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

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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.

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

R E S U M E N

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.

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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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The 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 extracellular 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 interleuporin 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 18F-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-[-¹⁸F]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 18F-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 arteries19 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.22 In the subsequent years, some other sporadic observations of FDG uptake in sites of inflammation have been reported, such as locations in proximity
of vascular graft.\textsuperscript{22} The first systematic work that closely correlated the FDG uptake in large arteries wall with atherosclerosis was published by a research group at the University of Pennsylvania.\textsuperscript{23} In a retrospective study, they evaluated 156 patients who had undergone FDG-PET due to cancer and observed that 50% of the total population (mean age 50 years) demonstrated vascular FDG uptake in large vessels (abdominal aorta, iliac and proximal femoral arteries). The amount of FDG uptake increased with age, arousing the suspicion of correlation with age-related vascular structural changes (subendothelial intimal thickening) and with atherosclerotic phenomena (notoriously more frequent in the elderly).

In animal studies, Ogawa et al.\textsuperscript{18} and Tawakol et al.\textsuperscript{24} pointed out that FDG uptake was related to the number of macrophages and not with the intimal thickening nor with the smooth muscle cells (two other components of the plaque). In particular, stable and inflamed plaques showed both an intimal thickening but with different cellular components: mainly macrophages in inflamed plaque, whereas mainly smooth cells in stable plaque.

An American study\textsuperscript{25} showed that the FDG uptake was significantly higher in the acute coronary syndrome versus the stable angina groups of patients both in the ascending aorta and the left main coronary artery. In addition, target-to-background ratios (TBR) of culprit lesions associated with acute coronary syndrome were greater than that of lesions stented for stable coronary syndromes. Moreover, TBR was correlated with C-reactive protein suggesting that FDG may be useful for noninvasive measurement of plaque inflammation. A recent prospective study\textsuperscript{26} showed high FDG (with associated macrophage accumulation) not only in the carotid around a “culprit” lesion from a recent event, but also in the contralateral carotid with low to moderate stenosis.

The presence of inflammation in human atherosclerotic plaques has also been confirmed by the high presence of inflammatory markers, in both the serum and the atheromatous plaques themselves. In particular, a paper by Wu et al.\textsuperscript{27} demonstrated a link between FDG uptake and circulating values of MMP-1 (matrix-metalloproteinase), which is a compound produced by macrophages. Its over-expression is strongly related to the thinning of the fibrous cap and subsequent plaque rupture. Recent studies reported a significant correlation between metabolism measured with FDG-PET/CT and inflammatory activity of the advanced atherosclerotic plaques measured by the gene expression of plaque vulnerability markers (GLUT-1, CD68, cathepsin K, HK2 and CD-68) both at univariate and multivariate analysis.\textsuperscript{28,29}

As mentioned above, atherosclerotic calcifications cannot be merely considered a “passive calcium deposition” inside the plaque, but the result of a dynamic series of events, often similar to that involved in new bone formation. Based on the concept of “molecular calcification” and the inability of current structural imaging methods to provide information on the “active calcification” of the plaque, some authors have proposed a PET tracer that is generally used as a marker for bone metabolism for early imaging atherosclerotic calcification. 18F-sodium fluoride, a tracer of bone metabolism, is an analog of the hydroxyl group of the hydroxyapatite bone crystals, and therefore an avid mineral bone matrix-seeker. The precise mechanism of its uptake is not fully known yet, but it can most likely indicate an ongoing active mineral deposition in atherosclerotic lesions. Consequently, plaques still accumulating 18F-sodium fluoride might not represent stable, non-progressive stages of disease.\textsuperscript{30,31}

According to the previous results, Rominger et al. added the observation that discordant localization of FDG uptake (measured as target-to-background ratio, TBR) and calcification (in their followed-up asymptomatic population) tended to be more frequent in patients with severe cardiovascular events during follow-up than in patient with no or light events (Fig. 1).\textsuperscript{32} These results are consistent with the nature of the atherosclerosis as a dynamic process, in which FDG uptake is most likely a biomarker for susceptible and unstable plaques, which can lead to a vascular event, whereas calcified plaques is a surrogate marker for the presence of atherosclerosis, irrespective or independent from plaque vulnerability.

**Technical issues and potential solutions**

Concerning the optimal time between FDG injection and PET scan acquisition, there is no consensus in the literature: some authors advise acquiring images at the same time as the standard for oncologic patients (60 min after injection)\textsuperscript{33,34}; other investigators recommend to begin PET scan about 90 min after FDG injection to allow time for uptake of FDG from the bloodstream into the cells of interest.\textsuperscript{34,35,36} many others suggest to wait around 3 h after FDG infusion in order to produce higher contrast between plaque and background (Fig. 2).\textsuperscript{17,18,24,37}

Interestingly, elevated glucose concentration in the blood does not appear to have a negative effect on FDG uptake in the inflammatory cells, contrary to what is observed in malignant disorders.\textsuperscript{38} This consideration is particularly important for the management of diabetic patients who are at high risk of the complications due to atherosclerosis.

Some investigators have reported FDG accumulation in the coronaries. However, some problems emerged from the effort to study coronary vessels. First, the coronary arteries are small and constantly in motion, especially in distal portions. Also, the respiratory cycle can induce a “mismatch” between CT and PET data sets. It is also worth noting that myocardial muscle also uses glucose as fuel, so FDG can be highly accumulated in myocardium near the arteries, reducing the possibility to clearly highlight the coronary tree. To overcome these issues, some researchers tried to reduce the FDG myocardial uptake inducing a “switch” of the myocardial metabolism from glucose to fatty acid in order to reduce the myocardial uptake around the arteries. Furthermore, they directed the efforts toward the analysis of others vessels (larger in diameter, like aorta) as a “surrogate” of coronaries.

Dunphy and coworkers\textsuperscript{19} retrospectively evaluated the FDG uptake in the vessel walls of 78 cancer patients, considering not only the main arteries but also the proximal coronaries. They observed FDG accumulation in 45% of the studied patient, and also a fourfold greater FDG uptake in coronary vessels of patients with a history of coronary artery disease. Furthermore, they demonstrated that the FDG uptake in the ascending aorta strongly correlated with coronaries FDG uptake, and therefore postulated that the analysis of main vessels can “substitute” the coronary artery evaluation, which is more difficult from a practical point of view.

Applying a dietary protocol including a “low carbohydrate, high-fat” meal the night before and ingestion of vegetable oil the morning of the study, Wykrzykowska et al.\textsuperscript{30} demonstrated a significantly high correlation between angiographic disease and coronary FDG uptake, and also a concordance (in another group of patients with a history of ischemic heart disease) between FDG and extra-cardiac vascular focal FDG uptake.

Rogers et al.\textsuperscript{25} prospectively studied 25 patients with Acute Coronary Syndrome (ACS) or stable angina after performing CTAngiography. The aim was to test the hypothesis that the maximum FDG uptake is within lesions that are expected to be inflamed, thus the plaques that are deemed to have recently caused ACS. Furthermore, they attempted to determine whether FDG uptake measured in ascending aorta and in the relatively “immobile” (due to its non-epicardial location) left main coronary artery can be useful as a “surrogate marker” for FDG uptake in coronaries. The results of this interesting study clearly showed a higher FDG uptake in both ascending aorta and left main artery in patients with ACS than in
patients with stable angina. The high FDG uptake in the ascending aorta underlies the potential use of main arteries FDG-uptake measure in providing substantial information on the proximal coronary tree, and thus, the atherosclerotic condition of the coronaries. This could avoid the problems related to the small coronaries diameter and to the high myocardial uptake that can prevent correct evaluation of the situation.

The quantification of inflammation and disease

A visual observation can be useful to qualitatively characterize the FDG uptake (thus, of the degree of inflammation), while SUV (standardized uptake value – the most commonly method used to quantify the FDG uptake in clinical practice) can provide quantitative and reproducible data about the disease.

One of the first attempts to quantify plaque inflammation occurred in the first work by Rudd et al., where the authors co-registered PET and CT images in patients with symptomatic carotid artery disease. To estimate plaque FDG concentration, they first obtained a “mean FDG concentration value” placing a three-dimensional volume of interest (VOI) (drawn around the area of the stenosis on the contrast CT scan) onto the co-registered PET images. Then, they obtained the estimated net FDG accumulation rate dividing the mean decay-corrected FDG concentration in the plaque VOI by the integral of the decay-corrected input function derived from venous plasma samples.

In comparing PET data and CT calcifications, Tatsumi et al. used a grading score to semi-quantitatively evaluate FDG uptake on PET/CT images as: grade 1 = slightly higher than blood pool and mediastinal uptake; grade 2 = clearly shown and greater than grade 1 but lower than liver uptake; grade 3 = equal to or greater than liver uptake. Moreover, they also used a SUV corrected for lean body mass (SUL) by placing a ROI manually on the transaxial image to completely surround the most intense area of FDG uptake. The SUL was then calculated by using the maximum pixel-activity value within the region of interest.

More precise measures have been subsequently obtained using CT findings to better identify the vessel volume, or normalize the vessel activity to avoid the influence of the blood background.

Taking advantage of the capabilities of hybrid FDG PET/CT machines, Bural et al. in evaluating 18 patients subdivided in groups per age, applied a new method of FDG uptake quantification by combining SUVs in the aortic wall with volumetric data provided by CT. In each of the four segments in which the aorta was divided (ascending thoracic, arch, descending thoracic, and abdominal), FDG uptake was measured as SUV mean. Furthermore, for each axial CT slice, a “net” wall surface was obtained, subtracting the inner surface area by the outer one (after drawing correspondent

Fig. 1. Transaxial FDG-PET image (A) and the corresponding images with fusion of PET and CT (B) and CT alone (C) reveal irregular uptake of FDG in the arch of the aorta. This image reveals FDG uptake only in the non-calcified plaques (arrow) and minimal uptake in the calcified regions (arrow head). These images demonstrate that non-calcified plaques contain a large number of activated macrophages while calcified regions are devoid of these cells.

Fig. 2. The images shown above demonstrate the importance of timing for acquiring images of FDG uptake in the plaques after the administration of this agent. Images on the left (A), which include images of PET alone, PET-CT fused, and CT alone, were taken 60 min after the administration of the compound and show significant background activity in the sagittal plane of the arch and thoracic aorta. There is no clear cut delineation of active plaques on this image. In contrast, images on the right (B) clearly demonstrate active uptake in the anterior wall of the thoracic aorta and the inferior aspect of the arch that are distinct from the areas without active plaques. Interestingly, aortic walls with significant calcification in the posterior aspect of the structure are devoid of activity, while inferior walls of the arch and anterior aspect of the thoracic aorta contain significant uptake and therefore represent active plaque formation at these sites. These images clearly demonstrate the importance of timing for image acquisition after the administration of FDG for visualizing plaques in the major vessels. Also, they reveal the effects of calcification on macrophage concentration in the plaques in the major arteries.
regions of interest). The net area values for each aortic segment were then multiplied by slice thickness to calculate the “total” arterial wall volume. Finally, multiplying the wall volume by the SUV, an “atherosclerotic burden (AB)" value was calculated, containing both the volumetric and metabolic information. The AB values of the three age groups were compared and the authors found that arterial volume, mean SUVs and AB increase with age both regionally (in each aortic segment) and in the whole aorta, as expected, but the progression of AB was exponential, while the progression of mean SUV and volume appeared linear, thus showing the stronger value of the combined variables than that of the two taken separately. On this basis, the author also suggested the future applications of this combined index in optimal diagnosis, follow-up and treatment of atherosclerosis. The same authors confirmed the reliability of this method, using it also in other large arterial vessels (iliac and femoral arteries).

Later, these authors subsequently modified the approach slightly with the aim to avoid the influence of the calcification volume on the evaluation of the whole aortic volume. In the refined method, the wall volume was, in fact, corrected by subtracting the volume of regional wall calcification (obtained via adaptation of a coronary artery calcium-scoring program to the aorta) on contrast enhanced CT to yield the “non-calcified” wall volume, which was then multiplied by the corresponding mean SUVs over each segment. The sum of these values over all aortic segments represented the global metabolic activity.

Tawakol et al. proposed to quantify FDG uptake using the normalization to blood FDG imaging calculated in a blood ROI, thus obtaining the so-called tissue-to-background ratio (TBR). This was performed drawing a ROI around each artery (on a CT basis) on each slice of the co-registered transaxial PET/CT images, obtaining the mean SUV in each ROI and then, averaging these values, the global mean SUV value for each artery. The background correction was then obtained dividing the average SUV for a large vein blood activity.

Using the same method, Rudd et al. compared TBR obtained using SUV mean and max, providing comparable and reproducible results. Therefore, the authors suggested that the mean TBR could be used for tracking systemic arterial therapies, whereas the maximum TBR could be optimal for detecting and monitoring local, plaque based-therapy in both aorta and peripheral arteries.

**FDG PET/CT atherosclerotic plaque imaging: from the “vulnerable plaque” to the “vulnerable patient”**

Atherosclerosis FDG imaging has been demonstrated across multiple vascular beds, including carotid, vertebral arteries, aorta, iliac, femoral and popliteal arteries and coronary vessels. After the first observations, which correlated the FDG uptake with inflammation in “at risk” plaque, the following studies have focused more on specific clinical issues.

From the standpoint that plaque is a risk factor and FDG-PET/CT can be used to identify at-risk patients in a pre-symptomatic phase, it is interesting to evaluate the literature about the usefulness of FDG-PET/CT for assessing a possible relationship with the risk and its possible and practical use in the clinical setting.

**Relationship with the cardiovascular risk factors**

The amount of FDG uptake in vessel walls increases with the number of cardiovascular risk factors: an interesting work published in 2002 demonstrated a positive correlation between FDG uptake in large arteries (abdominal aorta, iliac and proximal femoral arteries) and several other atherogenic risk factors. Mainly, the patient’s age and hypercholesterolemia showed the more significant correlation. These results were confirmed also by other investigators which demonstrated the relationship of FDG findings with serum inflammation markers, with metabolic syndrome-related factors (abdominal obesity, fasting triglycerides, HDL cholesterol, blood pressure and use of antihypertensive medications, hyperglycemia) and with diabetes population. In a recent study, Rominger et al. showed that FDG TBR was able to foresee vascular events during follow up of their otherwise asymptomatic population with an incremental value compared to the “classical” risk factors, suggesting its potential relevance in the risk stratification.

**Relationship with events and prognosis**

Several works have evidenced the link between FDG uptake on PET/CT and cardiovascular events, both previous and subsequent, demonstrating the relationship between the condition of “inflammation” of the high risk lesions and the occurrence of the acute event itself, also in terms of time.

A group of studies have compared the FDG uptake on atherosclerotic plaques and/or arterial wall with cardiovascular symptoms, in particular with a recent acute vascular event. Some research groups have given special attention to atherosclerotic carotid arteries, and to the correlation between the FDG uptake with recent cerebral attacks (transient ischemic attacks or minor strokes) demonstrating that FDG accumulation rate was significantly higher in symptomatic lesions (angiographically demonstrated to be the “culprit” lesions) than in contra-lateral asymptomatic lesions. Of note, these authors suggested the potential use of combined FDG-PET/CT and MRI as a potential tool for identifying the lesion responsible for the vascular event especially in cases in which angiography cannot completely help.

Regarding the role of PET in prognosis, Arauz et al. observed that in a population of patients with previous transitory ischemic attack or ischemic stroke in the carotid territory, all recurrences, restenoses or deaths during follow-up (6 months) occurred in patients with high carotid FDG uptake (SUV max ≥ 2.7), therefore suggesting a potential role of FDG-PET/CT in the outcome of these patients, regardless of surgical or medical treatment. Studying otherwise asymptomatic patients, two more recent studies confirmed the previously published results concerning the high value of the arterial FDG uptake in predicting subsequent cardiovascular event. In particular, the study by Rominger et al. showed that FDG uptake in the major arteries emerged as the strongest predictor of subsequent vascular events during follow-up. These results confirmed FDG-PET’s usefulness in risk-stratification without the standard cardiovascular risk factors.

**The evaluation of the response to therapy**

FDG-PET/CT allows a non-invasive measure of vessel wall inflammation with excellent reproducibility, making it an attractive modality to assess the efficacy of cardiovascular drugs with anti-inflammatory properties, especially in longitudinal multicenter trials of drugs. The reproducibility of the atherosclerotic damage is provided by the quantification of FDG uptake through the SUVmax, SUVmean and TBR that can improve the understanding of PET data pre- and post-treatment.

FDG-PET/CT was first used in animal models as a noninvasive tool for monitoring the effectiveness of anti-atherosclerotic therapies. Worthley et al. demonstrated a significant correlation between FDG uptake and changes in dietary habits and behavior of the disease, where they saw increased FDG uptake in the progression group after cholesterol feeding and decreased FDG uptake in...
the regression group after returning to a normal diet, which was related to changes in macrophage content.

In a very recent work using a micro-PET/CT, statin therapy along with low-cholesterol diet reduced the FDG uptake in inflamed atherosclerotic plaques of aorta, obtaining a significant difference versus FDG uptake of plaques stabilized by statin and diet. It is interesting to note that the same results have been also achieved with an anti-inflammatory drug, probucol, which reduced the macrophage density. 56 Interestingly, it was observed that statins can reduce plasma cholesterol but not macrophage infiltration, 58,59 which further illustrates the "inflammatory nature" of the plaque, and suggests the usefulness of this method for assessing the therapeutic effect of new drugs that can reduce the inflammation in atherosclerotic plaque independently of lowering the level of cholesterol.

In an interesting paper published in 2006, Ogawa et al. 56 demonstrated the potential usefulness of FDG-PET/CT in evaluating the efficacy of probucol (an oxidant drug) on the inflamed, macrophage-rich atherosclerotic plaques in Watanabe hyperlipidemic rabbits with myocardial infarction. Radioactivity in aorta was significantly lower in the probucol group than in control group (in particular, it progressively reduced during the treatment). This reduction was related to a significant reduction in macrophage infiltration. As the stabilization of vulnerable plaque is important for atherosclerosis therapy, the authors concluded that the clinical application of this imaging system would be efficient for assessing the therapeutics effects of drugs.

Moving to the works on human population, Tahara et al. 60 investigated the anti-inflammatory effect of simvastatin by using FDG-PET/CT. They demonstrated that simvastatin, but not diet alone, attenuated plaque FDG uptake and decreased SUVs. Thus, the authors postulated that simvastatin can provide a pleiotropic, anti-inflammatory effect, LDL independent, and that FDG-PET/CT metabolic imaging can clearly visualize anti-inflammatory effects of this drug on the plaque. Furthermore, some years later, FDG uptake measurement has been used for evaluating the effect of different doses (5 and 20 mg/d) of another statin (atarvastatin), demonstrating that six months of treatment with only 20 mg of atorvastatin was correlated with a significant reduction in TBR in the ascending aorta and femoral artery. 61

In a paper published in 2008, Lee et al. evaluated the change of vascular FDG uptake in response to a lifestyle modification, using serial PET/CT scans. In their population, FDG uptake was reversed in response to atherogenic risk reduction by lifestyle intervention. 62 Interestingly, both the studies by Tahara and Lee 60,62 found that the magnitude of FDG-PET/CT signal reduction was closely related with the rise in HDL-C.

In conclusion, FDG-PET/CT appears to have an important role in early diagnosis of inflammatory vulnerable plaque, stratifying risk, determining a therapeutic strategy and also estimating the therapy response. Although at present it is unknown whether atherosclerosis imaging could be superior to risk scoring algorithms for predicting cardiovascular events, in the future, high-risk patients who are identified by clinical means as well as genetic information and biomarkers, may be more accurately risk-stratified by imaging targeted at morphologic and functional characterization of high-risk plaques. Since drug effects vary among individuals, FDG-PET/CT can be particularly useful not only in monitoring the therapeutic effects, but also in selecting the appropriate drug for individual patients and in evaluating the efficacy of new drugs in multicenter clinical trials.

Conflicts of interest

The authors have no conflicts of interest to declare.

References

7. Lendon CL, Davies MJ, Born GV, Richardson PD. Atherosclerotic plaque caps are locally weakened when macrophage density is increased. Atherosclerosis. 1991;87:87–90.


