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Review Article

Role of ^{18}F-FDG positron emission tomography in carotid atherosclerotic plaque imaging: A systematic review

ABSTRACT

Stroke and other thromboembolic events in the brain are often due to carotid artery atherosclerosis, and atherosclerotic plaques with inflammation are considered particularly vulnerable, with an increased risk of becoming symptomatic. Positron emission tomography (PET) with 2-deoxy-2-[Fluorine-18] fluoro-D-glucose (^{18}F-FDG) provides valuable metabolic information regarding arteriosclerotic lesions and may be applied for the detection of vulnerable plaque. At present, however, patients are selected for carotid surgical intervention on the basis of the degree of stenosis alone, and not the vulnerability or inflammation of the lesion. During the past decade, research using PET with the glucose analog tracer ^{18}F-fluor-deoxy-glucose, has been implemented for identifying increased tracer uptake in symptomatic carotid plaques, and tracer uptake has been shown to correlate with plaque inflammation and vulnerability. These findings imply that ^{18}F-FDG PET might hold the promise for a new and better diagnostic test to identify patients eligible for carotid endarterectomy. The rationale for developing diagnostic tests based on molecular imaging with ^{18}F-FDG PET, as well as methods for simple clinical PET approaches, are discussed. This is a systematic review, following Preferred Reporting Items for Systematic Reviews guidelines, which interrogated the PUBMED database from January 2001 to November 2019. The search combined the terms, "atherosclerosis," "inflammation," "FDG," and "plaque imaging." The search criteria included all types of studies, with a primary outcome of the degree of arterial vascular inflammation determined by ^{18}F-FDG uptake. This review examines the role of ^{18}F-FDG PET imaging in the characterization of atherosclerotic plaques.

Keywords: ^{18}F-FDG, atherosclerosis, carotid artery, carotid endarterectomy, plaque imaging, vulnerable plaque

CAROTID ARTERY ATHEROSCLEROSIS

The majority (~85%) of all strokes are ischemic, following thromboembolic events, and the main cause is believed to be atherosclerosis.[1] Approximately a fifth of all stroke patients get a "warning sign" within 90 days before the stroke, enabling aggressive prophylactic treatment in this short period.[2] If carotid artery stenosis is present in such patients with nonfatal warning symptoms, including transitory ischemic attack, ipsilateral minor stroke, or transitory ocular symptoms, the risk of recurrence is higher.[3] The benefit of carotid endarterectomy in these patients was established in large trials conducted in the 1990s. The symptomatic patients were randomized to either medical treatment alone or carotid endarterectomy, showing that the operation reduced the risk of future stroke by 50%.[4]

Asymptomatic carotid artery atherosclerosis is, of course, also a risk factor for ipsilateral cerebral thromboembolic events, and primary prevention, medical or surgical, should be considered in such patients. However, the annual risk of stroke in asymptomatic patients with carotid artery stenosis is low, at least when comparing the event rates to the risk of perioperative death or stroke when performing carotid endarterectomy.[5] Furthermore, the stroke rate has decreased in recent years following the introduction of aggressive medical treatments (e.g., antiplatelet, statin and hypertension

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treatment) and improving the impact of public attention to reducing risk factors in the industrialized countries (e.g., decreasing smoking and increasing physical activity).[6] The current annual risk of ipsilateral ischemic symptoms in asymptomatic patients with significant carotid artery stenosis (>50%) is in the region of 1%/year.[7] In comparison, preoperative and 6 weeks' postoperative risk of stroke or death following endarterectomy has recently been estimated to be 4.9% on average, and the risk of death alone is 1.4%.[8]

Identifying a subgroup of patients with carotid artery plaque who are at high risk (i.e., higher than 4.9%) of suffering a stroke despite the best medical treatment would help to stratify asymptomatic patients in the selection for primary surgical treatment. In the same way, symptomatic patients, where the risk of recurrence may be low despite the warning signs, currently eligible for surgery might benefit from a new risk stratification tool used to abstain from surgical intervention, thus eliminating the risk of surgical complications.

METHODS

This study followed the Preferred Reporting Items for Systematic Reviews checklist. Ethics committee approval was not required as the study was a systematic review/meta-analysis. The study is a meta-analysis evaluating the role of ^{18}F-FDG PET imaging in patients with carotid artery atherosclerotic disease. The primary outcome was to determine differences in ^{18}F-FDG tracer uptake between significant symptomatic and asymptomatic carotid atherosclerotic plaques.

Search strategies

An electronic search was undertaken using EMBASE and PUBMED to search the MEDLINE database from January 2002 to November 2019. The search combined the terms, "atherosclerosis," "inflammation," "FDG," and "plaque imaging."

Search criteria

Inclusion criteria comprised all study types, including randomized controlled, cohort, case-control, case series, and experimental studies with human subjects undergoing ^{18}F-FDG PET scans examining carotid atherosclerotic disease in at least five patients. Studies were excluded if they included coronary or aortic analysis of PET imaging, involved imaging within animals, studies of vasculitis, or if the study did not provide clinical data (symptomatology). Furthermore, studies were also excluded if they examined carotid uptake in the absence of carotid atherosclerosis.

Statistical analysis

Estimation of the global effect for the primary outcome for carotid atherosclerotic disease (^{18}F-FDG uptake in symptomatic versus asymptomatic plaques) was assessed through an inverse variance weighted estimate of the pooled data (where applicable), using the random-effects model.

RESULTS

^{18}F-FDG tracer uptake in symptomatic and asymptomatic carotid atherosclerotic disease

A total of 747 patients were included within this analysis (mean age 65.2 ± 2.5, 74% male). Pooled comparisons of studies that analyzed a difference in symptomatic versus asymptomatic carotid atherosclerotic disease demonstrated that ^{18}F-FDG tracer uptake was significantly higher in symptomatic carotid lesions (standard mean difference 0.92; 95% confidence interval 0.52–1.27; $P < 0.0001$; $I^2 = 62\%$).

Patient selection for intervention

In the selection of patients with carotid artery stenosis eligible for endarterectomy, only the degree of stenosis and time passed since symptoms are used today as risk stratification parameters, and there is an ongoing debate as to whether asymptomatic patients should be offered surgical intervention at all.[9] For decades, cardiovascular interventions have been targeted against large atherosclerotic lesions with the degree of stenosis as a risk marker. The hemodynamic significant stenosis, where luminal narrowing caused turbulence or eventually low flow, was believed to be the main site of thrombus formation. This assumption was inevitable, as witnessed by the high efficacy of coronary stenting. However, in the majority of patients presenting with symptoms of cardiac ischemia, significant stenoses could not be identified[10] and it has repeatedly been shown that although revascularization in patients with coronary artery disease was efficient in bringing relief of symptoms, long-term survival was not improved.[11] Postmortem studies revealed that the majority of lethal plaques had low-grade stenosis, whereas they, independently of size, shared similar molecular and structural characteristics.[12]

Several histopathological traits of these vulnerable plaques at risk of giving symptoms have been identified, and investigations of surgically removed plaques from patients with symptoms of cerebral ischemia have shown that the pathophysiology of vulnerable carotid plaques is similar to that of the coronary plaques.[13] Symptoms occur either as sudden thrombosis at the site where the vulnerable plaque occludes the vessel, or because a thrombus is released from its origin, embolizing and occluding a downstream vessel. The latter pathogenesis is typical for the high flow carotid artery, where only approximately 3% of patients presenting with cerebral symptoms have an occluded carotid artery.[14]

Identification and differentiation of vulnerable plaques (i.e., atherosclerotic lesions at high risk of thromboembolic events) are important in all vascular beds to intensify and specify selection criteria for primary and secondary treatment. This article is focused on carotid artery plaques, as these plaques are readily accessible for both imaging and excision. However, results from recent studies underscore that 2-deoxy-2-[Fluorine-18] fluoro-D-glucose (18F-FDG) PET is likely to be used in all vascular beds, identifying, for example, coronary vulnerable plaques, or vulnerable patients in general.[15]

Histopathology of vulnerable plaques

The vulnerable plaque is defined as an atherosclerotic lesion at risk of giving symptoms.[16] These plaques are characterized by a thin fibrous cap surrounding a lipid core with scattered presence of necrotic debris or hemorrhages. As the core increases in size and the fibrous cap continually weaken, the plaque is destabilized. If the cap eventually ruptures, the highly thrombogenic core material will be exposed to the bloodstream, causing thrombus formation.[17] Dense inflammatory cell infiltration, primarily by monocytes and macrophages, is present in the vulnerable plaque. Degradation of the caps' extracellular matrix is a pivotal step in the process of destabilizing the plaque, and this effect is propagated by the release of proteolytic enzymes, such as matrix metalloproteinases and cathepsins, from the macrophages.[18] The surface molecule CD68 is specifically and constitutively expressed by macrophages, and CD68 is, therefore, conventionally used as a marker of inflammation in tissue analyses of surgically removed plaques.[19]

Imaging of the vulnerable plaque

The histopathological characteristics of the vulnerable plaque comprise two entities, the structural and the molecular, that can be targeted with modern imaging modalities. These entities are distinctly different from the plaque burden, or the degree of stenosis, which may be assessed using conventional digital subtraction angiography, computed tomography (CT) angiography, magnetic resonance imaging (MRI) angiography, or ultrasound duplex imaging [Figures 1-4].

Regarding plaque structure, B-mode ultrasonography, CT, and MRI have been used in prospective studies to confirm that certain morphological features of carotid plaques predict focal cardiovascular disease.[20] Furthermore, these modalities have been used in the detection of drug-modifying effects on plaque composition over time.[21] With molecular imaging, MRI and ^{18}F-FDG PET are of particular interest, as both modalities have shown to be able to depict increased inflammatory processes in vulnerable plaques certified by immunohistochemical and gene expression analyses.[22] Again, this feature has been used for demonstrating drug-modifying effects over time in patients receiving statins.[23] Other imaging modalities are emerging for both structural and molecular imaging of atherosclerosis, but to our knowledge, none, including the above mentioned, have reached clinical decision making. Randomized trials, incorporating plaque morphology with the degree of stenosis as a risk stratification tool before surgical intervention, are lacking.

Morphological identification of the vulnerable plaque using ultrasound

Ultrasound remains the primary and often only diagnostic tool used when investigating the carotid arteries. In a fast, cheap, and reliable manner, the bifurcation can be screened for the presence of atherosclerotic lesions using a combination of grayscale B-mode imaging and color duplex. If plaques are present, the degree of stenosis is determined using Doppler for the assessment of absolute flow velocities.[24] Accessibility for surgical intervention can be established at the same time, and most surgeons master the technique themselves.

Molecular identification of the vulnerable plaque using positron emission tomography

With the introduction of high-resolution molecular imaging for clinical indications, a novel strategy of targeting molecular activity can be implemented using PET scanning. It has repeatedly been suggested that molecular imaging can improve the specificity in the identification of plaques with a significantly higher risk of giving symptoms,[25] and PET with the tracer ^{18}F-FDG might be the new modality for the identification of the deleterious inflammatory characteristics of the vulnerable plaque. Observations of focal ^{18}F-FDG uptake in arterial walls were first reported in oncology PET studies and often in parenthetical sentences describing artifacts or pitfall observations that could mimic malignancies.[26]

^{18}F-FDG uptake has been suggested as a surrogate marker for medical treatment efficacy[27] or as a monitoring tool for overall cardiovascular risk assessment[28] but to date, no prospective studies have been published concerning the specific assessment of single plaque outcome in relation to ^{18}F-FDG uptake. The prevalence of high ^{18}F-FDG uptake in asymptomatic plaques is thus unknown, as is the prognostic value of increased plaque uptake in both asymptomatic and symptomatic patients. However, studies from symptomatic plaques support the idea that ^{18}F-FDG PET reflects inflammation and vulnerability, and pave the way for further prospective studies.

^{18}F-fluoro-deoxy-glucose

^{18}F-fluoro-deoxy-glucose is a glucose analog labeled with fluorine-18 (^{18}F) and tissue ^{18}F-FDG uptake reflects glucose metabolism. Tissue areas with relatively high metabolic

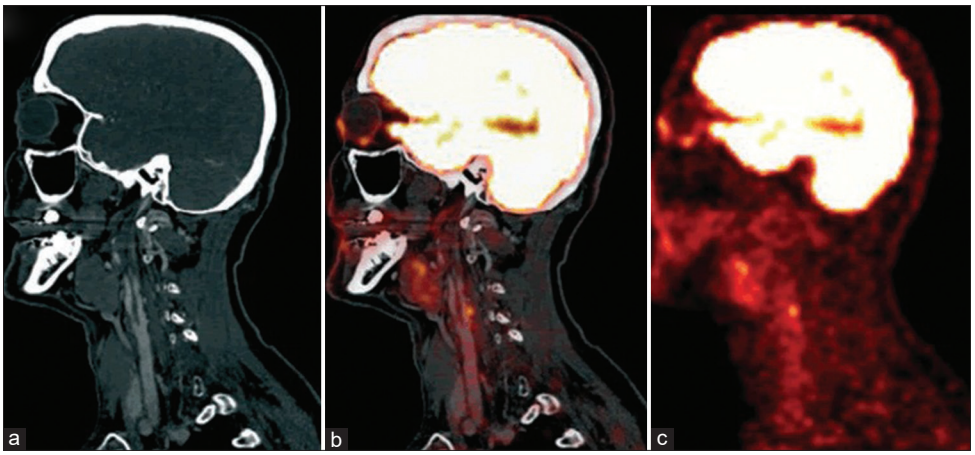

Figure 1: Computed tomography angiography (a), fused positron emission tomography/computed tomography (b) and positron emission tomography alone (c) demonstrating a left carotid plaque in a symptomatic patient showing high ^{18}F-FDG uptake

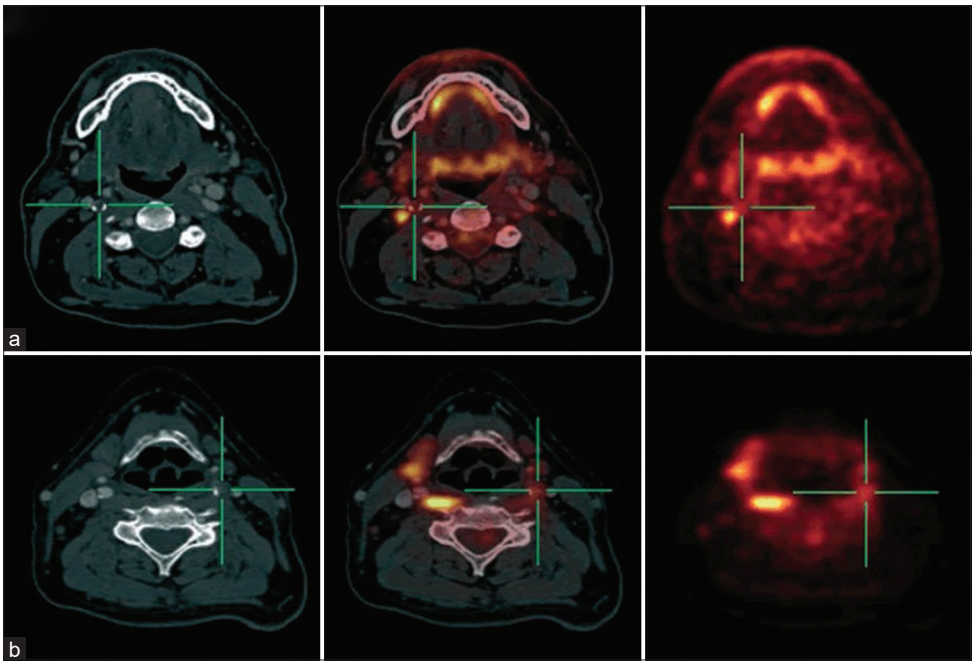

Figure 2: Contrast-enhanced computed tomography (left), fused positron emission tomography/computed tomography (middle) and positron emission tomography alone (right) in patients with symptomatic carotid artery stenosis. Right-sided carotid artery stenosis with vessel wall calcifications and mild 18F-FDG uptake (a). Note the normal physiological uptake in salivary glands. Left-sided carotid plaque with moderate ^{18}F-FDG uptake (b). Note the dense physiological uptake in the right longus capitis muscle and parotid gland

activity will show a relatively increased ^{18}F-FDG uptake. Normal high physiologic uptake in the fasting and the resting patient is seen in the brain, salivary glands, thyroid gland, heart, liver, kidneys, and urinary tracts as ^{18}F-FDG is cleared by the kidneys. Muscles might show uptake when activated (seen in neck musculature with head movements or in vocal cords when talking), and focal uptake is clearly visualized in tumors and inflammation.

Mechanism of increased 2-deoxy-2-[Fluorine-18] fluoro-D-glucose (^{18}F-FDG) uptake in inflammatory lesions

Many radiopharmaceuticals have been evaluated extensively in both preclinical and clinical studies as potential diagnostic agents to identify the sites of infection. Although there are several imaging agents, only a few of them are being used in routine clinical practice. There is a definite role of ^{18}F-2'-deoxy-2-fluoro-d-glucose (^{18}F-FDG) in assessing disease extent, disease activity in patients with infection and inflammation, and evaluation of response to treatment. The high tissue radioactivity after administration of ^{18}F-FDG corresponds to increased glucose uptake and consumption through the hexose monophosphate shunt, which is the main source of energy for chemotaxis and phagocytosis. ^{18}F-FDG, an analog of glucose, is taken up by living cells through cell membrane glucose transporters, and subsequently, it is phosphorylated with hexokinase inside most cells. Activation

of phagocytes, also known as respiratory burst activation, lead to increased ^{18}F-FDG uptake. In sterile inflammation, administered ^{18}F-FDG is mainly taken up by neutrophils and macrophages. A high degree of ^{18}F-FDG uptake is detected in neutrophils during the acute phase of inflammation, whereas macrophages and polymorphonuclear leukocytes uptake ^{18}F-FDG during the chronic phase. ^{18}F-FDG is phagocytized by macrophages and phagocytic cells through d-glucose transporter. Through glycolysis, ^{18}F-FDG is phosphorylated by hexokinase resulting in ^{18}F-FDG-6 phosphate.

Timing of the positron emission tomography/computed tomography

In the pioneer study from 2002, it was noted that late acquisition of atherosclerotic plaque ^{18}F-FDG uptake showed a better contrast between target and background, as the luminal blood activity diminished with time.[29] Most prospective studies published since then have, with reference to these first observations, used PET acquisition times from 90 to 180 min after ^{18}F-FDG injection. This conflicts with current clinical practice in oncology PET scans, where acquisitions are typically made 45–60 min after ^{18}F-FDG injection. If an early acquisition could be used for PET imaging of atherosclerosis, it would provide a protocol that could easily be implemented in the current daily clinical workflow, and it would favor both staff and patients.

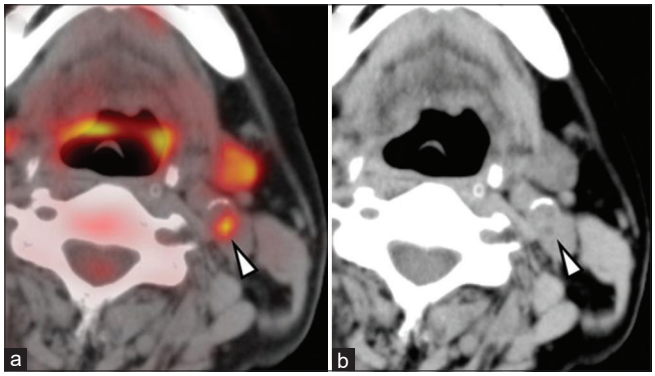

Figure 3: Transaxial ^{18}F-FDG positron emission tomography/computed tomography image (a) demonstrating focal avid ^{18}F-FDG uptake in the carotid plaque (arrowhead). Corresponding axial computed tomography image (b) showing a low attenuating plaque in the left carotid artery (arrowhead)

Quantification of ^{18}F-FDG uptake

Results of retrospective studies that investigated the suspected coincidence between inflammation in carotid plaques and cerebrovascular events are still awaited and recommendation on proper quantification of the ^{18}F-FDG uptake, therefore, relies on the basic theory; that vulnerability (i.e., risk of an event from the investigated plaque) is a function of macrophage abundance. In this context, the maximum standardized uptake value (SUV_{max}) and a target to background ratio (TBR), using venous blood pool activity as background and plaque activity as the target, have been shown to correlate to macrophage extent in carotid artery plaques in 3-h PET acquisitions.[30] The use of these quantification methods in late acquisitions is thus recommended.

The SUV corrects for injected dose, decay, and patient weight is calculated using the formula:

$$SUV_{max}\left(g/ml\right)=\frac{\text{Max activity}\left(Bq/ml\right)\times\text{weight}\left(kg\right)}{\text{Dose}\left(Bq\right)\times 1000\left(g/kg\right)}$$

Mean (SUV_{mean}) or maximum pixel activity (SUV_{max}) can be read within the region-of-interest (ROIs), and averaging all ROIs for each plaque the ^{18}F-FDG uptake can be quantified as either an average SUV_{max} or as a TBR:

$$TBR=\frac{\text{Plaque average SUV}_{max}}{\text{Background average SUV}_{mean}}$$

Clinical implementation

Several problems in assessing ultrasonographic plaque morphology have prevented this imaging method from

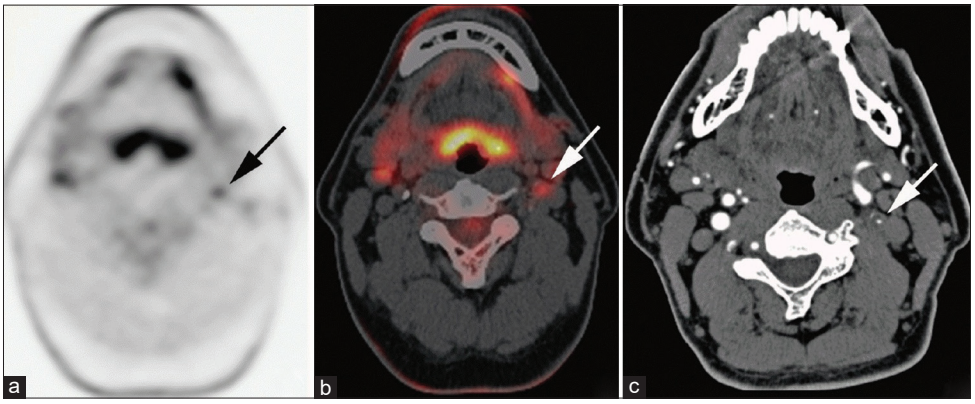

Figure 4: Transaxial ^{18}F-FDG Positron emission tomography alone image (a) and positron emission tomography/computed tomography image (b) demonstrating high uptake in the left internal carotid artery. Computed tomography angiography image (c) demonstrating severe stenosis of the left internal carotid artery with an atherosclerotic plaque

reaching the level of clinical decision-making. The two-dimensional nature of the ultrasound image makes quantification of echolucent areas in the heterogeneous plaques difficult, and the shadowing from calcified portions of plaques hamper the investigation. Furthermore, it is difficult to report findings objectively.[31] At present, the method is not sensitive enough as a standalone investigation of vulnerability to complement the degree of stenosis in stratifying patients at high stroke-risk to endarterectomy. With the introduction of computer-assisted image normalization and grayscale pixel analyses, the reproducibility of ultrasound imaging has been greatly enhanced. G-PET could be considered as the perfect tool for monitoring plaque inflammation over time. Rominger *et al*.[32] conducted a cohort study involving 932 cancer-bearing patients without vascular events (ischemic stroke, myocardial infarction, and revascularization). They suggested that ^{18}F-FDG accumulation in systemic blood vessels, including the carotid artery, is an independent, potent prognostic factor for subsequent vascular events. Paulmier *et al*.[33] investigated 101 cancer-bearing patients and found in the marked ^{18}F-FDG accumulation group, the incidences of previous cardiovascular events and those within 6 months were significantly higher. Joseph *et al*.[34] analyzed 42 cases in the dal-PLAQUE trial (Randomized Control Trial of a cholesteryl ester transfer protein inhibitor, dalcetrapib), and suggested that short-term changes in arterial-wall inflammation on ^{18}F-FDG PET reflect the subsequent long-term progression of arteriosclerosis. Figueroa *et al*.[35] investigated 24 patients on short-term changes in ^{18}F-FDG accumulation and long-term changes in the arterial-wall morphology. They measured changes in ^{18}F-FDG accumulation in the carotid artery at the time of registration and after 6 months, and examined arterial-wall thickening and changes in the wall area on MRI at the time of registration and after 2 years, suggesting that short-term changes in ^{18}F-FDG accumulation reflect long term changes in the arterial wall. Marnane *et al*.[36] investigated 60 patients with stroke, TIA, or retinal embolism within 2 weeks after onset and ≥ 50% stenosis of the carotid artery. They investigated the relationship between carotid plaque ^{18}F-FDG accumulation at the time of onset and subsequent recurrent stroke. The mean SUV was the only prognostic factor for recurrence. Hyafil *et al*.[37] investigated 18 patients and suggested that carotid artery lesions with marked inflammation despite a low percent stenosis are involved in embolism in patients with cerebral infarction in whom the source of embolism was unclear (embolic stroke of undetermined source [ESUS]) using ^{18}F-FDG PET/MRI.

Chowdhury *et al*.,[38] in their meta-analysis of 14 articles have described that ^{18}F-FDG PET imaging in the carotid circulation has provided an enhanced ability to study atherosclerotic inflammation in symptomatic patients. The studies presented demonstrated that it is well validated, reproducible, and may have the ability to differentiate vulnerable plaque (in symptomatic patients) from more stable plaque (in asymptomatic patients). ^{18}F-FDG uptake is significantly higher in symptomatic carotid disease than in asymptomatic disease. Kafouris *et al*.,[39] identified 67 different ^{18}F-FDG PET-based textural features were extracted from carotid images of 21 patients with high-grade carotid stenosis undergoing endarterectomy and demonstrated that normalized run-length nonuniformity was the most optimal textural features for identifying characteristics of plaque vulnerability based on histological analysis and concluded that texture analysis can be applied in ^{18}F-FDG PET carotid imaging providing valuable information for plaque characterization. Joshi *et al*.[40] studied a prospective cohort of 16 patients and concluded that higher uptake of ^{18}F-FDG in culprit lesions. Tarkin *et al*.[41] studied a prospective cohort of 16 patients for atherosclerotic inflammation using 68Ga-DOTATATE tracer and concluded that significant uptake of ^{18}F-FDG in symptomatic plaques versus control. Vesey *et al*.,[42] studied a prospective case-control group of 26 patients and concluded that ^{18}F-FDG higher uptake in culprit vessel versus control. Quirce *et al*.[43] studied a prospective patient cohort of 18 patients and found no significant difference in FDG uptake in symptomatic versus asymptomatic plaques. Skagen *et al*.[44] studied a prospective patient cohort of 36 patients and found a significantly higher hot average in symptomatic versus asymptomatic carotid plaques. Shaikh *et al*.[45] studied a cohort of 35 patients and found a significantly higher hot average in symptomatic versus asymptomatic carotid plaques. Taqueti *et al*.[46] studied a cohort of 32 patients and found that ^{18}F-FDG signals correlate highly with markers of macrophage density, in symptomatic plaques. Muller *et al*.[47] studied a cohort of 123 symptomatic stroke patients and found significantly higher FDG uptake in symptomatic high-risk carotid plaques. Marnane *et al*.[36] studied a cohort of 60 symptomatic stroke patients and found higher uptake of ^{18}F-FDG in patients with recurrent strokes. Grandpierre *et al*.[48] retrospectively studied a cohort of 23 cancer patients admitted with stroke due to carotid disease and found higher FDG uptake in the patient who had a stroke in the carotid artery was compared to no stroke patients. Kwee *et al*.[49] studied a prospective patient cohort of 50 patients and found a significant correlation between FDG signal and CT characteristics in symptomatic plaques. Arauz *et al*.[50] studied a prospective patient cohort of 13 patients and found patients with symptomatic carotid disease had higher FDG uptake, as well as with stenosis. Davies *et al*.[51] studied a prospective patient cohort of 12 patients and found higher FDG uptake ratios in symptomatic carotid disease. Rudd

et al.[52] studied a patient cohort of 8 symptomatic patients and found higher ^{18}F-FDG PET signals in symptomatic versus asymptomatic disease.

Interfering drugs on ^{18}F-FDG imaging and appropriate timing of ^{18}F-FDG imaging

Focal ^{18}F-FDG uptake at the sites of inflamed plaques is characteristic of atherosclerosis in contradiction to diffuse uptake in vessel wall seen in vasculitides. This inflammatory uptake has been demonstrated to precede plaque calcification. Statins have anti-inflammatory properties and are commonly used in patients with atherosclerosis. ^{18}F-FDG uptake in plaques reflects the response to therapy. With successful statin therapy, plaque inflammation reduces and so does ^{18}F-FDG uptake. In the same way, uptake also correlates with disease progression. This has been demonstrated in patients with atherosclerotic plaques in different vascular beds followed up with ^{18}F-FDG PET.

Given that, there is increasing use of ^{18}F-FDG uptake to assess arterial inflammation and atheroma vulnerability and to monitor the effects of pharmacologic therapies, imaging at 2 h show a decline in ^{18}F-FDG arterial wall uptake. By imaging at 1 h, this should allow a better workflow for imaging departments and make the ^{18}F-FDG PET examination more acceptable to the patient, which is an important factor for any test. There is no significant advantage of delayed imaging could favorably impact clinical practice.

Atherosclerotic plaque imaging with positron emission tomography/magnetic resonance imaging and intracranial vessel wall magnetic resonance imaging

MRI is becoming increasingly available as part of hybrid PET/MRI systems and may have additional advantages over PET/CT systems in the evaluation of vascular inflammation. MRI does not expose patients to additional ionizing radiation. Furthermore, unlike with PET/CT, the acquisition of both MRI and PET imaging can be done simultaneously, allowing for better co-registration and motion correction, which may improve coronary artery imaging. Imaging of atherosclerotic lesions using MRI can identify high-risk and prognostically significant anatomic features of vulnerable plaques (e.g., fibrous cap thickness, and the presence of a necrotic core, intra-plaque hemorrhage, or mural thrombus) that may be complementary to biological data obtained through PET. Although few clinical studies have formally compared PET/MRI with PET/CT systems for characterizing vascular inflammation, results thus far suggest that the FDG-signal is similar and well correlated between modalities.[53]

Vessel wall MRI (VW-MRI) is a modern imaging technique with expanding applications in the characterization of intracranial vessel wall pathology. VW-MRI provides added diagnostic capacity compared with conventional luminal imaging methods. MRI is considered the best imaging technique for the detection of intraplaque hemorrhage (IPH). During the subacute and chronic phases, IPH appears bright on T1-weighted imaging due to the relatively short T1 of methemoglobin. Lipid rich necrotic core could be detected as a focal hypointense region on T2-weighted image. MRI can assess fibrous cap status as opposed to the other noninvasive imaging modalities such as CT and ultrasonography. A regular (thick) FC is characterized by the presence of a juxtaluminal band of low signal on time-of-flight magnetic resonance images and/or a hyperintense juxtaluminal region on contrast-enhanced T1-weighted image.[54]

Future perspective

Echo-rich plaques tend to show low ^{18}F-FDG uptake, whereas echolucent plaques exhibit a wide range of ^{18}F-FDG uptake values.[55] Thus, although morphological traits of vulnerability are present, the plaque may or may not be metabolically active. In screening programs, plaque ultrasonographic morphology assessment could be used for stratification of patients eligible for further advanced imaging rather than for the final risk stratification. PET might be used in this context as a supplement to ultrasound later in the diagnostic hierarchy. One of the most important issues regarding ^{18}F-FDG PET is its spatial resolution. However, ^{18}F-FDG PET/CT and ^{18}F-FDG PET/MRI, which facilitate the visualization of the activity and rough site of inflammatory cells in the arterial wall, provide new information, as described above, beyond the limits of conventional morphological diagnosis. In future, ^{18}F-FDG PET/MRI may become a powerful tool for clarifying the pathogenesis of ESUS.[56] Furthermore, recently, 18-sodium fluoride, which is used to detect benign or malignant bone lesions, has been applied for the detection of plaque rupture sites or differentiation of active from inactive calcification.[57]

CONCLUSION

^{18}F-FDG PET is a promising method for noninvasive characterization of high-risk atherosclerotic plaques. High plaque ^{18}F-FDG uptake is associated with molecular markers of inflammation and vulnerability, and associations between ultrasonographic plaque echolucency, ^{18}F-FDG PET uptake and histopathological findings in surgically removed carotid plaques from patients with recent symptoms suggest a basis for further risk stratification improving patient selection for surgical intervention. Concerning carotid artery lesions, there are no data regarding the onset of asymptomatic lesions or the prediction of treatment-related risks. The studies presented in this systematic review demonstrate that it is

well validated, reproducible, and may have the ability to differentiate vulnerable plaques in symptomatic patients from more stable plaques in asymptomatic patients. ^{18}F-FDG uptake is significantly higher in symptomatic carotid disease than in asymptomatic disease. Future study results may provide new information. Prospective protocols elucidating the role of ^{18}F-FDG PET and ultrasound are underway, and future randomized trials are needed to establish the clinical usability of PET/CT.

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Conflicts of interest

There are no conflicts of interest.

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