66]. The observation of lower levels of adiponectin in the EAT of CAD patients [67] suggests that the pro-atherogenic properties of EAT in CAD are determined by both an increase of pro-inflammatory mediators and a decrease of anti-inflammatory cytokines.

Of note, the definitive demonstration of the causative role of EAT in the development and progression of CAD derives from animal studies. In fact, surgical resection of EAT depot in pigs arrests coronary atherogenesis [68-70].

As regards the intercorrelation between EAT and systemic inflammation, it is plausible to hypothesize a bidirectional continuum. The release of proinflammatory adipocytokines from EAT into the blood may contribute to the systemic inflammatory state; systemic inflammation in turn promotes the accumulation of EAT, which induces local and systemic inflammation and end-organ dysfunction [70-72].

PREVENTION AND THERAPEUTIC INTERVENTIONS

Given the recognized role of EAT in the development and progression of CAD, this adipose depot could represent a novel therapeutic target. First of all, dietary and lifestyle changes can affect the EAT volume and its inflammatory profile. Some studies have demonstrated that a marked wheight loss can lead to a reduction or stabilization of EAT volume [73 74]. Furthermore, in obese patients, Kim et al. [75] have shown that aerobic exercise is associated with lowering EAT mass. However, these data remain controversial and are only partially confirmed by studies conducted on patients underwent bariatric surgery, showing a greater decrease in VAT compared to EAT [76 77]. Interestingly, in experimental animals, Walker et al. [78] have tested EAT fatty acid composition and inflammatory gene expression after exposure to two different dietary patterns, containing respectively high levels of saturated or polyunsaturated fatty acids. High saturated fatty acids diet modulates EAT composition, increasing percentage of saturated fatty acid, and results positively associated with the expression of pro-inflammatory genes, providing a link between diet and EAT inflammation. Thus, changes in dietary quality could represent a nutritional strategy to reduce EAT inflammation and development of CAD.

As regards pharmacological interventions, new interesting perspectives could result from oral statin therapy. As known, this class of drug, in addition to lipid levels control, exerts relevant pleiotropic effects, such as modulation of cell signalling, differentiation and proliferation [79]. A recent study has reported a statin-induced decrease in EAT attenuation on computed tomography, independent of low-density lipoprotein cholesterol lowering, thus demonstrating a decrement in the metabolic activity of EAT by reduction in cellularity, vascularity and inflammation [80]. As reported by Parisi et al., the EAT thickness correlates with its inflammatory profile, thus the EAT volume reduction corresponds to a lower secretion of pro-inflammatory cytokines [44 81 82].

Furthermore, in the obese and diabetic populations, some studies have demonstrated that the use of glucagon-like-protein-1 receptor agonists (GLP-1R), in particular of liraglutide, induces a significant reduction of EAT (13%) after 12 weeks of treatment [83-85]. Moreover, liraglutide, but not metformin, reduces EAT by 29% and 36% at 3 and 6 months, respectively [84]. In an animal model, liraglutide also promotes browning and thermogenesis independently of nutrient intake [86].

Accordingly, sitagliptin, a DPP-4 inhibitor that prevents GLP-1 degradation, reduces EAT (15%) and VAT in diabetic individuals [87]. The thiazolidinediones, acting mainly through the PPAR-γ, regulate the expression of numerous factors secreted from adipose tissue that greatly influence insulin sensitivity [88].

Finally, novel opportunities could result from genetic manipulation using oligonucleotide inhibitors or microRNA mimics. MicroRNAs are short noncoding RNA molecules, that permit the fine-tuning of protein expression *in vivo* [89] and the modulation of important biological pathways, such as vascular proliferation (miR-21), remodeling (miR-143/miR145), and atherosclerosis (miR-126) [90]. It has been demonstrated that some microRNAs, involved in regulation of adiponectin, glucose and fatty acids, are upregulated in abdominal adipose tissue of obese patients [91 92]. Further studies are needed to demonstrate the same effect in EAT.

Unfortunately, outcome studies reporting the predictive value of diet and/or drug related EAT reduction in CAD patients are not yet available. These studies are

dramatically needed given the emergent role of EAT in the pathogenesis of several cardiovascular diseases.

CONCLUSIONS

Several studies have demonstrated the participating role of pro-inflammatory mediators in the atherogenic process. Because of the intimacy with myocardium and coronary vessels, the EAT seems to be the main source of pro-atherogenic molecules, involved in the development and progression of CAD. Realistically, the causative role of EAT in CAD is determined by both an increase of pro-inflammatory mediators and a decrease of anti-inflammatory molecules. Furthermore, chronic inflammatory disorders and age-related low-grade inflammation lead to the accumulation and inflammation of EAT, promoting in turn local and systemic inflammation with unavoidable implications in the pathogenesis of CAD. Finally, dietary/life-style changes and/or drug therapies can modify volume and secretory profile of EAT, thus suggesting that cardial visceral fat might represent, in the next future, a novel therapeutic target for CAD patients.

Conflict of interest

The Authors declare to have no conflict of interest.

References

1 Forman DE, Chen AY, Wiviott SD, et al. *Comparison of outcomes in patients aged < 75, 75 to 84, and ≥ 85 years with ST-elevation myocardial infarction (from the ACTION Registry-GWTG)*. Am J Cardiol 2010;106:e1382-8.

2 Lye M, Donnellan C. *Heart disease in the elderly.* Heart 2000;84:e560-6.

3 Ungar A, Galizia G, Morrione A, et al. *Two-year morbidity and mortality in elderly patients with syncope*. Age Ageing 2011;40:696-702. Doi: 10.1093/ageing/afr109.

4 Cacciatore F, Abete P, de Santis D, et al. *Mortality and blood pressure in elderly people with and without cognitive impairment*. Gerontology 2005;51:53-61.

5 Ungar A, Mussi C, Ceccofiglio A, et al. *Etiology of syncope and unexplained falls in elderly adults with dementia: Syncope and Dementia (SYD) study.* J Am Geriatr Soc 2016;64:1567-73.

6 Goldberg RJ, Yarzebski J, Lessard D, et al. *A two-decades (1975 to 1995) long experience in the incidence, in-hospital and long-term case-fatality rates of acute myocardial infarction: a community-wide perspective.* J Am Coll Cardiol 1999;33:1533-9.

7 Cacciatore F, Abete P, Mazzella F, et al. *Six-minute walking test but not ejection fraction predicts mortality in elderly patients undergoing cardiac rehabilitation following coronary artery bypass grafting.* Eur J Prev Cardiol 2012;19:1401-9. Doi: 10.1177/1741826711422991.

8 Martone AM, Bianchi L, Abete P, et al. *The incidence of sarcopenia among hospitalized older patients: results from the Glisten study.* J Cachexia Sarcopenia Muscle 2017;8:907-14.

9 Fox KAA, Dabbous OH, Goldberg RJ, et al. *Prediction of risk of death and myocardial infarction in the six months after presentation with acute coronary syndrome: prospective multinational observational study (GRACE)*. BMJ 2006;333:1091. Doi:10.1136/ bmj.38985.646481.55

10 Wang TY, Gutierrez A, Peterson ED. *Percutaneous coronary intervention in the elderly.* Nat Rev Cardiol 2011;8:e79-90.

11 McKellar SH, Brown ML, Frye RL, et al. *Comparison of coronary revascularization procedures in octogenarians: a systematic review and meta-analysis.* Nat Clin Pract Cardiovasc Med 2008;5:e738-46.

12 Kohchi K, Takebayashi S, Hiroki T, et al. *Significance of adventitial inflammation of the coronary artery in patients with unstable angina: results of autopsy.* Circulation 1985;71:709-16.

13 Li H, Cybulsky MI, Gimbrone MA Jr, et al. *An atherogenic diet rapidly induces VCAM-1, a cytokine regulatable mononuclear leukocyte adhesion molecule, in rabbit endothelium.* Arterioscler Thromb 1993;13:197-204.

14 Gu L, Okada Y, Clinton S, et al. *Absence of monocyte chemoattractant protein-1 reduces atherosclerosis in low-density lipoprotein-deficient mice.* Mol Cell 1998;2:275-81, 8.

15 Boring L, Gosling J, Cleary M, et al. *Decreased lesion formation in CCR -/- mice reveals a role for chemokines in the initiation of atherosclerosis.* Nature 1998;394:894-7.

16 Smith JD, Trogan E, Ginsberg M, et al. *Decreased atherosclerosis in mice deficient in both macrophage colony-stimulating factor (op) and apolipoprotein E.* Proc Natl Acad Sci USA 1995;92:8264-8.

17 Hansson G, Libby P. *The role of the lymphocyte*. In: Fuster V, Ross R, Topol E, Eds. *Atherosclerosis and CAD.* New York, NY: Lippincott-Raven 1996, pp. 557-68.

18 Virmani R, Burke AP, Farb A, et al. *Pathology of vulnerable plaque*. JACC 2006;47:C13-8.

19 Libby P. *Current concepts of the pathogenesis of the acute coronary syndromes*. Circulation 2001;104:365-72.

20 Libby P, Simon DI. *Inflammation and thrombosis: the clot thickens.* Circulation 2001;103:1718-20.

21 Tommasi S, Carluccio E, Bentivoglio M, et al. *C-reactive-protein as a marker for cardiac ischemic events in the year after a first, uncomplicated myocardial infarction*. Am J Cardiol 1999;83:1595-9.

22 Curcio F, Ferro G, Basile C, et al. *Biomarkers in sarcopenia: a multifactorial approach*. Exp Gerontol 2016;85:1-8.

23 Liuzzo G, Biasucci LM, Gallimore JR, et al. *The prognostic value of C-reactive protein and serum amyloid A protein in severe unstable angina.* N Engl J Med 1994;331:417-23.

24 Ridker PM, Rifai N, Stampfer MJ, et al. *Plasma concentration of interleukin-6 and the risk of future myocardial infarction among apparently healthy men.* Circulation 2000;101:1767-72.

25 Bays HE, González-Campoy JM, Bray GA, et al. *Pathogenic*

potential of adipose tissue and metabolic consequences of adipocyte hypertrophy and increased visceral adiposity. Expert Rev Cardiovasc Ther 2008;6:343-68. Doi: 10.1586/14779072.6.3.343.

26 Bays H, Blonde L, Rosenson R. *Adiposopathy: how do diet, exercise, weight loss and drug therapies improve metabolic disease?* Expert Rev Cardiovasc Ther 2006;4:871-95.

27 Ailhaud G. *Adipose tissue as a secretory organ: from adipogenesis to the metabolic syndrome*. CR Biol 2006;329:570-7.

28 Salans LB, Bray GA, Cushman SW, et al. *Glucose metabolism and the response to insulin by human adipose tissue in spontaneous and experimental obesity*. *Effects of dietary composition and adipose cell size*. J Clin Invest 1974;53:848-56.

29 Bray GA, Glennon JA, Salans LB, et al. *Spontaneous and experimental human obesity: effects of diet and adipose cell size on lipolysis and lipogenesis*. Metabolism 1977;26:739-47.

30 Alkhouri N, Gornicka A, Berk MP, et al. *Adipocyte apoptosis, a link between obesity, insulin resistance, and hepatic steatosis*. J Biol Chem 2010;285:e3428-38.

31 Guarner V, Rubio-Ruiz ME. *Low-grade systemic inflammation connects aging,metabolic syndrome and cardiovascular disease.* Interdiscip Top Gerontol 2015;40:99-106. Doi: 10.1159/000364934.

32 Frigolet ME, Torres N, Tovar AR. *White adipose tissue as endocrine organ and its role in obesity*. Arch Med Res 2008;39:715-28.

33 Mathieu P, Poirier P, Pibarot P, et al. *Visceral obesity: the link among inflammation, hypertension, and cardiovascular disease.* Hypertension 2009;53:577-84. Doi: 10.1161/HYPERTENSIONAHA.108.110320

34 Neeland IJ, Ayers CR, Rohatgi AK, et al. *Associations of visceral and abdominal subcutaneous adipose tissue with markers of cardiac and metabolic risk in obese adults*. Obesity 2013;21:e439-47. Doi: 10.1002/oby.20135

35 Britton KA, Massaro JM, Murabito JM, et al. *Body fat distribution, incident cardiovascular disease, cancer, and all-cause mortality.* J Am Coll Cardiol 2013;62:921-5.

36 Nakamura T, Tokunaga K, Shimomura I, et al. *Contribution of visceral fat accumulation to the development of CAD in non-obese men.* Atherosclerosis 1994;107:e239-46.

37 Marques MD, Santos RD, Parga JR, et al. *Relation between visceral fat and CAD evaluated by multidetector computed tomography.* Atherosclerosis 2010;209:e481-6.

38 Lee YH, Lee SH, Jung ES, et al. *Visceral adiposity and the severity of CAD in middle-aged subjects with normal waist circumference and its relation with lipocalin-2 and MCP-1*. Atherosclerosis 2010;213:e592-7.

39 Imai A, Komatsu S, Ohara T, et al. *Visceral abdominal fat accumulation predicts the progression of noncalcified coronary plaque.* Atherosclerosis 2012;222:e524-9.

40 Fox CS, Massaro JM, Hoffmann U, et al. *Abdominal visceral and subcutaneous adipose tissue compartments: association with metabolic risk factors in the Framingham Heart study*. Circulation 2007;116:e39-48.

41 De Fronzo RA. I*nsulin resistance, lipotoxicity, type 2 diabetes and atherosclerosis: the missing links. The Claude Bernard Lecture 2009*. Diabetologia 2010;53;e1270-87.

42 Sacks HS, Fain JN. *Human epicardial adipose tissue: a review.* Am Heart J 2007;153:907-17.

43 Rabkin RW. *Epicardial fat: properties, function and relationship to obesity*. Obes Rev 2007;8:253-61.

44 Parisi V, Petraglia L, D'Esposito V, et al. *Statin therapy modulates thickness and inflammatory profile of human epicardial adipose tissue.* Int J Cardiol 2019;274:326-30. Doi: 10.1016/j.ijcard.2018.06.106

45 Mazurek T, Zhang L, Zalweski A, et al. *Human epicardial adipose tissue is a source of inflammatory mediators*. Circulation 2003;108:2460-6.

46 Parisi V, Rengo G, Perrone-Filardi P, et al. *Increased epicardial adipose tissue volume correlates with cardiac sympathetic denervation in patients with heart failure*. Circ Res 2016;118:1244-53. Doi: 10.1161/CIRCRESAHA.115.307765

47 Parisi V, Paolillo S, Rengo G, et al. *Sleep-disordered breathing and epicardial adipose tissue in patients with heart failure.* Nutr Metab Cardiovasc Dis 2018;28:126-32. Doi: 10.1016/j.numecd.2017.09.012

48 Ahn SG, Lim HS, Joe DY, et al. *Relationship of epicardial adipose tissue by echocardiography to CAD.* Heart 2008;94:e7.

49 Picard FA, Gueret P, Laissy JP, et al. *Epicardial adipose tissue thickness correlates with the presence and severity of angiographic CAD in stable patients with chest pain*. PloS One 2014;Oct 21. Doi: 10.1371/journal.pone.0110005

50 Mazurek T, Opolski G. *Pericoronary adipose tissue: a novel therapeutic target in obesity-related coronary atherosclerosis.* J Am Coll Nutr 2015;34:244-54. Doi: 10.1080/07315724.2014.933685

51 Mazurek T, Kochman J, Kobylecka M, et al. *Inflammatory activity of pericoronary adipose tissue may affect plaque composition in patients with acute coronary syndrome without persistent ST-segment elevation: preliminary results*. Kardiol Pol 2013;72:410-6.

52 Ogawa M, Magata Y, Kato T, et al. *Application of 18-F-FDG PET for monitoring the therapeutic effect of antiinflammatory drugs on stabilization of vulnerable atherosclerotic plaques.* J Nucl Med 2007;47:1845-50.

53 Nakanishi K, Fukuda S, Tanaka A, et al. *Epicardial adipose tissue accumulation is associated with renal dysfunction and coronary plaque morphology on multidetector computed tomography*. Circ J 2016;80:196-201.

54 Bourlier V, Zakaroff-Girard A, Miranville A, et al. *Remodeling phenotype of human subcutaneous adipose tissue macrophages*. Circulation 2008;117:806-15. Doi: 10.1161/CIRCULATIONAHA.107.724096

55 Lumeng CN, Bodzin JL, Saltiel AR. *Obesity induces a phenotypic switch in adipose tissue macrophage polarization.* J Clin Invest 2007;117:175-84.

56 Hirata Y, Tabata M, Kurobe H, et al. *Coronary atherosclerosis is associated with macrophage polarization in epicardial adipose tissue.* J Am Coll Cardiol 2011;58:248-55.

[57] Margaritis M, Antonopoulos AS, Digby J, et al. *Interactions between vascular wall and perivascular adipose tissue reveal novel roles for adiponectin in the regulation of endothelial nitric oxide synthase function in human vessels*. Circulation 2013;127:2209-21.

[58] Cheng KH, Chu CS, Lee KT, et al. *Adipocytokines and proinflammatory mediators from abdominal and epicardial adipose tissue in patients with CAD*. Int J Obes (Lond) 2008;32:268-74.

[59] Verma S, Li SH, Wang CH, et al. *Resistin promotes endothelial cell activation: further evidence of adipokine-endothelial interaction*. Circulation 2003;108:736-40.

[60] Gentile MT, Vecchione C, Marino G, et al. *Resistin impairs insulin-evoked vasodilation.* Diabetes 2008;57:577-83.

[61] Weikert C, Westphal S, Berger K, et al. *Plasma resistin levels and risk of myocardial infarction and ischemic stroke.* J Clin Endocrinol Metab 2008;93:2647-53.

[62] Fain JN, Cheema PS, Bahouth SW, et al. *Resistin release by human adipose tissue explants in primary culture*. Biochem Biophys Res Commun 2003;300:674-8.

[63] Reilly MP, Lehrke M, Wolfe ML, et al. *Resistin is an inflammatory marker of atherosclerosis in humans.* Circulation 2005;111:932-9.

[64] Lee SH, Ha JW, Kim JS, et al. *Plasma adiponectin and resistin levels as predictors of mortality in patients with acute myocardial infarction: data from infarction prognosis study registry*. Coron Artery Dis 2009;20:33-9.

[65] Payne GA, Borbouse L, Kumar S, et al. *Epicardial perivascular adipose-derived leptin exacerbates coronary endothelial dysfunction in metabolic syndrome via a protein kinase C-beta pathway.* Arterioscler Thromb Vasc Biol 2010;30:1711-7.

[66] Kumada M, Kihara S, Ouchi N, et al. *Adiponectin specifically increased tissue inhibitor of metalloproteinase-1 through interleukin-10 expression in human macrophages*. Circulation 2004;109:2046-9.

[67] Pischon T, Girman CJ, Hotamisligil GS, et al. *Plasma adiponectin levels and risk of myocardial infarction in men.* JAMA 2004;291:1730-7.

[68] McKenney-Drake ML, Rodenbeck SD, Bruning RS, et al. *Epicardial adipose tissue removal potentiates outward remodeling and arrests coronary atherogenesis.* Ann Thorac Surg 2017;103:1622-30.

[69] McKenney ML, Schultz KA, Boyd JH, et al. *Epicardial adipose excision slows the progression of porcine coronary atherosclerosis.* J Cardiothorac Surg 2014;9:2.

[70] Packer M. *Epicardial adipose tissue may mediate deleterious effects of obesity and inflammation on the myocardium.* J Am Coll Cardiol 2018;71:2360-72. Doi: 10.1016/j.jacc.2018.03.509

[71] Patel VB, Shah S, Verma S, et al. *Epicardial adipose tissue as a metabolic transducer: role in heart failure and coronary artery disease.* Heart Fail Rev 2017;22:889-902.

[72] Baghdadi LR, Woodman RJ, Shanahan EM, et al. *The impact of traditional cardiovascular risk factors on cardiovascular outcomes in patients with rheumatoid arthritis: a systematic review and meta-analysis.* PLoS One 2015;10:e0117952.

[73] Nakazato R, Rajani R, Cheng VY, et al. *Weight change modulates epicardial fat burden: a 4-year serial study with non-contrast computed tomography.* Atherosclerosis 2012;220:139-44.

[74] Fu CP, Sheu WH, Lee IT, et al. *Effects of weight loss on epicardial adipose tissue thickness and its relationship between serum soluble CD40 ligand levels in obese men*. Clin Chim Acta 2013;421:98-103.

[75] Kim MK, Tomita T, Kim MJ, et al. *Aerobic exercise training reduces epicardial fat in obese men*. J Appl Physiol 2009;106:5-11.

[76] Foppa M, Pond KK, Jones DB, et al. *Subcutaneous fat thickness, but not epicardial fat thickness, parallels weight reduction three months after bariatric surgery: a cardiac magnetic resonance study*. Int J Cardiol 2013;168:4532-3. Doi: 10.1016/j.ijcard.2013.06.099

[77] Wu FZ, Huang YL, Wu CC, et al. *Differential effects of bariatric surgery versus exercise on excessive visceral fat deposits.* Medicine 2016;95:e2616.

[78] Walker ME, Matthan NR, Goldbaum A, et al. *Dietary patterns influence epicardial adipose tissue fatty acid composition and inflammatory gene expression in the Ossabaw pig*. J Nutr Biochem 2019;70:138-46. Doi: 10.1016/j.jnutbio.2019.04.013

[79] Corsini A. Bellosta S, Baetta R, et al. *New insights into the pharmacodynamic and pharmacokinetic properties of statins.* Pharmacol Ther 1999;84:413-28.

[80] Raggi P, Gadiyaram V, Zhang C, et al. *Statins reduce epicardial adipose tissue attenuation independent of lipid lowering: a potential pleiotropic effect*. J Am Heart Assoc 2019;8:e013104. Doi: 10.1161/JAHA.119.013104

[81] Parisi V, Rengo G, Pagano G, et al. *Epicardial adipose tissue has an increased thickness and is a source of inflammatory mediators in patients with calcific aortic stenosis*. Int J Cardiol 2015;186:167-9. Doi: 10.1016/j.ijcard.2015.03.201

[82] Parisi V, Leosco D, Ferro G, et al. *The lipid theory in the pathogenesis of calcific aortic stenosis.* Nutr Metab Cardiovasc Dis 2015;25:519-25. Doi: 10.1016/j.numecd.2015.02.001

[83] Morano S, Romagnoli E, Filardi T, et al. *Short-term effects of glucagon-like peptide 1 (GLP-1) receptor agonists on fat distribution in patients with type 2 diabetes mellitus: an ultrasonography study.* Acta Diabetol 2015;52:727-32.

[84] Iacobellis G, Mohseni M, Bianco SD, et al. *Liraglutide causes large and rapid epicardial fat reduction.* Obesity 2017;25:311-6.

[85] Ferrara N, Abete P, Corbi G, et al. *Insulin-induced changes in beta-adrenergic response: an experimental study in the isolated rat papillary muscle.* Am J Hypertens 2005;18:348-53.

[86] Beiroa D, Imbernon M, Gallego R, et al. *GLP-1 agonism stimulates brown adipose tissue thermogenesis and browning through hypothalamic AMPK*. Diabetes 2014;63:3346-58.

[87] Lima-Martínez MM, Paoli M, Rodney M, et al. *Effect of sitagliptin on epicardial fat thickness in subjects with*

type 2 diabetes and obesity: a pilot study. Endocrine 2016;51:448-55.

88 Della-Morte D, Palmirotta R, Rehni AK, et al. *Pharmacogenomics and pharmacogenetics of thiazolidinediones: role in diabetes and cardiovascular risk factors.* Pharmacogenomics 2014;15:2063-82. Doi: 10.2217/pgs.14.162

89 Gallagher IJ, Scheele C, Keller P, et al. *Integration of microRNA changes in vivo identifies novel molecular features of muscle insulin resistance in type 2 diabetes.* Genome Med 2010;2:9.

90 Small EM, Olson EN. *Pervasiveroles of microRNAs in cardiovascular biology.* Nature 2011;469:336-42.

91 Keller P, Gburcik V, Petrovic N, et al. *Gene-chip studies of adipogenesis-regulated microRNAs in mouse primary adipocytes and human obesity.* BMC Endocr Disord 2011;11:7.

92 Xie H, Lim B, Lodish HF. *MicroRNAs induced during adipogenesis that accelerate fat cell development are downregulated in obesity.* Diabetes 2009;58:1050-7.

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