REVIEW ARTICLE

Epicardial Fat and Hepatic Steatosis as Cardiovascular Risk Markers

Grasa epicárdica y esteatosis hepática como marcadores de riesgo cardiovascular

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ABSTRACT

Epicardial adipose tissue (EAT) is a metabolically active tissue which has raised great interest in the last decade as a cardiovascular risk marker. It is related with the production of proinflammatory cytokines and free fatty acids, the promotion of a state of hypercoagulability and with numerous cardiometabolic risk factors. Between EAT and coronary arteries, there is not only an intimate anatomical association, but also bidirectional physiological aspects of paracrine regulation. In addition, several studies have found a relationship between EAT and endothelial dysfunction, non-obstructive atheromatosis, oxidative stress, atrial fibrillation and diastolic dysfunction.

Parallel to these findings, there is a tight association between hepatic steatosis (the most prevalent chronic hepatic disease), coronary atheromatosis and cardiovascular risk. One of the interesting and differential characteristics of hepatic steatosis with respect to coronary artery disease is its dynamic, and to a certain point reversible, character.

Despite their association with atheromatosis and cardiovascular risk, and simple assessment from non-invasive imaging methods, epicardial fat and non-alcoholic fatty liver are seldom considered as risk markers in clinical practice.

Key words: Atherosclerosis – Adipose Tissue – Body Mass Index – Computed Tomography – Fatty Liver – Inflammation – Pericardium – Risk Factors

RESUMEN

El tejido adiposo epicardico (TAE) es un tejido metabólicamente activo que ha cobrado gran interés en la última década como marcador de riesgo cardiovascular. El TAE se relaciona con la producción de citoquinas proinflamatorias y de ácidos grasos libres, con la promoción de un estado de hipercoagulabilidad, y con numerosos factores de riesgo cardiometabólico. Existe una íntima relación entre las arterias coronarias y el TAE, no solo anatómica, sino en cuanto a aspectos fisiológicos bidireccionales de regulación paracrina. Además, numerosos estudios han encontrado una relación entre el TAE y la presencia de disfunción endotelial, ateromatosis no obstructiva, estrés oxidativo, fibrilación auricular, y disfunción diastólica.

En paralelo, existe una estrecha relación entre la esteatosis hepática (la enfermedad hepática crónica más frecuente), la ateromatosis coronaria, y el riesgo cardiovascular. Una de las características interesantes de esteatosis hepática y diferenciales con respecto a la enfermedad coronaria es su carácter dinámico y, en cierta medida, reversible.

A pesar de las asociaciones descriptas con la ateromatosis y con el riesgo cardiovascular, y de su evaluación sencilla a partir de métodos de imagen no invasivos, la grasa epicárdica y el HGNA son raramente considerados como marcadores de riesgo en la práctica clínica.

Palabras Clave: Aterosclerosis – Tejido Adiposo – Índice de masa corporal – Tomografía Computarizada – Hígado graso – Inflamación – Pericardio – Factores de Riesgo

Abbreviations

BMI	Body mass index	**HS**	Hepatic steatosis
CAC	Coronary artery calcification	**HU**	Hounsfield units
CRF	Cardiovascular risk factors	**IR**	Insulin resistance
CTCA	Computed tomography coronary angiography	**NAFL**	Non-alcoholic fatty liver
EAT	Epicardial adipose tissue	**NAHS**	Non-alcoholic hepatic steatosis
EFV	Epicardial fat volume	**PAT**	Pericardial adipose tissue
FFA	Free fatty acids	**PFV**	Pericardial fat volume
FAI	Fat attenuation index	**PVF**	Perivascular fat
HFpEF	Heart failure with preserved ejection fraction	**RPF**	Radiotranscriptomic pericoronary fat
HRP	High-risk plaque		

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INTRODUCTION

Epicardial adipose tissue (EAT) is the intrathoracic visceral fat depot located between the myocardium and pericardium in intimate contact with the coronary arteries. Historically considered a simple energy deposit, EAT is a metabolically active tissue which has raised great interest in the last decade as a cardiovascular risk marker. (1) Both EAT and abdominal visceral adipose tissue, with the same embryological origin, are related with the production of proinflammatory cytokines and free fatty acids (FFA), promoting a state of hypercoagulability and numerous cardiometabolic risk factors. (2-4) Specifically, diabetic patients present larger EAT volume, with a proinflammatory and metabolically more active profile independently of other cardiovascular risk factors (CRF) (5-7)

The role of EAT in the development and progression of coronary atheromatosis has been demonstrated not only through the severity but also by the presence and extension of non-obstructive atheromatosis (8, 9) Concurrently, numerous studies have found a relationship between these fat depots and the incidence of endothelial dysfunction, atrial fibrillation, and diastolic dysfunction. (10-13) More recently, it has been shown that EAT does not have a homogeneous composition and distribution, and that these differences are associated with regional changes in the composition of adjacent atherosclerotic plaques, especially regarding the presence of coronary inflammation. (14-16)

In addition, there is a close relationship between hepatic steatosis (HS), coronary atheromatosis and cardiovascular risk. Hepatic steatosis is the most frequent chronic liver disease, with an estimated 20% to 30% prevalence in the general population. It is the second cause of liver transplant, (17) and is closely associated with the different components of metabolic syndrome. (18) Moreover, several studies have shown a relationship between HS and visceral fat, but it is still unclear whether it has an active role in the development and progression of atheromatosis or its presence only reflects the coexistence of other cardiometabolic risk markers.

Despite the implementation of improved prevention strategies, residual cardiovascular risk is partly attributed to coronary inflammation; therefore, it would be very important to incorporate monitoring tools and vulnerability markers to assess both the acute inflammation and chronic vascular and perivascular changes. (19-21)

Limitations of general obesity markers

Elevated cardiovascular morbidity and mortality in obese patients compared with the general population is mostly linked to their association with multiple CRF. (22, 23) However, general obesity markers, as body mass index (BMI), present multiple limitations that have globally led to inconsistent and even divergent results regarding their ability to predict events. Effectively, numerous studies have demonstrated a negative relationship between BMI and coronary artery disease, as well as a debatable association between obesity and survival, particularly in elderly adults. (24, 25) This controversial or paradoxical behavior is in part due to the defective definition of obesity based on BMI, a poor adiposity index as it is more a surrogate of weight than body fat, which cannot identify the proportion of the different regional body fat depots related with cardiometabolic profiles and divergent prognoses. (26-28) Even waist circumference presents limitations and occasionally contradictory results regarding its predictive value. (29, 30) This is possibly attributed to the fact that abdominal obesity was originally defined through BMI as a reference value and not by its relationship with the risk of events, and that despite being an approximate estimation of abdominal fat, the assessment of waist circumference does not differentiate between subcutaneous and visceral fat. This previously ignored disquisition is essential in view of current evidence showing that only visceral and not subcutaneous fat is associated with the incidence of heart failure with preserved ejection fraction (HFpEF). (31)

Pathophysiological aspects of epicardial fat

In addition to adipocytes, adipose tissue consists of stromal cells (fibroblasts and inflammatory cells) and interstitial tissue. Adipose tissue produces a great number of molecules, including pro- and anti-inflammatory cytokines, fatty acid metabolites and reactive oxygen species which regulate numerous physiological aspects of adjacent tissues. (32) Compared with other visceral adipose tissues, EAT is characterized by increased fatty acid synthesis and catabolism, so it has been proposed as a "buffer" fat that protects the heart against cardiac steatosis generated by FFA. (33) However, with EAT expansion and inflammation, the "cross-talk" between both tissues would be altered with interaction between pro-inflammatory adipocytokines and the intramyocardial fat depot which also accompanies the insulin resistance (IR) process. (34) We have recently demonstrated that in patients with coronary artery disease and type II diabetes, higher activity of triglyceride-rich lipoprotein catabolic enzymes would promote increased FFA flow into the tissue, favoring EAT expansion. (5)

Specifically, perivascular EAT has a paracrine action on coronary arteries, regulating multiple aspects of vascular biology, including inflammation [with pro-inflammatory cytokine (IL-1β, IL-6 and TNF-α) and chemokine (MCP-1) secretion], vascular tone, oxidative stress and local nitric oxide production (Figure 1). (32, 35, 36) Epicardial adipose tissue can secrete both pro-inflammatory (leptin, resistin) as anti-inflammatory (adiponectin) adipokines, and their balance depends on the degree of tissue inflammation and expansion. Recent evidence suggests that perivascular fat (PVF) could act as a thermometer of underlying atherosclerotic plaques, detecting

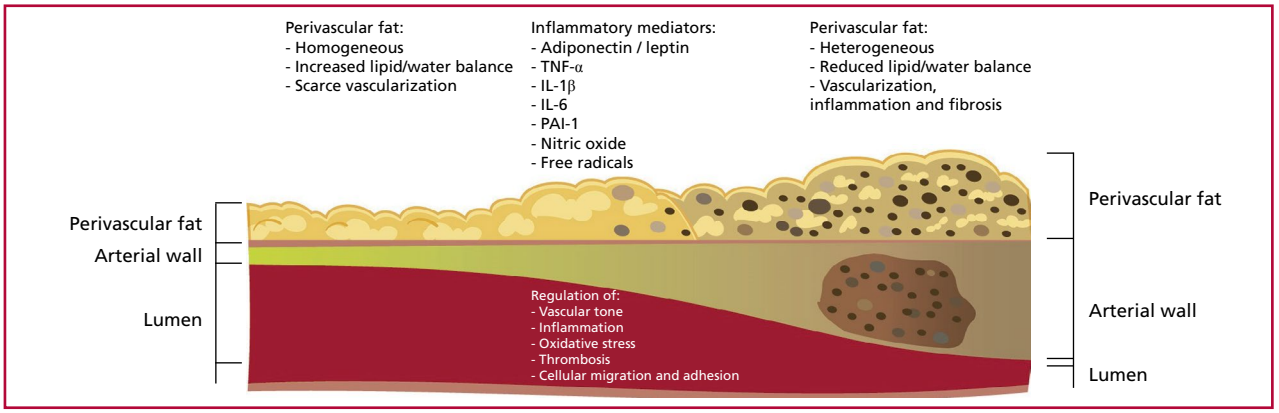

Fig. 1. Role of perivascular fat (PVF) in the development and progression of coronary artery disease. In the healthy vessel, PVF is homogeneous, with lipid-rich adipocytes (scarce fluid), scant vascularization and very few inflammatory cells. As lesions develop, PVF becomes heterogeneous, adipocytes decrease in size due to reduced fat content and lower cellular differentiation, with increased aqueous phase and evidence of increased vascularization, inflammatory cells (including macrophage polarization to a higher concentration of M1 activated macrophages) and fibrosis. A lipidic-necrotic nucleus starts developing at the intima level with foam cells and microcalcifications, and both media (with positive coronary remodeling) as well as fibrous cap thinning. These bidirectional phenomena (from the arterial wall towards PVF and vice versa), are mediated by numerous vasoactive substances that regulate vascular tone, inflammation, oxidative stress and coagulation (PAI-1). IL: interleukin. TNF: tumor necrosis factor. PAI-1: Plasminogen activator inhibitor-1.

local changes in oxidative stress and acting accordingly (for example, secreting adiponectin in the presence of increased oxidative stress). In addition, in the presence of local coronary inflammation and the ensuing cytokine diffusion to the perivascular interstitial space, the lipidic adipocyte content is reduced and the aqueous/edema phase of PVF increases. (37) Therefore, there is an intimate relationship between coronary arteries and EAT, not only anatomically but also in bidirectional physiological aspects (Figure 1). In the presence of an expanded and dysfunctional EAT, the pro-inflammatory effect of epicardial fat acts not only on the underlying vessel; pro-inflammatory mediators are also released to blood flow, and although the volume of EAT is much lower than that of abdominal visceral adipose tissue, it contributes to the systemic pro-inflammatory state. In addition, completing this bidirectional cycle, systemic inflammation promotes the accumulation and inflammation of epicardial fat. (38) It is not a coincidence that patients with diseases associated with systemic inflammation, as psoriasis, rheumatoid arthritis, HIV or obesity, have a significant increase of EAT (39-41)

One of the most paradigmatic aspects generating hypotheses about the association between epicardial fat and atheromatosis stems from the study of myocardial bridges and experimental research in animals with epicardial fat resection. In the former, there is characteristic absence of atheromatosis at the level of the intramyocardial segment. (42) In a study evaluating coronary anomalies by computed tomography coronary angiography (CTCA) in 109 myocardial bridges, none of the intramyocardial segments had signs of atheromatosis, despite its presence in 65%

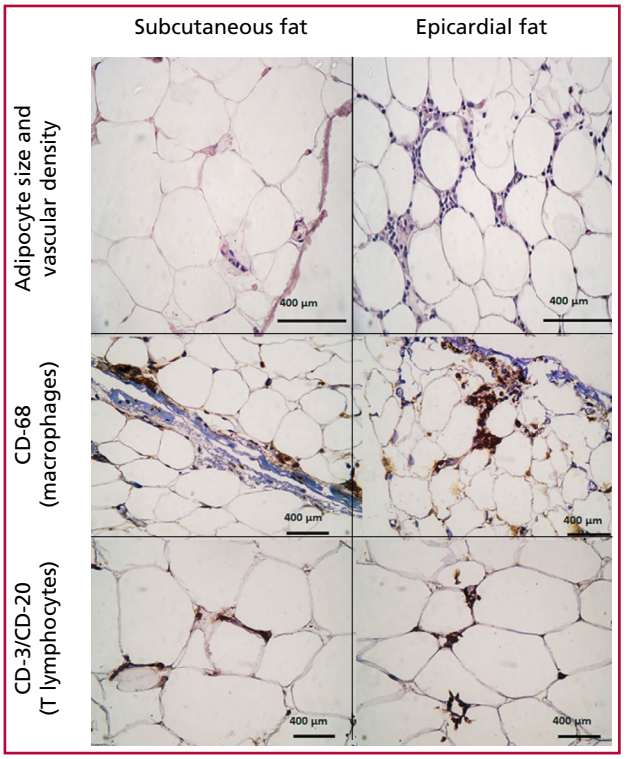

Fig. 2. Histological characteristics and inflammatory infiltrate of epicardial adipose tissue (EAT, upper right ventricular area) and subcutaneous adipose tissue (SAT, thoracic area), obtained from patients with coronary artery disease referred for myocardial revascularization surgery. Epicardial adipose tissue adipocytes are smaller and the tissue is more vascularized than that of SAT. Immunohistochemical studies show that EAT presents macrophage (CD68+) and lymphocyte T (CD3/CD20) infiltrates. The brown dye indicates positive immunochemistry.

of hosting vessels. (43) In an elegant study that included epicardial fat resection adjacent to the middle third of the anterior descending coronary artery in pigs under atherogenic diet and with serial evaluation by intravascular ultrasound, McKenney et al. identified progression of atheromatosis in the proximal and distal segments, without significant changes at the level of the segment without EAT. (44) There is even macrophage polarization with a higher concentration ratio between activated macrophages (M1) and macrophages with anti-inflammatory properties (M2) in the EAT of patients with coronary artery disease compared with patients without this disease. (45) Effectively, it has also been demonstrated that EAT of patients with coronary artery disease present enhanced vascular density, macrophage infiltration and type 2 and 9 metalloproteinase (MMP) activity, the main enzymes in charge of atherosclerotic plaque degradation and also linked to coronary remodeling (Figure 2). (46) These enzymes participate in EAT expansion, although their ability to migrate towards underlying atherosclerotic plaques to increase their vulnerability remains to be proved.

On the other hand, and for reasons still unknown, subcutaneous adipose tissue has been associated with lower risk of coronary and peripheral atheromatosis and mortality. (47-49) In a seminal work including patients with elective coronary bypass graft surgery, Mazurek et al. collected paired samples of EAT adjacent to the proximal third of the right coronary artery and of subcutaneous cellular tissue adjacent to saphenous veins, and compared the expression of different inflammatory markers. (50) In this study, EAT showed significantly higher levels of inflammatory mediators than subcutaneous fat, including IL-1, IL-6, TNF-α, and MCP-1, independently of obesity, diabetes or basal medication. Septal thickenings and inflammatory cellular infiltrates were identified in the cellular content of EAT, including, T lymphocytes, macrophages and mastocytes, while no inflammatory cells were identified in subcutaneous fat. In addition, no associations were found between this local inflammation and cytokine plasma levels.

Recently, the molecular and lipidomic study of EAT biopsies showed that patients with coronary artery disease present a lipidomic profile with prevalence of pro-inflammatory lipids, higher ceramide, diglyceride (saturated and monounsaturated) and monoglyceride concentration than patients without this disease. (51)

Therefore, EAT functions as an endocrine organ intimately linked with cardiovascular risk through inflammatory regulation.

In a parallel population study, including 3,291 asymptomatic subjects with mean age of 50 years, Sung et al. identified the association between visceral fat (EAT, periaortic fat and HS) and presence of inflammatory markers as C-reactive protein and neutrophil/lymphocyte ratio. (4) In addition, this work demonstrated an association between the severity of HS and other markers of visceral adiposity as inflammatory markers.

Pathophysiological aspects of hepatic steatosis

Hepatic steatosis is the result of liver-synthetized triglyceride accumulation from FFA released by adipose tissue (lipolysis), excess carbohydrates (de novo lipogenesis) or excess triglycerides in the diet. (52) Nonalcoholic fatty liver (NAFL) is defined as the presence of steatosis (>5% of hepatocytes by histological analysis) in the absence of secondary causes that may generate it, as chronic alcohol consumption, chronic infection due to viral hepatitis, medications (e.g. corticoids, methotrexate, valproate, etc.) or autoimmune hepatic diseases. (53) The underlying pathophysiological mechanism for NAFL is associated with altered intermediate metabolism (lipids and glucose) and IR. (18) Insulin is a lipogenic hormone and in normal conditions suppresses hepatic gluconeogenesis. (54) Insulin resistance is greater in subjects with NAFL and has a central role in its development and progression. (55) One consequence of IR is the increase of peripheral lipolysis, mainly of visceral adipose tissue, with increased serum levels of FFA, leading to a rise in hepatocyte toxic lipids, such as diacylglycerols and ceramides which are involved in inflammatory pathways. The histological spectrum of NAFL extends from simple steatosis to steatohepatitis, fibrosis and cirrhosis (Figure 3).

Although the mechanism is not well elucidated, it is believed that the association between NAFL and atherosclerosis is linked to multiple factors differently involving IR, alteration of lipoprotein metabolism, low-degree inflammation, oxidative stress and decreased adiponectin levels (Figure 3) (57-59)

The activation of the NF-kB pathway in patients with steatohepatitis leads to an increase in the transcription of various pro-inflammatory genes. (60) In the same line, numerous inflammatory (C-reactive protein, IL-6 and TNF-), oxidative and procoagulant [plasminogen activator inhibitor-1 (PAI-1), fibrinogen and factor VII] markers are found in patients with steatohepatitis. (61) A recent sub-analysis of the Multi-Ethnic Study of Atherosclerosis (MESA) population, which included 668 asymptomatic individuals with NAFL, showed that among many biomarkers (including C-reactive protein), IL-6 was the independent predictor of both coronary artery calcification (CAC >0) and moderately extensive coronary calcification (CAC >100). (62) Concomitantly, and in line with the mechanisms described at the epicardial fat level (Figure 1), elevated levels of PAI-1 in early adulthood are independently associated with NAFL in the second half of life. (63)

Epicardial fat assessment by imaging methods

Epicardial fat can be quantified with diverse precision through several non-invasive methods, including transthoracic echocardiogram, magnetic resonance

imaging (MRI), computed tomography (CT) and positron-emission computed tomography (PET), unenhanced TC scan being the reference method due to its speed, availability, greater spatial resolution and volumetric acquisition (Figures 4 and 5). (64)

The simple identification of epicardial fat with CT scan [with a lower limit ranging between -190 and -250 Hounsfield units (HU), and an upper limit between -30 and -50 HU] has led to the development of tools that allow the automatic assessment of epicardial fat volume (EFV) using artificial intelligence algorithms with accuracy comparable to that of expert reviewers. (65) There are no well-established boundaries for EFV evaluation, although most studies use the pulmonary artery bifurcation or the point situated 15 mm above the cranial border of the left main coronary artery as superior limit and the diaphragm as inferior limit. (64) Evaluation of EFV can be achieved using both unenhanced cardiac CT scan (calcium score) and contrast-enhanced CTCA, though in the latter case it is suggested to increase the detection threshold to -15 HU, since contrast-enhanced studies usually underestimate fat by 30%. (64, 66) Also, conventional unenhanced, non-ECG gated thorax CT scans (Figure 4) are equably reproducible and present the same predictive value as gated studies (Figure 5). (67, 68)

It should be mentioned that pericardial adipose tissue (PAT) includes both EAT and paracardiac fat tissue (outside the pericardial sac). Although it is of simpler assessment, closely related with EAT and with prognostic value demonstrated in numerous prospective studies, there are significant embryological and structural differences between paracardiac and epicardial adipose tissue. (16, 69)

Regardless of the assessment strategy used, one of the major limitations in the use of EFV as a risk marker in clinical practice is the absence of normal and cutoff point standardized values, with reported significant differences according to populations, sex and body surface area. (68, 70)

Non-invasive assessment of hepatic steatosis

There are several non-invasive methods for HS identification, with different precision, availability, cost,

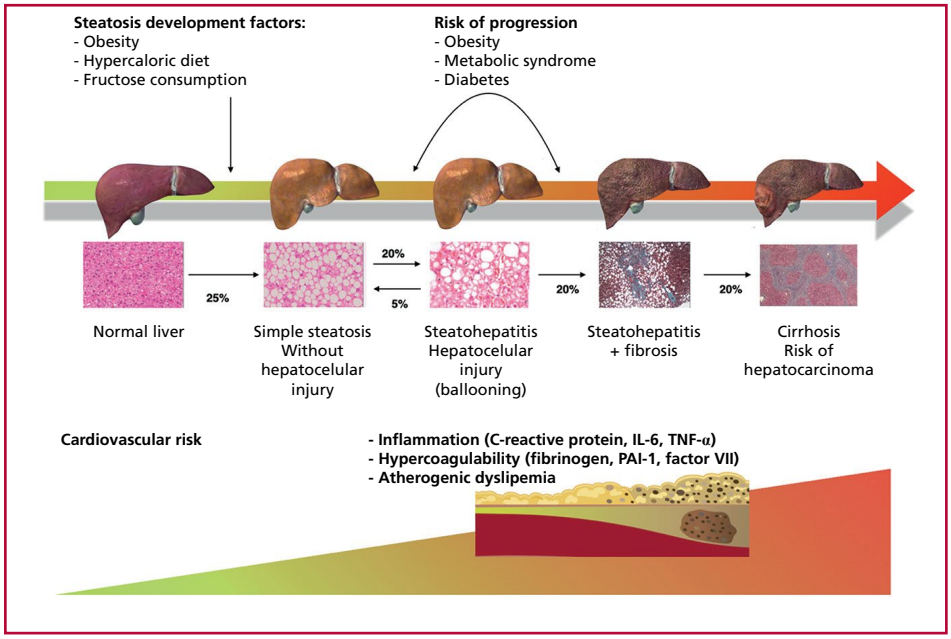

Fig. 3. Natural history of the non-alcoholic fatty liver (NAFL). The main risk factors which condition the development of steatosis are obesity, hypercaloric diet and fructose consumption (sugar component and main component of high-fructose corn syrup) and factors favoring steatohepatitis, fibrosis and cirrhosis are obesity, components of the metabolic syndrome and diabetes. The lower panel depicts the relationship between NAFL progression, atherogenesis and risk of cardiovascular events. Inflammation, procoagulant factors and atherogenic lipids increase as the hepatic disease progresses, promoting the development of atheromatosis and cardiovascular events.

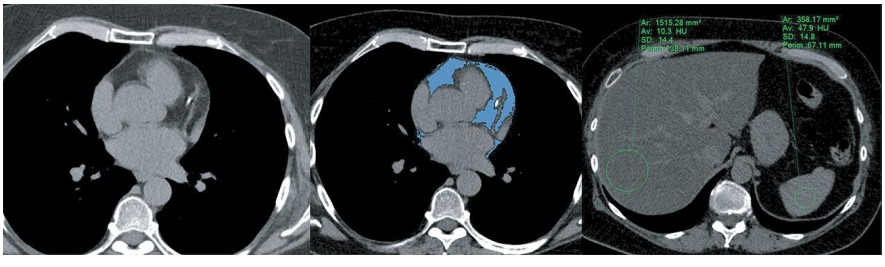

Fig. 4. Quantification of epicardial fat, assessment of coronary artery calcification and identification of hepatic steatosis by conventional chest CT scan. Notice the presence of calcification at the level of the anterior descending artery, with increased epicardial fat volume (in blue) and severe hepatic steatosis (10 HU and 0.21 liver/spleen ratio).

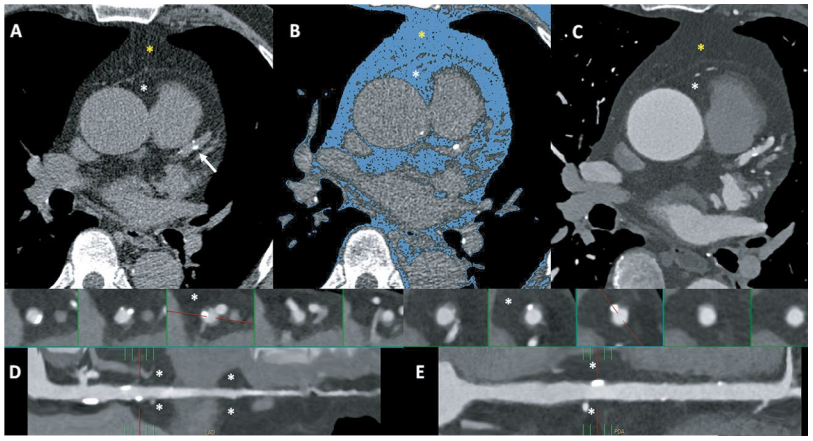

Fig. 5. Calcium score (panels **A** and **B**) and CT coronary angiography (panels **C-E**) in a hypertensive 72-year old male patients with atypical chest pain. Both the unenhanced study (calcium score) as the coronary angiography allow the discrimination between epicardial fat (white asterisk) and paracardiac fat (yellow asterisk), as well the calculation of their volume and density. Multiplane reconstructions of the anterior descending (panel **D**) and right coronary (panel **E**) arteries are used to assess perivascular fat (asterisk).

sensitivity and specificity. (71) Conventional ultrasound is a widely available, non-expensive tool, very useful for screening through qualitative assessment. However, it has low sensitivity to detect histological steatosis below 20%. Computed tomography, of similar sensitivity, is more specific and allows steatosis quantification and focal steatosis detection. In unenhanced studies, normal liver attenuation levels are between 50 and 65 HU, and generally 8 to 10 HU higher than those of the spleen. Among different cutoff points to detect HS, the most accepted attenuation level limits are below 48 to 51 HU (and lower than in the spleen). The MESA study group, among others, uses a simpler definition consisting in the presence of a liver (UH)/spleen (UH) attenuation ratio <1. (62) An attractive CT feature is the ability to evaluate within the same scan the upper portion/hepatic parenchyma dome, the extension and distribution of coronary calcification and EAT (Figure 4).

Magnetic resonance imaging is the most accurate method to assess HS, although it is less available, more expensive, has longer acquisition time and it is difficult for the evaluation of patients with very high BMI and/or claustrophobia. Each of these three modalities has evolved in the last years, developing specific techniques to evaluate NAFL which exceed the present article.

Relationship between epicardial fat and non-coronary artery disease

Some studies have described a relationship between EAT and atrial fibrillation (AF), (10, 72) which although not yet clearly defined, has been attributed to probably mixed mechanisms differently related not only to the diffusion of the already mentioned pro-inflammatory factors, but to external mechanical compression with reduced compliance and ventricular diastolic dysfunction due to myocardial fibrosis. (38, 73) In a study including patients with planned ablation, pericardial fat volume (PFV) was associated with the presence, severity and recurrence of AF, independently of general parameters of obesity. (74) Concurrently, in a recent study, van Woerden et al. identified higher EAT volume in patients with HFpEF compared with a control group, independently of BMI. In addition, EAT was associated with the presence of type 2 diabetes, AF and several inflammatory markers. (75) It has even been postulated that HFpEF with identified heart rate in obese patients can be attributed to the presence of microvascular dysfunction and altered myocardial relaxation related in different degrees to myocardial fibrosis, dilatation and AF, and a pro-inflammatory state associated with increased EAT. (76) The recent finding of a significant correlation between EAT and both myocardial lipid content and interstitial fibrosis suggests that, effectively, EAT somehow infiltrates the myocardium. (77)

Moreover, EAT inflammation can synthetize aldosterone, which not only perpetuates the inflammatory state and promotes fibrosis, but also favors volume overload, worsening HFpEF. (38)

Relationship between regional fat depots, atheromatosis and events

There is consistent evidence associating EAT with atheromatosis markers. Even some studies suggest that accelerated atheromatosis commonly present in HIV positive patients could be attributed to increased EAT in this population. (78) We have recently shown a significant relationship between pericardial and visceral fat with coronary and extra-coronary atherosclerotic plaque burden, while general adiposity markers, including CT-calculated total body fat volume, were not related with atherosclerotic burden. (49) These findings are in line with a large number of studies evidencing that EAT was not related with general fat depots but with coronary and extra-coronary atheromatosis markers, independently of CRF. (1-3) In the Heinz Nixdorf Recall study, which included 4,093 individuals between 45 and 75 years of age with known cardio-

vascular disease, subjects in the upper EAT quartile presented significantly higher risk of hard events after an 8-year follow-up, even following adjustment by CRF (HR 1.54; 95% CI 1.09-2.19) and calcium score (HR 1.50; 95% CI 1.07-2.11). (79) This last finding, in line with results from other studies, supports the concept that the relationship between epicardial fat and vascular events would have different mechanisms than those of risk associated with coronary calcification. In a cohort including 998 individuals between 45 and 85 years from the MESA study, a significant association was found between PFV and risk of coronary events, independently of CRF and BMI (HR 1.26; 95% CI 1.01-1,59), while no significant relationships were registered between events and BMI or waist circumference. (80) In the smaller Rancho Bernardo Study (n=343) but followed-up for 12 years, patients in the upper tertile of PFV presented 2.6 higher global mortality risk than those in the lower tertile, independently of CRF. (81) The EISNER study, in 456 asymptomatic individuals with mean age of 60 years demonstrated a significant relationship between EAT and coronary calcification. (82) The predictive capacity of PFV has also been shown by conventional chest CT scan. In a retrospective cohort including 1,250 patients with clinically indicated chest CT scan, we identified PFV as an independent predictor of all-cause mortality. (68)

Relationship between fat composition and event occurrence

Computed tomography coronary angiography evaluates high-risk plaque (HRP) characteristics, such as positive remodeling, low-attenuation plaques (<30HU), signs of annular enhancement and microcalcifications. (83) Recently, a meta-analysis published by Nerlekar et al. showed the relationship between EAT extension and presence of HRP (OR 1.19; 95% CI 1.06-1.33). (84)

However, structural changes both at the coronary or PVF levels, that may be viewed by methods such as CT scan, would indicate more advanced stages of the disease than molecular or functional changes. This has prompted the search of noninvasive approaches that would allow an early detection of metabolic changes. It has already been mentioned that EAT distribution and composition is not homogeneous and that it is associated with the presence and distribution of atheromatosis and risk of events. These local gradients can be accurately discriminated by CT scan, assessing PVF density (HU) (the higher density fat, closer to zero, reflecting a lower lipidic content and presence of edema, greater vascularization and/or fibrosis). (14-16)

Goeller et al. reported significantly higher PVF attenuation levels in culprit lesions of patients with acute coronary syndrome compared with non-culprit lesions (-69.1 HU vs. -74.8 HU; p=0.01) and even compared with control severe lesions (-76.4 HU; p=0.01). (85)

It is thought that these CT-detectable changes in PVF composition (Figure 1) precede the formation of coronary plaques, their early detection being highly important as most plaque ruptures and coronary events generally have non-obstructive lesions as substrate. (14. 15, 83) In this respect, complex analyses that include genetic studies, immunomarkers and advanced tomographic evaluations (assisted and then trained with machine learning tools) based on cardiac surgery biopsies, with posterior validation in large prospective studies, identified pericoronary fat attenuation index (FAI) and radiotranscriptomic profile of pericoronary fat (RPF) texture with ability to detect the presence of coronary inflammation. (15)

This group of Oxford investigators validated FAI as a coronary inflammation marker associated with worse prognosis in two large prospective cohorts of completely different populations (Figure 6) In the CRISP-CT study, a higher FAI (less negative) of -70 HU was identified as a robust predictor of cardiac and all-cause mortality, independently of demographic data, EAT, atheromatosis extension and HRP (14) In this study, FAI, also validated against PET CT scan, predicted the occurrence of major cardiovascular events even before plaque development. (37) Pericoronary fat attenuation index (Figure 6) is not only a sensitive but also a dynamic marker of coronary inflammation, being reduced by statin and aspirin administration. (14) Chronic changes in PVF, associated with fibrosis and microvascular remodeling, can be assessed through RPF texture assisted by machine learning algorithms. (86)

These characteristics were validated in 1,575 patients of the SCOT-HEART trial, with improved prediction of major events independently of CRF, calcium score, severity and HRP assessed by CTCA. (15) It must be pointed out that both FAI, reflecting acute changes (inflammation), as RPF, indicating chronic structural changes, are acquired by conventional CTCA. Therefore, these complementary methods may be possibly combined in a single CTCA study, together with multiple known evaluations and with independent prognostic value.

Relationship between hepatic steatosis and cardiovascular risk

Simple HS has a good prognosis, However, patients who develop steatohepatitis are at greater risk of chronic hepatic disease progression (fibrosis/cirrhosis). (87) Age (>50 years), type II diabetes, obesity and metabolic syndrome have been identified as factors associated to the progression of simple steatosis to steatohepatitis. (88) In patients with NAFL, cardiovascular disease is the most prevalent cause of death, regardless of the liver disease stage. (89) This increase of cardiovascular risk has been associated with different mechanisms, including the promotion of atheromatosis, arrhythmias and systolic and diastolic dysfunction. Nonetheless, there is still an ongoing controversy on whether the association between

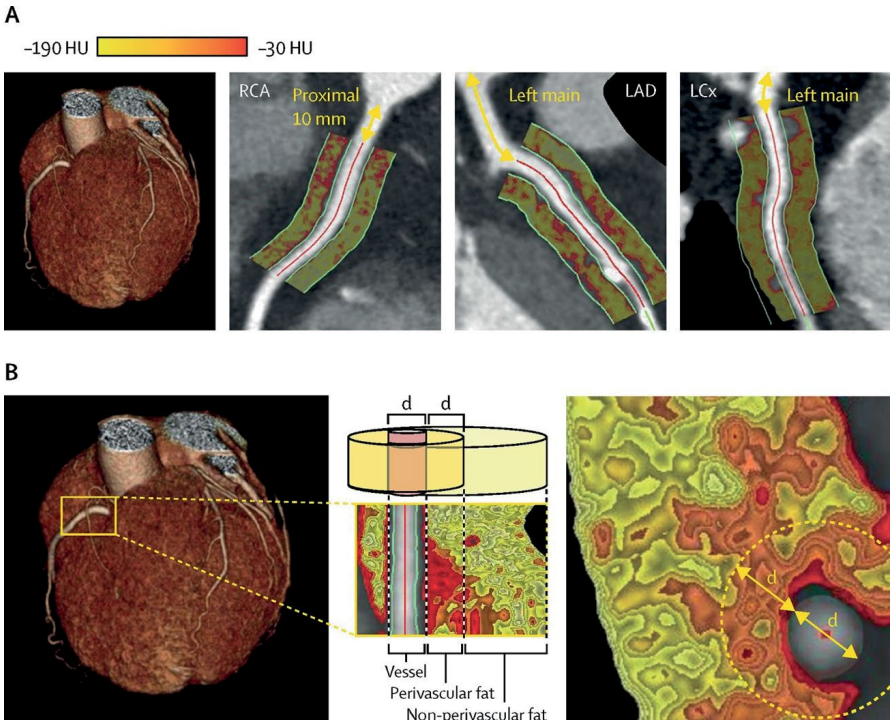

Fig. 6. A) Pericoronary fat attenuation (FAI) of the three main epicardial coronary artery proximal segments, with the corresponding FAI maps. **B)** Example of pericoronary FAI phenotype around the proximal segment of the right coronary artery. Pericoronary fat was defined as fat located at a radial distance equal to the vessel diameter (d). HU: Hounsfield units. LAD: Left anterior descending artery. LCx: Circumflex artery. RCA: Right coronary artery. (From: Oikonomou EK, et al. Lancet 2018, 392(10151):929-939).

NAFL and cardiovascular disease is a consequence of multiple shared risk factors, or else NAFL independently contributes to cardiovascular disease. Moreover, although steatohepatitis is related to an increased risk of events, this relationship is not well established regarding simple steatosis. (90)

In a recent meta-analysis including 83,395 patients from 26 studies, NAFL was independently associated with the presence of subclinical atheromatosis assessed by carotid Doppler, calcium score, arterial stiffness or endothelial dysfunction (OR 1.6; 95% CI 1.45-1.78). (91) Specifically, in the 13 studies which included 12,269 patients evaluated by carotid Doppler, NAFL was associated with greater risk of pathological studies (OR 1.74; 95% CI 1.47-2.06; $p<0.00001$); and in the 7 studies including 29,531 patients with unenhanced CT scan, NAFL was associated with increased calcium score (OR 1.40; 95% CI 1.22-1.60; $p=0.02$). In another meta-analysis which included 16 studies with 34,043 patients with median follow-up of 6.9 years, Tagher et al. identified a significant relationship between NAFL and the occurrence of fatal and/or non-fatal cardiovascular events (HR 1.64, 95% CI 1.26-2.13. (92) In addition, patients with severe NAFL (steatosis and fibrosis) presented higher cardiovascular mortality (OR 3.28; 95% CI 2.26-4.77), possibly linked to chronic inflammation. (92)

Future perspectives

One of the interesting features of NAFL which is different from coronary artery disease, is its dynamic, and up to a certain point reversible, character. A decrease of 3% in body weight is associated with histological improvement in NAFL patients, though weight reduction must be greater than 7% and 10% to improve non-alcoholic hepatic steatosis and fibrosis, respectively. Nevertheless, the question on whether the decrease in steatosis could be used as a marker of cardiovascular risk reduction remains open.

An interesting aspect of the relationship between fat depots and cardiovascular events is the difference between sexes. There is a well-known relationship between male sex and risk of cardiovascular events. Even though the mechanisms that link them are not well established, the difference in risk between sexes could be attributed to the fact that women, despite having higher fat content, have more subcutaneous fat and a significantly lower proportion of visceral fat than men. (93) Overall, the evaluation of the extension and composition of regional fat depots could not only help to elucidate these sex differences in the near future, but also improve and personalize risk stratification, identifying patients with elevated residual risk related with inflammation. Considering the accuracy, quantitative and qualitative assessment, cost and availability of current diagnostic methods, CT emerges as the most appropriate modality for risk stratification, specially as it allows the joint assessment of fat depots and atheromatosis extension.

Regarding feasibility, the emergent incorporation of automatic calculation tools, assisted by machine learning, will probably allow consistent and reproducible measurements of regional fat depots, regardless of the type of acquisition and interpretation, favoring

their incorporation in clinical practice in the near future. (65)

Despite the described associations with atheromatosis and cardiovascular risk, epicardial fat and NAFL are rarely considered as risk markers in clinical practice. Although biochemical studies clearly indicate the risk these tissues imply for cardiovascular health, their study is hampered by the complexity and inaccessibility to assess them from tissue samples. Due to their possibility of simultaneous and complementary evaluation through a single noninvasive imaging modality, the calcium score or CTCA could become, in the forthcoming future, prognostic tools that might reflect the current cardiometabolic state and dynamic/reversible changes (steatosis), as well as chronic structural changes (coronary calcification). Part of this dynamic and differential character between HS and EAT was reported in a recent study of 1,250 patients between 35 and 74 years, with unenhanced thorax CT scan, where despite significant associations between HS and both CAC and PFV, the only predictors of all-cause mortality were CAC and EFV. (68).

Conflicts of interest

None declared.

(See authors' conflicts of interest forms on the website/Supplementary material)

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