Rev Esp Med Nucl Imagen Mol. 2013;32(4):246–252

Special collaboration

Role of FDG PET/CT in investigating the mechanisms underlying atherosclerotic plaque formation and evolution

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ARTICLE INFO

Article history:
Received 9 January 2013
Accepted 4 April 2013

Keywords:
Atherosclerosis
Etiology
Vulnerable plaque
Stable plaque
Inflammation cells
FDG PET/CT
Molecular imaging

ABSTRACT

This review article is focused on the role of FDG-PET/CT in visualizing atherosclerosis and on the relevance of inflammatory cells such as macrophages and T-lymphocytes in the formation of the atherosclerotic plaque. The vulnerability of the inflammatory plaque and the risk derived from the provocation of cardio- and cerebrovascular incidents independently from the presence of stenotic vessels are discussed as well as the evolution toward calcified plaque. The important role of FDG-PET/CT in early diagnosis of inflammatory plaque is discussed in both animal studies and in clinical setting. The possibility of curing inflammatory plaques, type of drugs, and the possibility of monitoring the anti-inflammatory treatment by FDG-PET/CT are also discussed.

Papel del FDG PET/CT en la investigación de los mecanismos subyacentes a la formación y evolución de la placa aterosclerótica

Palabras clave:
Aterosclerosis
Etiología
Placa vulnerable
Placa estable
Células inflamatorias
FDG PET/TC
Imagen molecular

RESUMEN

Este artículo se centra en el papel de la FDG PET/TC en la identificación de la aterosclerosis y en la relevancia de las células inflamatorias como los macrófagos y los linfocitos T en la formación de la placa aterosclerótica. Se discute también sobre la vulnerabilidad de la placa inflamatoria y el riesgo asociado a determinar incidentes cardio y cerebro-vasculares independientemente de la presencia de vasos estenóticos, así como sobre la evolución hacia la placa calcificada. El importante papel de la FDG PET/TC en el diagnóstico precoz de la placa inflamatoria se discute tanto en estudios con animales como a nivel clínico. Se discute, finalmente, la posibilidad de curar la placa inflamatoria, el tipo de fármacos utilizados y la posibilidad de controlar el tratamiento anti-inflamatorio a través de FDG PET/TC.

Introduction

Atherosclerosis is a systemic disease process constituted by fatty deposits, inflammation cells and fibrosis within the walls of both large and small arteries. It is the cause of many events and diseases such as stroke, angina pectoris, acute myocardial infarction, heart failure, transient ischemic attack, peripheral arterial disease, asthma hypertension and chronic obstructive pulmonary disease. Most of the current information about the epidemiology of atherosclerosis comes from prevalent studies performed during the past decades, which often reflect medical environments that were very different from the present, where many preventive interventions, including hypertension control, lipid-lowering and antiplatelet therapies, are more widely used. The identification of asymptomatic high-risk atherosclerotic patients who could benefit from neo-adjuvant therapy before rupture of the nascent plaques remains a major challenge for preventive medicine. In recent decades, imaging modalities have shown the ability to detect and quantify atherosclerosis in multiple different vascular beds and during early stages with the intent to assess the patient's cardiovascular risk. Both the coronary artery calcification (CAC) as evaluated by computed tomography (CT) of the chest and carotid artery intima-media thickness (IMT) as evaluated by B-mode ultrasound of the neck have been used in large studies with outcomes data and may help to define the burden of atherosclerosis in individuals before they develop clinical events. However, there are still limited data demonstrating whether screening with these and other imaging modalities can improve patient outcomes or whether it only increases downstream medical care costs.[1]

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2253-654X/$ – see front matter
http://dx.doi.org/10.1016/j.remn.2013.04.001

The key role of macrophages in plaque vulnerability

The methods based on vascular narrowing did not show a great relevance in determining the risk of events, because acute events often occur also in patients with a relatively low thinning of the vascular bed (reduction of 30–40%). On the contrary, the main factors demonstrated to be crucial in determining the risk of sudden cardiovascular events are the plaque composition and its biologic activity. In fact, patients with acute coronary events usually harbor multiple ruptured of atherosclerotic plaques.[2]

In this view, as inflammation is a more distinct characteristic of "at-risk" plaques versus the "stable" plaques, the best approach to identify high risk patients can be a noninvasive targeted inflammation imaging across several vascular beds, capable of systematically quantifying the plaque burden and being highly reproducible. Quantifying such inflammation is useful for two reasons. First, it might allow more precise characterization of the risk scores to better define those patients at high risk and to identify more "targeted" therapy. Secondly, serial noninvasive inflammation imaging would allow testing the efficacy of novel anti-atherosclerotic drugs.[3]

To prevent the serious complication of atherosclerosis, an ideal molecular imaging modality should use an agent capable of reaching a high concentration only in the critical atheromas (at-risk plaques), while distinguishing the other atheromas with minimal or no concentration of the agent (stable or non-active disease). Lastly, the agent should be capable of visualizing the characteristic behavior of the "vulnerable" plaque in terms of cellular, biochemical and molecular components with high specificity.

In this scenario, macrophages are probably the more interesting "target population", since these cells are deeply involved in plaque formation and evolution, and are the basis of complex processes involving foam cells formation, inflammatory response and apoptosis. Yet, macrophages are considered determinant in plaque vulnerability and rupture, since a large amount of macrophages and active inflammation are closely related to the cap erosion and the exhibition of the plaque content.[4] Macrophages have also been implicated in weakening the fibrous cap of plaques due to the secretion of matrix-metalloproteinase (MMP), a family of enzymes that degrades the extra-cellular matrix components, specifically proteoglycans and collagen elastin, thereby possibly serving to thin the collagen skeleton of the fibrous cap and leading to plaque rupture and fissuring.[5–7]

Also, it has been demonstrated that during the advanced stages of the plaque, inside the immuno-inflammatory environment, T-lymphocytes (in particular the interpheron gamma producer T-cells probably activated by auto-antigens) accumulate more than macrophages in lesions with plaque rupture in patients with unstable angina. This then promotes plaque de-stabilization and triggers vascular inflammation and down-regulating extracellular matrix.[8]

Therefore, the switch to a selective recruitment of T-lymphocytes with a relative reduction of macrophages probably could represent a key-point toward plaque vulnerability and disruption. In this view, imaging the plaque at the time of the highest macrophage concentration (just before the T-lymphocytes switch) is particularly important because it capturing the situation just before the point of no return, i.e. the rupture.[9]

It is worth noting that in the early stages of the inflammation, neutrophils are rather self-sufficient in their energy production, so usually there is no need of glucose consumption until there is a "critical" mass of macrophage-rich-infiltrates. In the subsequent stages, although macrophages predominantly use fatty acid for their metabolism, the plaque begins to show a macrophage-rich core with a high metabolic rate, and therefore restricted to an anaerobic metabolism. Given these anaerobic conditions, inflammatory cells favor production of adenosine triphosphate via the glycolytic pathway.[10,11] Therefore, the greater the degree of inflammation in a plaque, the greater the rate of glucose consumption.[12]

With this in mind, since macrophages become a "glucose-avid" population, a method such as ^{18}F-FDG-PET/CT, which measures the glucose metabolism, could be considered ideal. In a recent study, Folco et al.[13] exposed some cells to conditions similar to those inside an atheroma and demonstrated that hypoxia can also be a very important mechanism involved in FDG uptake in atherosclerotic plaques. In fact, cells in a low-oxygen concentration environment usually tend to switch their metabolism toward a higher use of glucose, and therefore become FDG-avid.

Role of PET/CT in inflammation and calcification of atherosclerotic disease

FDG (2-deoxy-2-(^{18}F)fluoro-D-glucose) is a glucose analog with a hydroxyl group replaced with positron-emitting radioactive isotope fluorine-18 at the 2′ position in the glucose molecule, and is a marker of glycolytic metabolism. The main application of FDG-PET scan is in oncology. The rate of glycolysis in malignant cells is generally significantly higher than in normal cells of the surrounding tissues due to the over-expression of some glucose transporter molecules (especially GLUT1, GLUT3) at the tumor cell surface and to the increased activity of the glycolytic enzymes such as hexokinase. However, due to the absence of the —OH group, after entering the cell, FDG cannot be dephosphorylated, nor broken down along the glucose metabolic pathway and stored as glycogen. For this reason, FDG is trapped in the cells. Consequently, FDG concentration generally remains high within the tumor cells, allowing malignancies to be clearly identified using ^{18}F-FDG-PET/CT.

In recent years, beyond the "classical" applications in oncology, FDG-PET/CT has been increasingly used for diagnosing some non-neoplastic diseases and assessing therapy response in follow-up, which has demonstrated FDG-PET/CT's usefulness in evaluating inflammatory and infectious disorders such as sarcoidosis, vasculitis, inflammatory bowel disease, prosthesis infection and rheumatoid arthritis. The rationale of FDG usage is that these conditions are biologically characterized by a high metabolic rate of glucose consumption.[14]

In this context, FDG-PET/CT has proven to be highly sensitive in imaging inflamed arterial walls, showing a sensitivity of more than 80% in the detection of vasculitis of large arteries,[15] not only for the primary diagnosis of the disease, but also as a prognostic marker for the subsequent development of aortic aneurysms.[16] A great advantage of FDG-PET/CT is to image all large arteries in a single whole-body scan. Since atherosclerosis has been largely demonstrated to evolve as an inflammatory disease, especially in advanced stages, FDG-PET/CT has been proposed as an interesting tool to evaluate the disease.

Studies using laboratory data showed that there is no measurable uptake into the normal vessel wall.[17,18] Incidental FDG uptake has been reported, commonly in aorta and large vessels, and more rarely in coronary arteries[19] in patients imaged for various malignancies. In these cases, it was first hypothesized and then histologically demonstrated that these findings were related to an inflammatory state (atherosclerosis-related).[20]

The first observation on the FDG uptake in large vessels walls in the presence of an inflammatory disease was described by Theron and Tyler.[21] They evaluated the results of an endovascular approach on arterial stenosis and occlusion of the aortic arch due to Takayasu's arteritis, and comparing them with angiographic, cerebral hemodynamic and FDG-PET findings, where the authors observed an FDG uptake on large vessels.[21] In the subsequent years, some other sporadic observations of FDG uptake in sites of inflammation have been reported, such as locations in proximity