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Validation of FDG uptake in the arterial wall as an imaging biomarker of Atherosclerotic Plaques with ¹⁸F-Fluorodeoxyglucose Positron Emission Tomography-Computed Tomography (FDG-PET/CT)

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Abstract

Background and Purpose—From the literature the prevalence of FDG uptake in large artery atherosclerotic plaques shows great heterogeneity. We retrospectively reviewed 100 consecutive patients who underwent FDG-PET/CT imaging of their whole body, to evaluate FDG uptake in the arterial wall.

Materials & Methods—We retrospectively evaluated 100 whole-body PET-CT scans. The PET co-registered CT images were reviewed with for abnormal ¹⁸F-FDG uptake. The mean standard uptake value (SUV) was measured in regions of interest (ROIs). The prevalence of PET+ plaques was determined based on the qualitative PET review, used as the gold standard in a receiver-operating characteristic (ROC) curve analysis to determine an optimal threshold for the quantitative PET analysis.

Results—The qualitative, visual assessment demonstrated FDG uptake in the arterial walls of 26 patients. A total of 85 slices exhibited FDG uptake within the arterial wall of 37 artery locations. 11, 17 and 2 patients exhibited FDG uptake respectively within the wall of carotid arteries of the aorta, and of the iliac arteries. Only 4 of the 26 patients had positive FDG uptake in more than one artery location.

In terms of quantitative analysis, a threshold of 2.8 SUV was associated with a negative predictive value of 99.4% and a positive predictive value of 100% to predict qualitative PET+ plaques. A

threshold of 1.8 SUV was associated with a negative predictive value of 100% and a positive predictive value of 99.4%. Area under the ROC curve was 0.839.

Conclusion—The prevalence of PET uptake in arterial walls in a consecutive population of asymptomatic patients is low and usually confined to one type of artery and its clinical relevance in terms of vulnerability to ischemic events remains to be determined.

Introduction

Atherosclerosis affects all vascular beds, including the aortic, coronary, carotid, and peripheral vascular beds, and is the first cause of morbidity and mortality in industrialized countries, with the most serious outcomes being myocardial infarction and stroke. Historically, imaging of atherosclerosis has centered on assessing the degree of luminal stenosis. More recently, improved understanding of the biology of atheromatous lesions and the development of alternative therapeutic agents that can initiate actual plaque regression have led to the concept of vulnerable atherosclerotic plaque. Functional imaging techniques such as fluorodeoxyglucose (FDG) positron emission tomography (PET) have been suggested as capable to detect vulnerable plaques^{1–3}. Refinements such as PET-computed tomography (CT) enable the correlation between morphological and functional information and ensure that the PET uptake arises from atherosclerotic plaques.

FDG uptake in large artery atherosclerotic plaques has been reported in a number of studies^{4–12}. However, the reported prevalence of FDG uptake in large artery atherosclerotic plaques varies a lot, ranging from 15%¹³ to 85%¹⁴, with also variations depending on the type of large artery considered - 27%¹⁵ to 85%¹⁴ for the carotid arteries; 16%¹⁶ to 80%¹⁷ for the aorta, 34%¹⁸ to 54%¹⁹ for the iliac arteries, and 45%¹⁶ to 70%¹⁹ for the femoral arteries.

Reasons for this heterogeneity include the small number of patients included in these studies - 8²⁰, 17²¹ or 20¹⁵ -, and the absence of a clear definition of PET-positive plaques - subjective assessment^{13,15,16,22} versus quantitative approach^{14,19–21,23}. In the studies using a quantitative approach, variable thresholds were used - 1.6²³, 2.5¹⁹, 2.7¹⁴, or 3.5²⁰. Finally, different authors used different references as their denominator to calculate prevalence: while some studies used the number of patients^{16,19,23} others used the number of slices^{13,15,21}.

In this study, we retrospectively reviewed a large series of consecutive patients who underwent FDG-PET/CT imaging of their whole body, to systematically evaluate the frequency, location and intensity of FDG uptake in the arterial wall of the carotid arteries, aorta and iliac arteries.

Methods

Study population

We retrospectively evaluated a total of 100 consecutive patients referred for whole-body FDG-PET/CT scans for routine clinical care between April 2006 and February 2007. The indications for the PET-CT study were neoplasm of the head and neck. A detailed list of the indications for the PET-CT imaging studies is shown in Table 1. These indications were

recorded along with demographic variables and risk factors including: age, gender, race/ethnicity, smoking status and alcohol consumption, history of diabetes, dyslipidemia or cardiovascular disease. The risk factors recorded in our study were assessed according with the medical records of the patients recorded at any time of their medical history (hospitalization, medical consult/visit). We also recorded antineoplastic treatments, radiation therapy and chemotherapy, if applicable. This study was approved by our institutional review board with a waiver of consent.

FDG-PET/CT Imaging Protocol

After an overnight fast (minimum 6 hours), 15 mCi (adjusted by weight) of 2-(F-18) fluoro-2-deoxy-D-glucose (FDG) were intravenously administered. A random blood glucose level was measured in each patient, and only those patients whose blood glucose level was less than 200 mg/dl were studied. Approximately 45 minutes following the intravenous administration of FDG, a transmission contrast-enhanced CT scan was performed from the vertex through the proximal thighs, followed by emission PET imaging over the same region using a Siemens Biograph 16 slice PET/CT scanner. Patients were imaged in the supine position.

CT protocol

The image acquisition protocol for the transmission CT scan was as follows: spiral mode, 0.6-second gantry rotation, collimation: 16 x 1.5 mm, pitch: 1.375:1, slice thickness: 1.5 mm, reconstruction interval: 1.5 mm, acquisition parameters: 120 kVp/240 mA. In-plane resolution (pixel size) for the CT was 0.6mm x 0.6mm. A cranio-caudal scanning direction was selected, covering from the vertex through the proximal thighs. One hundred and fifty milliliters (mL) of Iohexol (Omnipaque, Amersham Health, Princeton, NJ; 300 mg/mL of iodine) was injected into an antecubital vein with a power injector at a rate of 4 mL per second.

PET protocol

The image acquisition protocol for the emission PET scan was as follows: Vertex to mid-thighs images in 7 beds were reconstructed iteratively with a 2D ordered subset expectation maximization (2D-OSEM) algorithm with approximately 4mm by 4mm pixel size, using 6 iterations and 8 subsets (reconstructed resolution = 8 mm FWHM). Slice separation was 5 mm. The images were corrected for attenuation using the CT data.

Image analysis of PET/ CT studies

PET images were co-registered with the structural MDCT images using a dedicated workstation enabling multimodal standard (rigid) image fusion (Siemens Leonardo workstation). Attenuated corrected PET, non-attenuated corrected PET, CT, and fusion images were simultaneously reviewed along with the 3D MIP images on the workstation. Two analyses – qualitative and quantitative - were performed on selected, fused PET/CT images. Images used for analysis were systematically selected as follows:

For each carotid artery, images were selected at the level of the carotid bifurcation (CBIF), as well as every 5 mm for 3 cm of the common carotid artery (CCA)

immediately proximal to the carotid bifurcation, and every 5 mm for 3 cm of the internal carotid artery (ICA) immediately distal to the carotid bifurcation.

For the aorta, images were selected every 10 mm starting at the level of the tracheal bifurcation and continuing inferiorly, for the ascending aorta (AA) down to the level of the aortic valve, and for the total length of the descending aorta (DA) down to the iliac bifurcation.

For each common iliac artery, images were selected at the level of the iliac bifurcation (IBIF), as well as every 5 mm below the IBIF down to the bifurcation of the common iliac arteries into internal and external iliac arteries.

Qualitative image analysis of PET images

The selected PET images were reviewed in conjunction with the co-registered CT images by two board-certified nuclear physicians in consensus for abnormal ¹⁸F-FDG uptake of the wall of the aforementioned arteries for all patients. FDG uptakes were further characterized as focal, linear or circumferential. Diffuse patterns of increased ¹⁸F-FDG were described. If there were structures showing high uptake adjacent to the evaluated arteries, such as adenopathies, those were recorded.

Quantitative image analysis of PET images

For the quantitative analysis of the PET images, the CT images were used to guide placement of the regions of interest (ROIs) over the walls of the considered arteries. On each selected CT image level for the carotid arteries, aorta and iliac arteries, a board-certified radiologist blinded to the PET images draw a circular/oval ROI immediately around the outer wall of the considered artery. Therefore the size of the ROI varied according to the size of the corresponding artery at each selected level; in addition, the body contour was delineated.

The PET images corresponding to the selected CT images were interpolated in all three dimensions to match the pixel size of the CT data. The body contour delineated on the CT images was automatically copied onto the corresponding PET image, and the PET image was shifted in order for the CT body contour to best match the body contour as visualized on the PET image. This was to compensate for possible patient movement between the CT and PET acquisitions and for respiratory motion (frozen on the CT but averaged on the PET) that might cause small discrepancies in PET to CT alignment. The ROIs drawn around the arteries on the CT images were then copied to the corresponding, interpolated PET images, and the same shift as the one applied to the body contour was applied to these ROIs.

Measurements were automatically computed from the ROIs transferred onto the PET images, and the results automatically written to an electronic file. The ROIs themselves were also saved. The measurements included mean standard uptake value (SUV) within ROI, standard deviation of uptake within ROI, as well as ROI size (in mm³) and the amount of shifts introduced during the transfer of the ROIs from CT to PET. SUVs were corrected by injected activity.

The FDG uptake measured in the ROIs drawn immediately around the outer wall of the arteries represents the sum of the uptake in the vessel wall and of the activity in the blood. To correct for the activity in the blood, FDG uptake in SUV as measured in the left ventricular cavity (keeping far from regions of significant myocardial uptake to minimize spill-over activity) was subtracted from the ROIs SUV values.

ROIs obtained in images where structures showing high uptake, such as adenopathies, were identified adjacent to the evaluated arteries during the qualitative PET review by the two board-certified nuclear physicians were discarded.

Qualitative image analysis of CT images

The selected CT images were reviewed independently by a board-certified neuroradiologist blinded to the PET images. The latter assessed each CT image for the degree of stenosis, the presence or absence of plaque on CT, and whether the plaque was calcified or not.

Statistical analysis

The prevalence of PET+ plaques was determined based on the qualitative PET review. Prevalence was reported on a patient basis, for each type of artery and on a slice basis. Patients with PET+ plaques concurrently in multiple types of arteries were recorded, and kappa statistics was performed to determine the significance of the association of PET+ plaques between different types of arteries.

The qualitative PET review was used as the gold standard in a receiver-operating characteristic (ROC) curve analysis to determine an optimal threshold for the quantitative PET analysis.

Finally, the association between PET+ plaques and the clinical risk factors and the degree of stenosis on CT, the presence or absence of plaque on CT, and whether the plaque was calcified or not on CT, was assessed. We first performed univariate analysis, testing each clinical condition using a mixed effect regression model for continuous variables and a mixed effect logistic model for dichotomous variables. Individual clinical variables associated with a moderate statistical significance ($p \leq 0.2$) in the univariate analysis were considered for the multivariate analysis (Table 2). Colinear variables (e.g. smoking and alcohol consumption) were discarded, and only the parent variable (smoking) was examined in the multivariate analysis. Multivariate analysis consisted of mixed-effect logistic and regression analysis for dichotomous and continuous variables, respectively, with a random effect for patients and using a p-value of 0.1- as a threshold for statistical significance. All analyses involved mixed effect models, in order to take into account the multiple measurements per patient. Model selection was repeated using a stepwise forward and backward approach to assess whether the variables included in the final model were influenced by the approach for the multivariate analysis (sensitivity analysis).

Results

Patients

100 consecutive patients referred for whole-body PET-CT scans for routine clinical care were evaluated. These patients had a mean age of 58.2 years (range: 21 to 94 years old) and included 71 men and 29 women. Sixty-two patients were White, 24 Asian, and 3 African-Americans. All 100 patients had a documented cancer disease for which they were referred for a clinical FDG-PET/CT study (Table 1). The vascular risk factors in our patient population are reported in Table 2. In all 100 patients, the interval between the end of radiation and/or chemotherapy and the PET-CT study was at least 3 months, i.e. sufficiently long to reduce the inflammatory changes and to avoid false positive results due to the immediate inflammatory reaction to radiation and/or chemotherapy.

FDG-PET/CT Studies

Among the 100 patients, 7 patients had poor quality imaging studies (CT and/or PET) and were excluded. Therefore, 93 FDG-PET/CT studies in 93 patients were evaluated retrospectively. For each PET/CT study, in each of the 93 patients, between 66 and 81 slices were considered for analysis (median 67; interquartile range: 48 – 71; minimum: 19; maximum: 80). More specifically, we evaluated for each patient: 26 carotid slices (6 common carotid arteries, 1 bifurcation and 6 internal carotid arteries on each side); an average of 37 aortic slices (5 ascending aorta slices and an average of 32 descending aorta slices (ranging from 26 to 41, according to the different length of each subject's aorta); and 9 iliac slices (1 bifurcation, and 4 common iliac arteries for each side). This represented a total of 5,493 slices in 93 patients, available for qualitative and quantitative analyses.

ROI size (in mm) is variable depending on the size of the artery and ranged between 2.5 mm (diameter) for the iliac arteries and 20 mm (diameter) for the aorta.

Qualitative PET image analysis

The qualitative, visual assessment demonstrated FDG uptake in the arterial walls of 26 patients, classified as qualitatively positive (PET+), while the remaining 67 patients were classified as qualitatively negative (PET-).

A total of 85 slices exhibited FDG uptake within the arterial wall of 37 artery locations. Six patients had 1 PET+ slice, 10 patients had 2 PET+ slices, 4 patients had 3 PET+ slices, 1 patient had 4 PET+ slices, 3 patients had 6 PET+ slices, 1 patient had 8 PET+ slices and 1 patient had 17 PET+ slices.

We described and differentiated the FDG uptake in 41 focal (Figs. 1 and 2), 39 circumferential (Fig. 3) and 5 diffuse patterns.

Eleven patients exhibited FDG uptake within the wall of carotid arteries (1.66% of the total of the carotid slices: 0.64% of carotid bifurcation, 1.17% of common carotid arteries, and 2.36% of internal carotid arteries). Among these 11 patients: 2 patients had 1 PET+ carotid slice; 4 patients had 2 PET+ carotid slices; 2 patients had 3 PET+ carotid slices; 1 patient

had 4 PET+ carotid slices; 1 patient had 6 PET+ carotid slices and 1 patient had 7 PET+ carotid slices.

Seventeen patients exhibited FDG uptake within the wall of the aorta (1.68% of the total of the aortic slices: 0.96% of ascending aorta and 1.79% of descending aorta). Among these 17 patients: 5 patients had 1 PET+ aortic slice; 6 patients had 2 PET+ aortic slices; 2 patients had 3 PET+ aortic slices; 1 patient had 4 PET+ aortic slices; 1 patient had 6 PET+ aortic slices; 1 patient had 7 PET+ aortic slices; 1 patient had 10 PET+ aortic slices.

Two patients exhibited FDG uptake within the wall of the iliac arteries (0.38% of the total of the iliac slices). The 2 patients had 1 PET+ iliac slice.

Only 4 of the 26 patients had positive FDG uptake in more than one arterial location: 3 patients had PET+ slices in both the carotid arteries and the aorta ($\kappa = 0.0825$; p value = 0.416), and 1 patient had PET+ slices in both the aorta and the iliac arteries ($\kappa = 0.0695$; p value = 0.334). No patient had PET+ slices in both carotid and iliac arteries.

Quantitative PET image analysis

The qualitative PET review was used as the gold standard in a receiver-operating characteristic (ROC) curve analysis to determine an optimal threshold for the quantitative PET analysis (Fig. 4). A threshold of 2.8 SUV was associated with a sensitivity of 58.8%, a specificity of 100%, a negative predictive value of 99.4% and a positive predictive value of 100%. A threshold of 1.8 SUV was associated with a sensitivity of 100%, a specificity of 95.1%, a negative predictive value of 100% and a positive predictive value of 99.4%. Area under the ROC curve was 0.839. There were no significant differences in terms of optimal thresholds for the different types of arteries evaluated in this study ($p = 0.220$).

Association between FDG PET uptake and clinical risk factors/CT features

The association between PET+ plaques and the clinical risk factors and the degree of stenosis on CT, the presence or absence of plaque on CT, and whether the plaque was calcified or not on CT, was performed using a mixed effect model with a fixed effect for patients. The results of the univariate analyses are listed in Table 2. Smoking and alcohol consumption were found to be collinear.

In the multivariate analysis taking into consideration the significant variables from the univariate analyses hypertension, dyslipidemia, presence of calcified atherosclerotic plaque on CTA), only dyslipidemia persisted as statistically significant coefficient: 1.578, 95 confidence interval: $-0.979-3.953$, $p = 0.093$).

Discussion

¹⁸F-FDG used in PET imaging for evaluation of cancer is a molecular probe that targets the glucose transporters. Glucose transporters are over-expressed by most types of malignant cells. Activated macrophages also over-express glucose transporters in a setting of infection/inflammation. FDG uptake in atherosclerotic plaques has been associated with inflammatory

changes in the arterial wall ^{1,2}. Indeed, it has been shown that FDG accumulates in plaque macrophages and that the relative uptake is correlated with macrophage density ²¹.

With our study we provided a uniform and systematic approach which evaluated carotid arteries, ascending and descending aorta and iliac arteries in a very large series of consecutive patients. This study takes advantage of PET-CT, a combined functional and structural whole-body imaging modality, for several reasons, including ease of co-registration of the PET and CT images, faster scan times and the wide availability of combined scanners as part of cancer-imaging programs ²⁴. This combined approach holds great potential for the purpose of combining information from the two modalities to ensure that the uptake is in arterial walls.

In our population of cancer patients we found relatively low prevalence of PET+ plaques, in fact only 26 out of 93 patients showed a positive FDG uptake for a total of only 85 slices out of 5,493 evaluated in our study. Previous studies attempt to the same aim of studying the prevalence of positive PET uptake of atherosclerotic plaques in the population but the small number of subjects included in some of the aforementioned studies, the absence of clarity and of a systematic approach in the design of the analysis and the frequent use of convenience samples to the detriment of the value of the gold standard, invalidated the clinical relevance and the prognostic value of those studies.

Excellent reproducibility has been previously shown in the carotid arteries, in the ascending aorta, and in the peripheral arteries ²⁴ but those studies tended to be isolated to one type of artery. In our study we evaluated systematically the internal carotid arteries, both ascending and descending aorta and the iliac arteries in a very large series of consecutive patients.

In agreement with our recent paper using CT, we showed that carotid atherosclerosis does not predict coronary, vertebral, or aortic atherosclerosis, and indeed significant atherosclerotic disease is more often isolated to one type of artery while nonsignificant atherosclerotic disease tends to be a systemic process ²⁵. We also found that PET uptake is associated with presence of dyslipidemia, suggesting that PET uptake may be used as a hallmark of metabolic syndrome. It has been reported that vascular FDG uptake can be attenuated by simvastatin in patients. This is in agreement with the evidence that statins have not only effects on reducing LDL-C, plaque volume and carotid intima media thickness but also anti-inflammatory and antioxidative effects ²⁶. Further prospective studies are needed to confirm these findings.

In our study we did not find CT feature associated in the multivariate analysis, although the amount of calcium associated with PET uptake has been found in the univariate analysis.

The great advantage of PET is the ability of looking at inflammation, and, therefore to study atherosclerosis as a dynamic inflammatory disorder and to image both the biological composition and inflammatory state of the atherosclerotic plaque, which is not necessarily related to the degree of stenosis or its size ²⁷. In the end, we found that 1.8 SUV is a perfectly sensitive threshold and 2.8 SUV is a perfectly specific threshold. These results are similar to those previously found in patients with carotid atherosclerosis ¹⁷.

There are some limitations to the interpretation of the results of our study. Since none of the patients of our study had symptoms, prevalence may be higher in a symptomatic population, for instance in carotids in TIA patients. This study was also limited by its sample size (n=100), with the possibility of some of the observed associations to be due to chance. Large-scale studies are therefore required to confirm our results. Moreover, given the small evidence of risk factors and acute cerebrovascular events in the population of this study, the clinical relevance of atherosclerotic plaques showing FDG uptake in terms of vulnerability to ischemic events remains to be determined. Finally, we had only one reviewer blinded to PET findings draw the ROIs on the CT. These ROIs were automatically transferred to PET images and the SUV measurements automatically computed from the transferred ROIs. Because of this procedure, we felt that the risk of bias introduced in the PET measurements by the fact that there was only one reviewer was very low.

Conclusion

In conclusion, the prevalence of PET uptake in arterial walls in a consecutive population of asymptomatic patients is low and usually confined to one type of artery. The clinical relevance of atherosclerotic plaques showing FDG uptake in terms of vulnerability to ischemic events remains to be determined.

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Fig. 1. 49-year-old male patient with a history of squamous cell carcinoma of the tongue. The patient underwent radiation therapy and chemotherapy. The PET-CT study demonstrate a soft and calcified plaque of the abdominal aorta, with focal PET uptake in the right antero lateral aspect of the aortic wall.

Fig. 2. 83-year-old male patient with a history of bladder carcinoma with diffuse metastases. The CT component of the PET-CT study does not demonstrate any “anatomical” atherosclerotic plaque, but the PET demonstrate focal uptake in the aortic wall.

Fig. 3.

74-year-old female patient with a history of supraglottic squamous cell carcinoma, treated with radiation therapy and chemotherapy. The PET-CT study demonstrate a very intense circumferential uptake in the abdominal aortic wall, with corresponding soft and calcified plaque on the CT.

Fig. 4. Receiver-operating characteristic (ROC) curve analysis performed to determine an optimal threshold for the quantitative PET analysis, using the qualitative PET review as the gold standard.

Table 1

Indications for the PET-CT studies in our 100 patients.

Buccal squamous cell carcinoma (tonsillar or tongue carcinoma) (28)
Nasopharyngeal, oropharyngeal and hypopharyngeal squamous cell carcinoma (26)
Parotid adenocarcinoma (8)
Glottic/supraglottic carcinoma (6)
Lymphoma (6)
Sarcoma (reticulosarcoma, lymphosarcoma or chondrosarcoma) (5)
Skin carcinoma (5)
Neck squamous cell carcinoma (4)
Melanoma (3)
Thyroid carcinoma (3)
Metastases (3)
Esthesioneuroblastoma (1)
Paraganglyoma (1)
Schwannoma (1)

Table 2

Univariate analyses of the association PET+ plaques and the clinical risk factors and CT features of arterial plaques.

	Value	Coefficient	95% confidence interval	p value
<i>Age</i>	58±14	−0.024	−0.056 – 0.008	0.142
<i>Gender</i>	71 men and 29 women	−0.432	−1.567 – 0.703	0.456
<i>Race</i>	62 White, 24 Asian, and 3 African-Americans	−0.706	−1.724 – 0.312	0.174
<i>Smoking</i>	3%	18.115	−6.336 – 32.567	0.997
<i>Alcohol consumption</i>	3%	0.653	−1.134 – 0.923	0.132
<i>Hypertension</i>	5%	2.903	0.278 – 5.528	0.030
<i>Diabetes</i>	6%	0.605	−1.289 – 2.500	0.531
<i>Dyslipidemia</i>	1%	1.783	0.370 – 3.196	0.013
<i>Radiation and/or chemotherapy</i>	73%	−0.271	−1.511 – 0.969	0.668
<i>NASCET degree of stenosis on CTA</i>	6.8%±6.4%	0.527	0.012 – 22.982	0.739
<i>Presence of atherosclerotic plaque on CTA</i>	42%	0.909	0.612 – 1.351	0.638
<i>Presence of calcified atherosclerotic plaque on CTA</i>	25%	1.457	1.120 – 1.895	0.005