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REVIEW ARTICLE

Interplay between epicardial adipose tissue, metabolic and cardiovascular diseases

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Abstract Cardiovascular disease is the primary cause of death in obese and diabetic patients. In these groups of patients, the alterations of epicardial adipose tissue (EAT) contribute to both vascular and myocardial dysfunction. Therefore, it is of clinical interest to determine the mechanisms by which EAT influences cardiovascular disease. Two key factors contribute to the tight intercommunication among EAT, coronary arteries and myocardium. One is the close anatomical proximity between these tissues. The other is the capacity of EAT to secrete cytokines and other molecules with paracrine and vasocrine effects on the cardiovascular system. Epidemiological studies have demonstrated that EAT thickness is associated with not only metabolic syndrome but also atherosclerosis and heart failure. The evaluation of EAT using imaging modalities, although effective, presents several disadvantages including radiation exposure, limited availability and elevated costs. Therefore, there is a clinical interest in EAT as a source of new biomarkers of cardiovascular and endocrine alterations. In this review, we revise the mechanisms involved in the protective and pathological role of EAT and present the molecules released by EAT with greater potential to become biomarkers of cardiometabolic alterations.

Abbreviations: CAD, coronary artery disease; CD40L, CD40 ligand; CRP, C-reactive protein; EAT, epicardial adipose tissue; FFA, free fatty acids; GLP-1, glucagon-like peptide-1; HbA1c, hemoglobin A1c; HMG-CoA, 3-hydroxy-3-methyl-glutaryl-CoA; LDL, low density lipoprotein; LRP1, low-density lipoprotein receptor-related protein 1; MESA, Multiethnic Study of Atherosclerosis; MMP, matrix metalloproteinase; NFLAD, nonalcoholic fatty-liver disease; NSTEMI, non-ST-elevation myocardial infarction; SAT, subcutaneous adipose tissue; sCD40L, soluble CD40 ligand; SFRP4, secreted frizzled related protein 4; sLRP1, soluble low-density lipoprotein receptor-related protein 1; TGF-β, transforming growth factor beta; TIMI, thrombolysis in myocardial infarction; TIMP-3, tissue metalloproteinase inhibitor 3; TNF-α, tumor necrosis factor alpha; T1DM, type 1 diabetes mellitus; T2DM, type 2 diabetes mellitus; UCP-1, uncoupling protein 1.

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PALABRAS CLAVE
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Interacción entre tejido adiposo epicárdico, enfermedades metabólicas y cardiovasculares

Resumen Las enfermedades cardiovasculares son la primera causa de muerte en pacientes obesos y diabéticos. Las alteraciones del tejido adiposo epicárdico (TAE) contribuyen a la disfunción vascular y del miocardio en estos pacientes. Es por tanto de interés clínico determinar los mecanismos por los cuales el TAE influye en la enfermedad cardiovascular. Aquí resumimos los mecanismos que subyacen a la asociación entre TAE, síndrome metabólico y enfermedades cardiovasculares. Dos factores contribuyen a la estrecha intercomunicación entre el TAE, las arterias coronarias y el miocardio. Uno es la estrecha proximidad anatómica entre estos tejidos. El otro es la capacidad del TAE para secretar citocinas con efectos paracrinos y vasocrinos en el sistema cardiovascular. Estudios epidemiológicos han demostrado que el grosor del TAE está asociado no solo con el síndrome metabólico sino también con la aterosclerosis y la insuficiencia cardíaca. La evaluación del TAE utilizando técnicas de imagen, aunque eficaz presenta desventajas tales como la exposición a la radiación, la disponibilidad limitada y los costes elevados. Por lo tanto, existe un interés clínico en el TAE como fuente de nuevos biomarcadores de alteraciones cardiovasculares y endocrinas. En este artículo, revisamos los mecanismos implicados en el papel protector y patológico del TAE y presentamos las moléculas liberadas por el TAE con mayor potencial para convertirse en biomarcadores de alteraciones cardiometabólicas.

Clinical implications of epicardial fat

The inability of subcutaneous adipose tissue (SAT) to store the excess of fatty acids results in ectopic fat accumulation in tissues, such as the liver, skeletal muscle, heart, and pancreatic beta cells. Ectopic fat extension is currently considered clinically useful to identify individuals at risk for cardiovascular disease.[1] In fact, cardiovascular risk is linked not only to ectopic fat quantity but also and more importantly to ectopic fat location.[2] During the last decade, ectopic fat mass and content have typically been quantified by high precision, non-invasive imaging techniques.[3] The specific detection of visceral thoracic fat depots fully enclosed by the pericardial sac in the heart, termed epicardial fat (EAT), is of remarkable clinical interest. EAT covers 80% of the heart's surface[4] and constitutes 20% of the total cardiac weight.[5,6] EAT has thermoregulatory, metabolic and cardioprotective effects under normal physiological conditions.[7] However, in metabolic syndrome and obesity, EAT secretes an altered pattern of adipokines and other modulatory molecules.[8] A great number of these EAT-secreted molecules exert endocrine, paracrine, and vasocrine effects on the vasculature and heart[9,10] due to the anatomic proximity of EAT to coronary arteries and the myocardium. Considering that cardiovascular diseases are the primary causes of death in obese and diabetic patients[11–13] and that functional alterations of EAT contribute to both vascular and myocardial dysfunction in these groups of patients,[14,15] it is of great clinical interest to understand the mechanisms linking EAT and cardiovascular diseases. In this review, we summarize and present data on the mechanisms underlying the associations between EAT, metabolic syndrome and cardiovascular diseases and the potential secreted molecules reflecting the relevant mechanisms connecting adipose and cardiovascular tissues.

Mechanisms involved in the protective role of epicardial fat

A crucial advantage of EAT in front of other fat depots is that, under normal physiological conditions, EAT and pericardial fat have great flexibility to storage or release fatty acids due to their high rates of lipogenesis and lipolysis, serving as a storage depot for fatty acids and protecting the heart and the vasculature against high fatty acid oversupply.[16] The heart has a constant demand of fatty acids as energy substrate and, in situations of high energy demand, EAT acts as a local source of fatty acids for the heart, promoting an adequate cardiac function.[17] Other interesting characteristic of EAT is that this fat depot express the uncoupling protein-1 (UCP-1), a marker protein for brown fat. These results suggest that EAT could play a significant role in thermogenesis under certain circumstances.[18] UCP-1 expression in EAT seems to be higher than in other fat depots, suggesting the presence of brown adipocytes specifically in EAT.[19] Other positive EAT characteristic is that contains abundant progenitor cells and therefore, could be a source of myofibroblasts that produce extracellular matrix.[20] In this aspect, Bayes-Genis's group supported the use of pericardial-derived fat flaps to cover post-infarction scars and reduce infarct size.[21,22] This positive effect seems to be partly due to neovascular connections and cell trafficking at the flap-myocardium interface.

Differences in eat extension and weight between normal and pathological conditions

Under normal circumstances, the biggest mass of EAT is localized on the lateral and anterior walls of the right atrium, the apex, the atrioventricular and the

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