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NOVEL + EMERGING RISK FACTORS (K NASIR, SECTION EDITOR)

Imaging Plaque Inflammation in Higher-Risk Patients: What Do We Know and What Are We Looking For?

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Abstract Atherosclerosis is a chronic inflammatory condition complicating cholesterol accumulation within the artery wall. Inflammation is believed to play an important role in the formation, progression, and ultimately the rupture of atherosclerotic plaques (the principle event leading to most myocardial infarctions and strokes). An enhanced understanding of the inflammatory process within the atheroma may therefore facilitate risk stratification and treatment strategies. Molecular imaging techniques such as PET/CT have the ability to quantify arterial inflammation and assess the high-risk features of atheromas thus may be useful for identifying patients who are at higher risk for an atherothrombotic event. In this review, we focus on the potential of FDG-PET/CT as a tool to measure arterial inflammation, enhance risk stratification, and to evaluate novel therapies directed against atherosclerotic disease. Additionally, this review will provide a discussion on current challenges as well as future directions.

Keywords FDG-PET · Inflammation · Atherosclerosis

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Introduction

Atherosclerosis and its complications are the primary causes of cardiovascular morbidity and mortality worldwide [1]. The formation and development of an atherosclerotic lesion is a complex process that includes chronic inflammation as a central pathologic component [2]. Monocyte-derived macrophages play a key role both in the incipient phases of plaque formation as well as in the progression of mature plaques [3, 4]. Imaging modalities such as conventional angiography, ultra sonography (US), computed tomography (CT), and magnetic resonance imaging (MRI) provide clinically useful information on plaque structure or luminal narrowing [5–7]. However, this structural data provides an incomplete assessment of atherothrombotic risk, in part, since stenosis is only a modest predictor of future complications as most acute coronary events occur at sites of mild to moderate obstruction [8, 9•]. The evaluation of the arterial wall inflammation, in addition to assessment of structure and narrowing may therefore provide clinically important insights. Such structural and biological imaging can be achieved via combined PET/CT or PET/MR imaging.

Inflammation and Atherosclerosis

The development of atherosclerotic lesions is a complex process, with chronic inflammation and lipid accumulation as central interconnected pathologic components. Endothelial damage or dysfunction participates as a stimulus for the accumulation of lipids and inflammatory cells in the affected area. Inflammatory cells such as monocytes and T lymphocytes attach to the vascular endothelium via vascular cells adhesion molecules (e.g., VCAM-1) [10]. The monocytes subsequently transmigrate across the intimal layer and become intimal

macrophages. There, they internalize lipoprotein particles thru scavenger receptors and develop into lipid-laden foam cells, an ongoing process that can eventually lead to apoptosis and necrosis thus contributing to the growth of the lipid-rich core. The foam cells produce pro-inflammatory cytokines (TNF, IL-1, IL-6), promoting a chronic inflammatory response which leads to the recruitment of additional macrophages into the plaque [11]. They further produce matrix metalloproteinases (MMPs) thus contributing to the weakening of the plaque fibrous cap. Additionally, macrophages secrete tissue factor, which can promote thrombus formation after plaque rupture [12]. Accordingly, macrophages contribute to the formation, progression and rupture of plaques, and also accentuate the thrombosis that ensues.

The important relationship between inflammation and atherosclerotic events is further supported by clinical evidence. Multiple prospective studies performed on apparently healthy subjects have found that individuals with increased plasma biomarkers of inflammation (such as IL-6, soluble P-selectin, CD40, or MIC-1) have an increased risk of CV events [13–15]. The biomarker with the highest predictor value for future events was proved to be high-sensitivity CRP. Various large prospective studies have shown that elevated levels of hs-CRP are predictive of an increased risk for future cardiovascular events [16, 17].

Molecular Imaging with FDG PET/CT

PET/CT imaging, using 18F-fluorodeoxyglucose (FDG) has proven to be clinically invaluable as a diagnostic tool in oncology. It is widely used in the process of staging tumors, monitoring response to treatment, and detecting disease recurrence [18, 19]. Additionally, FDG-PET/CT has gained a role in the clinical evaluation of different inflammatory and infectious diseases like FUO, device infection, cardiac sarcoidosis, and endocarditis [20].

FDG is a radiolabeled glucose analogue, which is employed as a molecular probe to track cellular activity. 18F-FDG enters the cells thru glucose transporters and is phosphorylated by hexokinase to FDG-6-phosphate. While glucose becomes glucose-6-phosphate and further participates in glycolysis, FDG, once phosphorylated, becomes FDG-6-phosphate and is unable to move forward thru the glycolytic pathways or exit the cell, so it is trapped within the macrophages at a rate proportional to the glycolysis rate [21]. Thus, tissue uptake of FDG provides an index of glycolytic activity.

Glycolysis is of particular importance to macrophages. Macrophages have higher basal glycolytic rates compared to most cell types and are reliant on external glucose for metabolism as they are unable to store glycogen [22]. Importantly, macrophage glycolysis is substantially upregulated after pro-inflammatory (M1) but not alternative (M2) activation [23]. As a consequence, pro-inflammatory (M1) macrophages avidly accumulate FDG [24]. The relatively hypoxic environment within tumors, atheroma, and inflamed tissues leads to additional upregulation of macrophage pro-inflammatory activation, with stimulation of TNF alpha production and other potent pro-inflammatory cytokines [25]. As a result, FDG uptake is further stimulated. Macrophage FDG uptake may in part be responsible for the substantial success of FDG in clinical oncological imaging. Indeed, within tumors, tumor-associated macrophages (TAMs) can manifest higher FDG accumulation than the cancerous cells themselves [20]. Furthermore, within the atheroma, abundant cytokines exist in association with oxidized lipids. Modified LDL provides an additional stimulus for macrophage glycolysis and FDG uptake [26] whereby Ox LDL increases reactive oxygen species (ROS) production and HIF-1 alpha expression, which in-turn enhance macrophage glycolysis [27•].

Arterial FDG Uptake Provides a Noninvasive Index of Inflammation

Several preclinical studies have shown a direct correlation between arterial FDG uptake and histologically measured degree of inflammation [28, 29]. The first prospective study using FDG-PET to evaluate atherosclerotic tissue in humans was performed by Rudd et al. in 2002. In that study of patients with symptomatic carotid atherosclerosis, 18-FDG accumulation was significantly higher in symptomatic lesions compared to asymptomatic contralateral lesions [30]. A separate study, in which patients with carotid stenosis were imaged just prior to carotid endarterectomy, showed that the FDG signal correlates with macrophage density measured histologically in the subsequently excised carotid specimens [31]. Those studies thus established that FDG-PET imaging can be used to noninvasively assess the severity of inflammation in carotid plaques in patients. Other studies showed that in clinically stable patients, the arterial FDG signal is high reproducible [32, 33].

Relationship to Disease Progression and Event Risk

Arterial FDG uptake appears to provide insights about an individual's risk for atherosclerotic disease. The degree to which FDG accumulates within the arterial wall is related to the individual's cardiovascular risk factors and Framingham risk score [34]. Furthermore, several studies demonstrate that arterial FDG uptake is greatest in atherosclerotic plaques that contain structural features that are associated with a higher risk of rupture [35–37]. Figueroa et al. demonstrated that FDG uptake is greatest in plaques with high-risk features, defined

as positive remodeling, luminal irregularity, or low attenuation [36, 38].

Importantly, several studies have shown the arterial FDG signal provides insights about the rate of atherosclerotic disease progression within the underlying arterial segment. Fayad et al. demonstrated that FDG uptake within the carotid arteries is associated with the subsequent rate of plaque expansion of the underlying atheroma (using MRI to measure disease progression over 2 years in humans) [39••]. Abdelbaky et al. observed that arterial FDG uptake correlates with the subsequent rate of calcium deposition in the underlying arterial segment (another measure of plaque progression, by CT) [40]. Accordingly, high arterial FDG accumulation identifies arterial locations where atherosclerotic disease is most likely to progress.

Moreover, a body of research has emerged showing that arterial FDG uptake may improve prediction of cardiovascular disease (CVD). In a cohort of patients with cancer, Rominger et al. [41] observed that a higher arterial FDG signal was associated with a high risk of subsequent CVD event. Figueroa et al. recently extended those findings. In a study of 513 cancer-free patients who underwent FDG-PET and computed tomography (CT) imaging, aortic target to background ratio (TBR) strongly predicted subsequent CVD independent of traditional risk factors during the 6-year follow-up period. The addition of FDG uptake to FRS scores substantially improved risk discrimination. Moreover, FDG data resulted in the net accurate reclassification of 27 % of individuals over Framingham risk score. Of note, arterial TBR was inversely associated with the timing of CVD. The study concluded that arterial FDG uptake improved incident CVD prediction beyond FRS and provided information on the potential timing of such events [42•].

Thus far, limited prospective data are available regarding the ability of arterial FDG measures to predict subsequent atherothrombotic events. A small prospective study recently showed in individuals presenting with a stroke that increased FDG uptake in carotid arteries was associated with an increased risk of stroke recurrence [43]. Several large prospective studies that are evaluating FDG PET/CT imaging are currently underway: the BioImage and the PESA studies, studies that might clarify the utility of noninvasive imaging approaches for predicting cardiovascular outcomes in asymptomatic individuals [44, 45].

FDG-PET/CT Imaging Assessment of Therapies

The observations that 18-FDG-PET imaging provides a reproducible measure of arterial inflammation and is predictive of disease progression and of clinical events provide justification to use this modality to assess anti-atherosclerotic treatments. To that end, the imaging approach has been applied to the study of dozens of drug classes, in both humans and animal models. A question of substantial importance to the field is to what degree do the arterial PET/CT imaging findings in drug treatment trails predict the clinical efficacy of the drugs tested (Fig. 1). To answer this question, one would need to compare the findings of FDG-PET/CT imaging studies to the findings of clinical endpoint studies using the same drug. At this time, there are four drug classes for which arterial FDG-PET/CT imaging data and clinical events data are available: 1. statins, 2. thiazolidinediones (TZDs), 3. cholesterylester transfer protein (CETP) antagonists, and 4. lipoprotein-associated phospholipase A2 (LPPLA2) antagonists. Below is a review of the imaging and clinical endpoint trial findings for those drug classes.

1. Statin therapy

   Statins reduce plasma LDL cholesterol, and several human studies have shown that statins reduce circulating markers of inflammation such as hsCRP [46, 47] thus supporting the hypothesis that statins may have important anti-inflammatory effects. FDG-PET/CT was used in several clinical trials to more directly study the anti-inflammatory effects of statins on the arterial wall. The first such study, by Tahara et al., compared the effects of low-dose simvastatin with dietary management using an unblinded, single-center study design. After a 3-month period, there was a significant reduction in arterial FDG uptake in the simvastatin-treated patients compared to diet-treated comparator group [48]. In a more recent double-blind, multicenter trial, adults with risk factors or with established atherosclerosis were randomized to atorvastatin 10 mg versus 80 mg. FDG uptake within the artery wall was assessed using PET/CT. The study demonstrated that FDG uptake was rapidly reduced (starting at 4 weeks). Moreover, arterial inflammation fell nearly twice as much in the high-dose (vs. low-dose) atorvastatin group [49]. Accordingly, the findings of the FDG-PET/CT imaging studies are consistent with findings from several clinical endpoint trials, which have repeatedly shown a reduction in CVD events with statin therapy and also showed a substantial clinical benefit for atorvastatin 80 mg over atorvastatin 10 mg [50].
2. Thiazolidinediones

   Thiazolidinediones (TZDs) are used in the treatment of type 2 diabetes and effectively reduce plasma glucose and hemoglobin A1c levels. A study by Mizoguchi et al. evaluated the ability of the TZD pioglitizone to reduce arterial FDG uptake. In that study, individuals with diabetes or glucose intolerance were randomized to TZDs vs. another glucose-lowering strategy (the sulfonylurea glimepiride), and both groups were treated to achieve a similar degree of glucose control over a 16-week period. While both treatments reduced fasting plasma glucose and

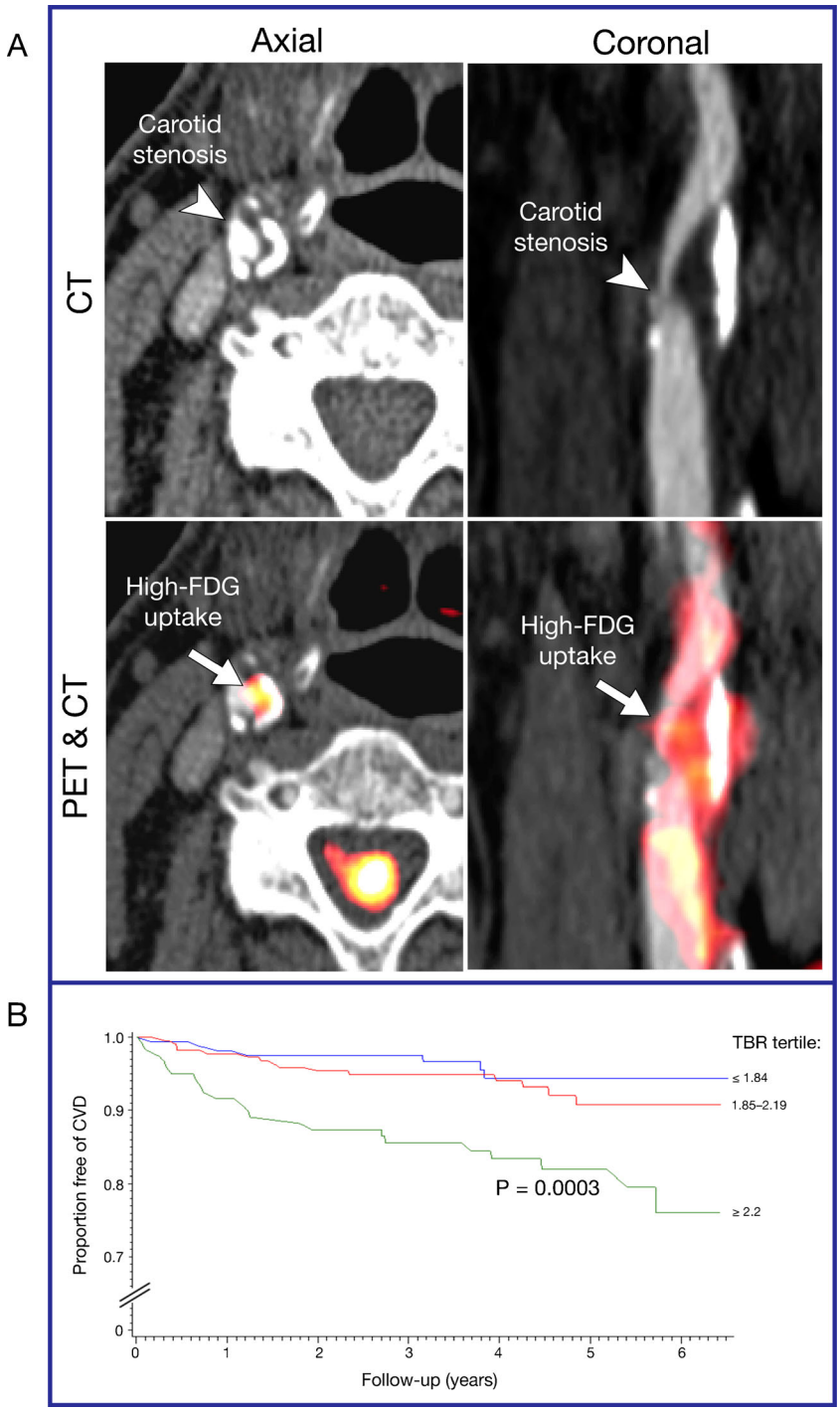

Fig. 1 **a** Arterial FDG PET/CT images. Axial and coronal sections of CT and PET/CT images of carotid atherosclerosis with severe luminal narrowing are shown. The *top images* show a carotid arterial plaque associated with severe stenosis, high-risk morphological features, and high FDG uptake. The *lower panel* also shows severe stenosis, but *without* high-risk morphological features or high FDG uptake (modified with permission from Figueroa et al., Circ Cardiovascular Imaging 2012) [36]. **b** Arterial FDG uptake independently predicts CVD risk. In a study of over 500 individuals who underwent FDG-PET/CT imaging, arterial FDG uptake (here divided into tertiles of FDG activity) provided an independent prediction of CVD risk. Moreover, the net reclassification index (NRI), which represents the fraction of individuals whose risk was accurately reclassified by PET/CT imaging was a robust 27 % (modified with permission from Figueroa et al., JACC CV Imaging 2013) [42]

hemoglobin A1c values comparably, pioglitazone, but not glimepiride, decreased atherosclerotic plaque inflammation. Further, compared with glimepiride, pioglitazone significantly increased high-density lipoprotein cholesterol level. High-sensitivity C-reactive protein was decreased by pioglitazone, whereas it was increased by glimepiride [51]. In concert with those imaging findings, clinical trials with TZDs have similarly shown a benefit of pioglitazone over sulfonylureas [52].

3. Cholesterylester Transfer Protein Antagonists

Cholesterylester transfer protein (CETP) transfers cholesterol from HDL cholesterol to very low-density or low-density lipoproteins. Inhibition of CETP results in higher HDL levels. In 2011, the randomized, double-blind multicenter dal-PLAQUE trial employed MRI and FDG-PET/CT imaging of the artery wall to evaluate the effects of dalcetrapib on atherosclerostic structure and inflammation. The study demonstrated that dalcetrapib did not

impact any of the prespecified PET/CT endpoints despite a substantial rise in the HDL cholesterol levels. In concert with those findings, the 16,000-patient clinical endpoint trial evaluating dalcetrapib, the dal-OUTCOMES study, subsequently showed that the drug does not alter the incidence of CV events [53].

4. Lipoprotein-Associated Phospholipase A2 Antagonists

Lipoprotein-associated phospholipase A2 (Lp-PLA2) is a vascular-specific inflammatory enzyme that is associated with a substantially increased risk of CVD events. Rilapladib, a novel LPPLA2 antagonist, was recently studied in a randomized, double-blinded, multicenter imaging trial using FDG-PET/CT and MR imaging [54]. That study showed that inhibition of LPPLA2 did not result in a reduction in atherosclerotic inflammation. In concert with those findings, two studies (that randomized nearly 32,000 individuals with atherosclerotic disease) subsequently showed no benefit for LPPLA2 inhibition for reducing atherothrombotic events [55, 56].

Accordingly, from the studies to date, there appears to be directional concordance between changes in atherosclerotic inflammation by FDG-PET/CT and changes in the risk of atherothrombotic events. Further study is ongoing, which will refine our understanding of the manner by which imaging can predict therapeutic efficacy.

Current Challenges and Future Directions

The 18F-FDG/PET imaging of the coronary arteries is complicated by several technical factors. The small size of the arteries and cardiac and respiratory motion during image acquisition and high-background myocardial uptake jointly collude to make measurement of the coronary signal challenging. Several groups have sought to address some of these limiting factors. Dietary modification has been used to address the problem of high myocardial activity, which otherwise can overwhelm the signal emanating from the adjacent epicardial arteries. One often-employed approach is to prescribe a high-fat, low-carbohydrate diet prior to imaging. This approach shifts myocardial metabolism from glycolysis to mitochondrial oxidation of fatty acids and has shown moderate success [57, 58]. Additionally, the use of motion-compensated reconstructions can improve image quality [59]. Despite the fact that several groups have demonstrated the ability to measure coronary signals [57, 60], coronary imaging using FDG as a tracer remains challenging and awaits further technological advances.

One tracer that has been shown to provide a high signal to background ration in the coronaries is F18-sodium fluoride. This tracer localizes to areas of active bone formation and remodeling. The tracer 18F-NaF is incorporated into exposed hydroxyapatite crystals and hence is a marker for active calcium deposition [61]. In a recent prospective clinical trial [62•], NaF-PET was employed for detection of coronary plaque micro-calcifications in subjects with acute myocardial infarction and stable angina. Increased tracer uptake was noted in 93 % of culprit plaques and autoradiography of the endarterectomy specimens confirmed the accumulation of tracer in areas of plaque rupture rich in macrophages and micro-calcifications.

Novel tracers are being actively evaluated for detection of inflammation. Further, several oncologic tracers have been evaluated for use for the detection of atherosclerotic inflammation. Recently, uptake of 68 Ga-DOTATE, a somatostatin analogue with specific binding affinity for somatostatin receptor-2 present on macrophages, was found to correlate with the presence of calcified LAD plaques [63]. The choline tracers: 11C-choline and 18F-FMCH, taken up by activated macrophages and incorporated into cell membranes, as well as 11C-PK 11195, a selective ligand of the translocator protein expressed in activated macrophages, were furthermore used with moderate success. Another tracer, F18-fluorodeoxy*mannose* binds to the mannose receptors present on M2-activated macrophages [64•] and hence can report of a separate aspect of inflammation compared to FDG (which provides information on M1 activated macrophages). Other tracers are targeting separate processes with atherosclerotic plaques, such as hypoxia and microvessel formation. Growth of atherosclerotic plaques is accompanied by neovascularization which represents a high-risk feature for future plaque rupture [65], and instable plaques are associated with a higher microvessel density than stable ones. Tracers with specific affinity for cell surface integrin receptors expressed on new blood cell membranes like 18-F-galacto and 18F-fluciclatide were tested in human atherosclerotic carotid plaques imaging and significantly higher TBR ratios in stenotic areas compared with nonstenotic areas were demonstrated [66]. The development of PET/MR technologies may further address the coronary tree challenges. Derived simultaneously to the PET, the MR acquisition has the potential to provide higher image quality through improved correction algorithms.

Conclusions

Molecular imaging of atherosclerosis with FDG-PET/CT has shown promise in the quantification of plaque inflammation, risk stratification, and prediction of future events and as an efficient reproducible tool in monitoring therapeutic effects of anti-inflammatory medication. Although not without challenges, especially in evaluation of the coronary tree, molecular imaging modalities have advanced at a rapid pace in recent years. Novel tracers and the recent emergence of hybrid PET/MRI imaging provide a new bleeding edge of molecular

imaging of atherosclerosis and may provide more profound, clinically useful insights into atherosclerotic plaque biology.

Compliance with Ethics Guidelines

Conflict of Interest Ahmed Tawakol reports grants and personal fees from Takeda, personal fees from Actelion, grants and personal fees from Roche/Genentech, and personal fees from Amgen outside the submitted work. Amorina Ishai has no conflicts relevant to this work.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by the author.

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- •• Of major importance

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