REVIEW ARTICLE

Epicardial Adipose Tissue as Predictor of Coronary Artery Disease. A New Parameter to Stratify Cardiovascular Risk?

Tejido adiposo epicárdico como predictor de enfermedad coronaria. ¿Un nuevo parámetro para la estratificación del riesgo cardiovascular?

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ABSTRACT

The association between visceral adipose tissue and cardiovascular disease has been clearly established. Likewise, it has been determined that ectopic adiposity is associated with a higher cardiovascular risk compared to subcutaneous adiposity. In this context, multiple investigations have evaluated the role of epicardial adipose tissue (EAT) in cardiovascular disease. EAT is located between the myocardial surface and the visceral layer of the pericardium, and can be quantified by noninvasive techniques such as echocardiography, computed tomography, or magnetic resonance imaging. The EAT is not simply a storage organ. Currently, it is considered to be a metabolically active tissue capable of secreting multiple adipokines that act through different paracrine, endocrine, vasocrine and/or autocrine signaling pathways. Current evidence suggests that EAT may be a contributing factor in the pathogenesis of coronary heart disease, as well as being associated with its severity and progression. In this sense, some authors have postulated EAT as a new cardiovascular risk factor and as a potential therapeutic target.
The aim of this review is to analyze the association between EAT and cardiovascular disease, mainly coronary artery disease.

Keywords: Epicardial adipose tissue - Cardiovascular risk - Coronary heart disease.

RESUMEN

La asociación entre el tejido adiposo visceral y la enfermedad cardiovascular ha sido claramente establecida. Asimismo, se ha determinado que la adiposidad ectópica se asocia con un mayor riesgo cardiovascular en comparación a la adiposidad subcutánea. En este contexto, múltiples investigaciones han evaluado el rol del tejido adiposo epicárdico (TAE) en la enfermedad cardiovascular. El TAE se localiza entre la superficie miocárdica y la hoja visceral del pericardio, y puede cuantificarse mediante técnicas no invasivas como ser el ecocardiograma, la tomografía computada o la resonancia nuclear magnética. El TAE no es simplemente un órgano de depósito. Actualmente, se considera que es un tejido metabólicamente activo capaz de secretar múltiples adipoquinas que actúan mediante diferentes vías de señalización parácrina, endócrina, vasócrina y/o autócrina. La evidencia actual sugiere que el TAE puede ser un factor contribuyente en la patogénesis de la enfermedad coronaria, asociándose además con su gravedad y progresión. En ese sentido, algunos autores han postulado al TAE como un nuevo factor de riesgo cardiovascular y como un potencial blanco terapéutico.
El objetivo de esta revisión es analizar la relación del TAE con la enfermedad cardiovascular, principalmente con la enfermedad coronaria.

Palabras clave: Tejido adiposo epicárdico - Riesgo cardiovascular - Enfermedad coronaria

INTRODUCTION

Cardiovascular disease is the leading cause of morbidity and mortality worldwide. By 2030, non-communicable diseases are expected to account for three quarters of deaths, representing 66% of the disease burden worldwide. (1) Despite this discouraging scenario, these diseases are largely preventable.

The association between visceral fat and cardiovascular disease is well known, and the metabolic and cardiovascular risk depends not only on the amount of adipose tissue, but also on its type and body distribution. (2) In that sense, compared with subcutaneous fat, ectopic fat deposition is associated with higher cardiovascular risk. In this setting, the role of epicardial adipose tissue (EAT) in cardiovascular disease has been investigated.

The EAT is located between the myocardial surface and the visceral layer of the pericardium and is not separated from the myocardium and coronary vessels by fascia. Like visceral fat, EAT originates

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from the mesoderm during embryogenesis. It should be noted that EAT differs from pericardial adipose tissue, which is located between the visceral layer and the parietal layer of the pericardium and has its embryological origin in the ectoderm.

The aim of this review is to analyze the association between EAT and cardiovascular disease, mainly coronary artery disease (CAD).

Diagnostic methods to analyze epicardial adipose tissue

There are several non-invasive techniques to determine EAT. Echocardiography and computed tomography scan are the main methods proposed. Echocardiography is a simple, safe, low-cost, reproducible and widely available method; computed tomography is a more precise method and allows assessment of EAT thickness and volume.

Epicardial adipose tissue is identified by echocardiographists as the echo-free space between the outer wall of the myocardium and the visceral layer of the pericardium. Iacobellis et al. suggest measuring EAT from the parasternal long-axis view, (3) perpendicularly on the free wall of the right ventricle at end-systole (because it is compressed during diastole and the absolute value may be underestimated), using the aortic annulus as an anatomic landmark. Three measurements should be made in 3 cardiac cycles, and the average value is then determined. This procedure shows high intraobserver and interobserver agreement. However, many authors criticize the variability in the measurements and add that as a two-dimensional image it does not allow quantification of the entire volume.

Alternatively, the use of magnetic resonance imaging and computed tomography scan have been suggested; CT scanning is nowadays the method of choice. Both studies allow for more precise estimation of thickness and volume, with less variability compared with echocardiography. (4-6) As technology progresses, new models are being developed to provide semi-automatic or automatic quantification based on artificial intelligence. Computed tomography would also provide simultaneous determination of the coronary calcium score. In addition, increased density of EAT would indicate local inflammation and neovascularization, adding a qualitative estimation. (7, 8) In contrast, these methods are more expensive, less accessible and, in the case of computed tomography, patients are exposed to ionizing radiation.

EAT values by sex and age and the cut-off point values to consider increased EAT have not been standardized yet.

Epicardial adipose tissue and atherosclerosis

Adipose tissue is not merely a storage organ; it is currently considered a metabolically active tissue capable of releasing multiple adipokines that act through different paracrine, endocrine, vasocrine or autocrine signaling pathways. (3, 9) Current knowledge suggests that EAT would not be an exception, as it would have a strong influence on adjacent and distant tissues. Adipocyte size is an important determinant of cytokine expression. In fact, some authors consider that there could be a mass-dependent mechanism that could determine its metabolic profile. (3)

Under physiological conditions, EAT exerts protective effects on the heart. In this context, Iacobellis et al. have demonstrated that EAT adipocytes have smaller size, different protein content and act as a buffer by synthesizing and breaking down fatty acids, protecting the myocardium from the lipotoxicity generated by them. (3, 10) In addition, EAT is also capable of releasing several anti-inflammatory and anti-atherogenic hormones, such as adiponectin, which regulates energy and glucose metabolism, improves endothelial function and reduces the proliferation of smooth muscle tissue cells. (11)

Under pathologic conditions, such as in patients with obesity or type II diabetes mellitus, adipocyte hyperplasia and hypertrophy in the EAT occurs along with changes in gene expression and metabolism. (3, 10) This results in greater release of free fatty acids due to increased lipolysis and impaired buffer capacity of EAT, with consequent increased lipotoxicity. Furthermore, it promotes the release of proinflammatory molecules and adhesion molecules that could act on smooth muscle cells and endothelial cells promoting the differentiation of mesenchymal cells to fibroblasts, migration of monocytes, macrophages and lymphocytes, and the transformation of macrophages into foam cells, thus creating a proatherogenic environment. (4, 9, 12, 13) In other words, the current evidence indicates that EAT may play a proatherogenic or anti-atherogenic role, depending on the patient's setting.

Multiple reports have evaluated the association between EAT and traditional cardiovascular risk factors. One of the most interesting findings was the significant association between increased EAT and the prevalence of metabolic syndrome and each of its components even after adjusting for possible confounders. (12, 14-16) The estimation of EAT could provide more accurate information than that obtained with other variables used for the quantification of adipose tissue, such as waist circumference or body mass index, since these parameters do not differentiate between visceral and subcutaneous adipose tissue.

Epicardial adipose tissue and coronary artery disease

The current evidence suggests that EAT may contribute to the pathogenesis of coronary artery disease and may also be associated with its severity and progression.

Atherosclerotic plaques in coronary arteries tend to be more prominent in the proximity of adipose tissue. (17) Coronary artery segments with an intramyocardial course, and therefore without direct contact with EAT, rarely present atherosclerotic plaques.

These findings could be explained by embryologic, histologic, morphologic and biomechanical differences between both locations, and by the differences in the physical conditions and of the surrounding tissues. In this regard, patients with coronary artery disease present an increased expression of activated macrophages and lymphocytes in EAT but not in subcutaneous adipose tissue. (18,19) In addition, the expression and secretion of inflammatory cytokines in EAT is higher in areas close to atherosclerotic lesions of the coronary arteries. (20-22)

Several studies have demonstrated a significant and independent association (adjusted for traditional risk factors) between increased EAT thickness or volume and the presence of atherosclerotic lesions of the coronary arteries, and even with the severity of stenosis and the presence of certain "high-risk" features. (23-26)

After analyzing several predictive models in a derivation cohort (n = 5743) and a validation cohort (n = 2844 patients) of stable patients with chest pain, Zhou et al. proposed to include EAT and coronary calcium score as tools to predict obstructive coronary artery disease. (27) In this case, EAT was quantified by computed tomography scan. After adjusting for potential confounders, EAT volume >100 mL was significantly associated with the presence of obstructive coronary artery disease. A predictive model incorporating EAT and coronary calcium score presented an area under the ROC curve of 0.873 (95% CI, 0.864–0.883) that was significantly better than that of model including only traditional risk factors (0.789; 95% CI, 0.777–0.801; p <0.0001). In addition, the model that included EAT as a predictor variable showed a higher net reclassification index than the models that did not include it.

A cohort study analyzing 517 non-obese patients assessed whether progression in EAT volume estimated by computed tomography scan could predict the progression of coronary artery stenosis (assessed by computed tomography angiography) and the development of related clinical events. (28) Patients with increased EAT volume during follow-up had a higher incidence of obstructive coronary artery disease and of plaques with high-risk features. Moreover, patients with increased EAT volume had higher risk of presenting an acute coronary syndrome after an average follow-up of 4 years (HR 3.78; 95% CI, 2.00-7.67; p<0.001) than those without increased EAT volume (Figure 1).

Beyond the association between EAT and anatomic involvement of the coronary arteries, recent research suggests that EAT may affect coronary artery function. In this sense, EAT resulted an independent predictor of myocardial ischemia in a recent publication. (29, 30)

A meta-analysis of 33 studies including 41 534 patients evaluated the association between EAT and the presence of obstructive or significant coronary artery stenosis (stenosis ≥50% and ≥70% in at least one coronary artery, respectively), coronary calcium score (score >0), the presence of myocardial ischemia, and major adverse cardiovascular events (MACE) after adjusting for traditional cardiovascular risk factors. (31) In all the articles included in the review, EAT was quantified by computed tomography scan. The main findings demonstrated a significant and independent association between EAT volume and the presence

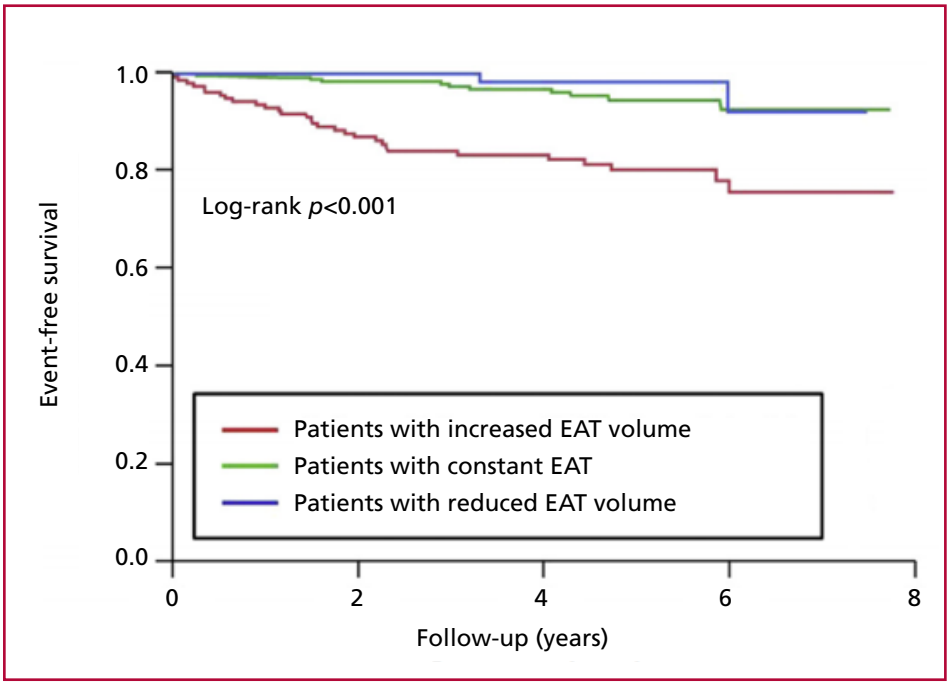

Fig. 1. Kaplan- Meier event-free survival curve according to changes in EAT volume. EAT: epicardial adipose tissue.
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of obstructive stenosis (RR 1.06; 95% CI, 1.03-1.08) and significant stenosis (RR 1.51; 95% CI, 1.26-1.82), myocardial ischemia (RR 1.06; 95% CI, 1.01-1.12) and a higher incidence of MACE (RR 1.04; 95% CI, 1.02-1.06). These findings demonstrate that quantification of EAT could provide information beyond the one obtained from traditional cardiovascular risk factors.

A post hoc analysis of the prospective EISNER ("Early Identification of Subclinical Atherosclerosis by Noninvasive Imaging Research") study (32) evaluated EAT volume and attenuation quantified from computed tomography in 2068 asymptomatic patients. After a mean follow-up of 14 years, there was a significant association between EAT volume (≥ 113 cm3) and the incidence of MACE, irrespective of the presence or absence of coronary calcium (HR 1.52; 95% CI, 1.23-1.89; p<0.001). Addition of EAT volume to risk assessment tools resulted in significant net reclassification index (0.218; 95% CI, 0.079-0.357; p = 0.002). (33)

However, despite the large body of evidence supporting the association between EAT and coronary artery disease, some studies reported conflicting results. (34-36) In fact, some authors raised the possibility that the metabolic and anatomic change in EAT could be secondary to coronary atherosclerotic lesions and not a predisposing factor.

Therapeutic possibilities

Considering the evidence so far provided, it is reasonable to consider that EAT could represent a therapeutic target. Many experimental studies have evaluated the possibility of reducing its volume with different treatments.

Some authors demonstrated a reduction in EAT after weight loss associated with hypocaloric diets and after bariatric surgery, with a greater reduction in visceral adipose tissue than in subcutaneous adipose tissue. (37,38)

As for drug treatment, statins have proved to decrease EAT thickness and volume independently of LDL cholesterol reduction without modifying subcutaneous adipose tissue. (39, 40)

Glucagon-like peptide type 1 receptor agonists (GLP-1 RAs) have demonstrated a significant decrease in EAT in patients with type II diabetes. These drugs slow gastric emptying and reduce appetite, leading to weight loss due to a reduction in adipose tissue. Interestingly, the reduction in EAT is greater than that observed in body mass index or waist circumference. (41,42)

Over the past few years, the benefit of sodium-glucose co-transporter-2 (SGLT2) inhibitors has been demonstrated initially in diabetic patients and then in many other conditions. Díaz Rodríguez et al. demonstrated SGLT2 expression levels in EAT and that dapagliflozin reduces adipocyte secretion of cytokines in vitro. (43) Recently, Iacobellis et al. conducted a randomized, double-blind, placebo-controlled study to analyze the effect of dapagliflozin on EAT thickness. (44) The use of dapaglifozin produced a significant reduction in EAT thickness. It is noteworthy to mention that the reduction in EAT thickness was greater than the changes in body weight (20% versus 8% at 24 weeks). In contrast, another randomized study did not find a significant association between the use of empagliflozin and EAT volume. (45)

A limitation of the aforementioned studies is that none of them evaluated whether the reduction in EAT volume induced by drug treatment was associated with a lower incidence of cardiovascular events.

Finally, an animal study showed that surgical resection of peri-coronary EAT decreases the progression of atherosclerosis, reduces cell proliferation, and contributes to atheroma plaque stabilization and positive remodeling. (46) Based on these results, the authors suggest further investigation using adipectomy at the time of coronary artery bypass grafting.

Final reflections

Since cardiovascular disease is the leading cause of death worldwide, significant effort and time have been devoted to identifying factors that allow cardiovascular risk stratification and prediction. For decades, we have understood that increased adipose tissue is associated with cardiovascular disease. The current evidence suggests the associating between increased EAT and traditional risk factors, atherosclerosis, myocardial ischemia, and related clinical events. Some studies presented even demonstrate that this association is stronger than that observed with traditional risk factors. In this context, many authors suggest considering EAT as a new modifiable cardiovascular risk factor. However, we know that the importance of perivascular adipose tissue is a developing concept and most published studies include a small population and have methodological limitations.

According to the National Ministry of Health, "*a screening program consists of applying a simple, sensitive and low-cost diagnostic test to many people, focused on the early detection of those most likely to suffer from a certain disease, with the ultimate aim of reducing morbidity and mortality due to this cause. This type of strategy is justified in diseases with serious health consequences, which have effective treatment and a high prevalence of preclinical disease*". (1) The quantification of EAT could fall under this definition according to the preliminary evidence analyzed. However, further research in this field is needed to determine the predictive value of this new tool more accurately and, mainly, to establish if it can be implemented in clinical practice.

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