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Should vascular wall ^{18}F -FDG uptake be adjusted for the extent of atherosclerotic burden?

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Abstract

Vascular wall ^{18}F -FDG uptake is often used as a surrogate marker of atherosclerotic plaque inflammation. A potential caveat is that vascular wall ^{18}F -FDG uptake is higher simply because more atherosclerosis is present. To determine if the degree of inflammation is high or low relative to the extent of atherosclerosis, vascular wall ^{18}F -FDG uptake may require statistical adjustment for a non-inflammatory marker reflecting the extent of atherosclerosis, e.g. calcification. Adjustments is probably needed if (1) vascular wall ^{18}F -FDG uptake correlates sufficiently strongly with arterial calcification and (2) adjustment for extent of calcification affects determinants of vascular ^{18}F -FDG uptake. This study addresses these questions. ^{18}F -FDG PET/low-dose-CT scans of 99 patients were used. Cardiovascular risk factors were assessed and PET/CT scans were analysed for standardized ^{18}F -FDG uptake values and calcification. ANOVA was used to establish the association between vascular ^{18}F -FDG uptake and calcification. Multiple linear regression (with and without calcification as independent variable) was used to show whether determinants of vascular ^{18}F -FDG uptake were affected by the degree of calcification. ^{18}F -FDG uptake was related to increased calcification in the aortic arch, descending and abdominal aorta. However, ^{18}F -FDG uptake showed considerable overlap between categories of calcification. Age and body mass index were main determinants of vascular ^{18}F -FDG uptake. In multiple regression analyses, most standardized beta coefficients of these determinants were not affected by adjustment for the degree of calcification. Although vascular ^{18}F -FDG uptake is related to total atherosclerotic burden, as reflected by vascular calcification, the association is weak and unlikely to affect the identification of determinants of atherosclerotic inflammation implicating no need for adjustment in future studies.

Keywords Atherosclerosis · Plaque inflammation · Positron emission tomography

Abbreviations

ANOVA	Analysis of variance
ASCVD	American society of cardiovascular disease
BMI	Body mass index
CT	Computed tomography
FDG	Fluorodeoxyglucose
GCA	Giant cell arteritis
hsCRP	High sensitivity c-reactive protein
MRI	Magnetic resonance imaging
PET	Positron emission tomography
ROI	Region of interest
SUV	Standardized uptake value

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Introduction

Cardiovascular disease resulting from atherosclerotic plaque inflammation remains one of the leading causes of morbidity and mortality worldwide [1]. Inflammation plays a pivotal role in the development and destabilization of plaques [2–4]. Increased atherosclerotic plaque inflammation is of clinical interest, since it has been reported to precede plaque rupture and thrombotic occlusion [5].

Inflammatory activity in the arterial wall can be assessed in-vivo using ^{18}F -Fluorodeoxyglucose Positron Emission Tomography (^{18}F -FDG PET). ^{18}F -FDG uptake correlates with macrophage invasion in atherosclerotic plaque, and is increased in carotid plaques in patients with recent cerebrovascular events [6, 7]. Also, high-risk atherosclerotic lesions, as defined by American Heart Association criteria, have the highest degree of ^{18}F -FDG uptake [8, 9]. Finally, ^{18}F -FDG uptake in the ascending aorta was an independent predictor of future cardiovascular events in several studies [10, 11]. Therefore, vascular wall ^{18}F -FDG uptake is considered a well-established in-vivo marker of plaque inflammation [12].

There is a potential caveat, however, in the association between vascular ^{18}F -FDG uptake and atherothrombotic event risk. Severe atherosclerosis is intrinsically associated with plaque inflammation [5]. Hence, vascular wall ^{18}F -FDG uptake may, at least partly, be simply a proxy for atherosclerotic burden, and vascular wall ^{18}F -FDG uptake may be higher simply because more atherosclerosis is present. Thus, any study addressing (determinants of) vascular ^{18}F -FDG uptake may run the risk of essentially studying atherosclerotic burden, rather than inflammation relative to the degree of atherosclerosis. To tackle this potential caveat, a marker of atherosclerotic burden that does not represent inflammation would be needed. Such a marker could be used to address two questions. First: to what extent is ^{18}F -FDG uptake related to this marker of atherosclerotic burden? Second: are determinants of vascular ^{18}F -FDG uptake confounded by this same marker?

A typical marker of atherosclerotic severity not related to inflammation is vascular wall calcification. Calcification reflects the presence of mature, calcified atherosclerotic plaques and independently predicts cardiovascular events and mortality [13, 14]. Calcification can be established using computed tomography (CT) or magnetic resonance imaging (MRI) [5]. There are conflicting results regarding the correlation between ^{18}F -FDG uptake and arterial calcification [15–18]. To our knowledge, no previous studies addressing prognostic value of arterial ^{18}F -FDG uptake have adjusted for calcification as a marker of atherosclerotic burden.

The primary objective of this study was to assess, per large-artery segment, the extent to which ^{18}F -FDG uptake

and calcification are correlated. Secondly, we explored whether clinical determinants of arterial ^{18}F -FDG uptake are different without or with additional adjustment for arterial calcification (i.e. as a proxy for total atherosclerotic burden). If both research questions turn out positive, future studies, addressing the diagnostic or prognostic value of plaque inflammation as measured by arterial ^{18}F -FDG uptake should include additional adjustment for a non-inflammatory proxy of atherosclerotic burden.

Materials and methods

Study design and participants

Adult patients referred for ^{18}F -FDG-PET/CT (PET/CT), regardless of clinical indication for PET/CT, at the department of Nuclear Medicine of the Amsterdam University Medical Center (location Boelelaan) were prospectively screened for eligibility. Patients were not eligible if they had a history of -or were clinically suspected for having an inflammatory disease that may affect the study results (e.g. vasculitis), or used medication that could potentially affect vascular inflammation (e.g. steroids, methotrexate or chemotherapy) within 1 month prior to the scan, or were unwilling to participate.

The medical ethics committee of the Amsterdam University Medical Center (location Boelelaan) approved the study protocol. All participants provided written informed consent.

On the day of the PET/CT scan patient demographics were collected and individual cardiovascular risk factors were assessed according to the components of the ASCVD cardiovascular risk score [19]. Several hours prior to the PET/CT scan blood pressure was measured at both arms after patients had rested for 5 min. The arm with the highest blood pressure was used for two additional measurements, and average systolic and diastolic blood pressure were calculated. Body mass index (BMI) was calculated using weight/height² (kg/m²). Waist circumference was measured at the height of the iliac crests. Patients were classified into, respectively, a group with high (i.e. prior cardiovascular event or ASCVD risk score $\geq 7.5\%$) or a group with low (i.e. ASCVD risk score $< 7.5\%$ or < 40 years of age) risk of cardiovascular events.

Blood sample collection and analysis

Blood was drawn from a peripheral intravenous catheter before administration of ^{18}F -FDG. A lipid profile was assessed directly following blood collection. High sensitivity C-reactive protein (hsCRP) is an inflammatory marker which is associated with increased cardiovascular risk [20].

It was measured using particle-enhanced immunoturbidimetric assay (Roche diagnostics, Mannheim, Germany).

F-FDG PET/CT scan

^{18}F -FDG PET/CT scans were performed using a Philips Gemini TF 16-slice PET/CT scanner (Philips Medical Systems, Eindhoven, The Netherlands). All patients fasted at least 6 h prior to the intravenous injection of ^{18}F -FDG (3.75 MBq/kg). After injection, patients rested in a quiet room for 60 min. Whole-body or Total-body PET images (below the cerebellum to either the inguinal region or toes, depending on scan indication) were acquired for approximately 22 min, i.e. 2 min per bed position. A low-dose CT-scan (120 kV, 35 mAs) was performed for attenuation correction. ^{18}F -FDG PET images were reconstructed using a time of flight ordered subset expectation maximisation algorithm, as implemented by the vendor, providing images with a matrix size of 144×144 and a voxel size of $4 \times 4 \times 4$ mm.

Image analysis

All PET images were analysed using a PET image analysis research tool developed at the department of Nuclear Medicine & Radiology of the Amsterdam University Medical Center. Vascular ^{18}F -FDG uptake was visually assessed by 1 experienced observer (using PET, CT and fused PET/CT images) in the following arteries: carotid, iliac and femoral arteries, aortic arch and ascending, descending and abdominal aorta. A region of interest (ROI) was drawn at the site exhibiting the most intense FDG uptake (hot-spot on one axial slice) on both CT and PET scans to ensure proper

anatomic coverage. (Fig. 1) Coronal and sagittal slices were viewed to ensure that the ROI was drawn in the artery and to exclude spill-over from adjacent tissue. The maximal standardized uptake value (SUVmax) in this ROI was calculated. SUV is the decay-corrected tissue concentration of ^{18}F -FDG divided by the injected dose and normalised for body weight. Previous research at our institution has shown that SUVmax resulting from this method is equal to SUVmax obtained from drawing ROI's encompassing the entire vessel wall, whereas the latter is much more time-consuming [21]. For all paired arteries (e.g. carotid, subclavian, iliac, femoral) one SUVmax was calculated (i.e. the side displaying the most intense FDG uptake).

Calcification scores, ranging from 0–4, were determined semi-quantitatively, using low dose CT scans, by 2 individual observers according to previously described methods using Osirix Lite v.8.0.2 [22]. (Pixmeo SARL, Geneva, Switzerland). A score of 0 indicated the absence of calcification, whereas 1, 2, 3 or 4 respectively indicated that calcification covered < 10%, 10–25%, 25–50% or > 50% of the vessel circumference. (Fig. 2) Vascular segments were not included for further analysis if Cohen's (weighted) kappa for inter- or intraobserver agreement were insufficient (i.e. < 0.5). This was true for the ascending aorta, the carotid and femoral arteries.

Statistical analysis

Continuous variables are expressed as mean (standard deviation) or median (interquartile range). Categorical variables are presented as proportions. Analysis of variance (ANOVA) was used to determine the association between vascular wall

Fig. 1 Axial slices of CT (a and c) and ^{18}F -FDG PET (b and d) images with regions of interest drawn at the site that visually exhibited the most intense uptake (c and d)

Fig. 2 Axial slice of a CT scan showing calcification (arrows) in the descending aorta comprising between 25 and 50% of the vessel wall circumference indicating a calcification score of 2

calcification and ^{18}F -FDG-uptake (SUVmax). The association between vascular wall ^{18}F -FDG uptake and cardiovascular risk factors was assessed using linear regression analysis (univariate followed by multivariate, including determinants with a p value <0.1 in univariate analysis). Dummy variables were constructed for calcification and were included in the multivariate analysis to assess whether this would affect the strength of determinants of ^{18}F -FDG-uptake (by changing standardized beta levels). In addition, we explored whether results were influenced if calcification groups were clustered. These multivariate analyses were performed in the total group and subgroups of patients with high and low cardiovascular disease risk. Statistical analyses were performed using SPSS analysis software. (SPSS version 23; SPSS Inc.)

Results

99 evaluable patients were included. Table 1 shows the characteristics of these patients. The average age was 57.7 years (standard deviation 12.7 years), 64 were female, 11 had diabetes mellitus, 16 used a cholesterol lowering agent, 9 had a history of cardiovascular disease and 14 were current smoker. Average body mass index was 25.9 (standard deviation 4.2) Median cardiovascular risk (ASCVD) score was 8.5 (interquartile range 3.6–10).

Table 2 shows the distribution of calcification and the average SUVmax in the investigated arterial segments. The abdominal aorta and iliac arteries show the highest degree of intense calcification (score 4) whereas mild calcification (score 1–2) appears to be evenly distributed among all vascular segments studied. The degree of calcification could not be reliably assessed in 3–10% of cases, depending on which vascular segment was assessed.

Table 1 Patient characteristics presented as either mean (SD), median (IQR) or number (n)

Patient characteristics (n=99)	
Male/female (n)	64/35
Age (years)	57.7 (12.7)
Systolic blood pressure (mmHg)	133.7 (15.6)
Diastolic blood pressure (mmHg)	82.8 (10.0)
Body mass index (kg/m^2)	25.9 (4.2)
HDL (mmol/l)	1.44 (1.14–1.82)
Total cholesterol (mmol/l)	5.1 (1.1)
LDL (mmol/l)	3.0 (0.9)
Triglycerids (mmol/l)	1.1 (0.8–1.6)
hsCRP (mg/l)	1.8 (0.9–4.1)
Diabetes mellitus (n)	11
Statin use (n)	16
History of cardiovascular disease (n)	9
Current smoker (n)	14
ASCVD risk score*	8.5 (3.6–10)

HDL high density lipoprotein, *LDL* low density lipoprotein, *hsCRP* high sensitivity c-reactive protein, *ASCVD* atherosclerotic cardiovascular disease, *SD* standard deviation, *IQR* interquartile range

*Patients <40 years of age ($n=7$) and with history of CVD not included since the score is not validated for this group

The relationship between SUVmax and calcification is illustrated in Fig. 3. There was a statistically significant association between calcification and SUVmax values in the aortic arch ($p=0.001$), descending aorta ($p=0.012$), and abdominal aorta ($p=0.036$). However, differences in ^{18}F -FDG uptake between calcification categories were small and showed considerable overlap.

Results of univariate and multivariate linear regression are displayed in Table 3. Age, body mass index (BMI), diabetes mellitus, systolic blood pressure and triglycerids were significant determinants of ^{18}F -FDG uptake in all vascular segments analysed. However, in multivariate analysis only age and BMI remained significant in all vascular segments.

Consistent with the ANOVA analysis, calcification was an independent determinant of vascular wall ^{18}F -FDG uptake in the aortic arch and the abdominal aorta. Introducing vascular wall calcification as an independent variable slightly altered standardized beta-coefficients for age in the aortic arch and abdominal aorta, whereas no relevant alterations for either age or BMI were observed in the other vascular segments.

Supplemental Table 1 shows the results for the low and high cardiovascular risk subgroups. Overall, results are similar to the total group. Remarkably, calcification was an independent determinant of vascular wall ^{18}F -FDG uptake in the low risk, but not in the high risk subgroup. In our exploratory analysis in which calcification groups were clustered (data shown in Supplemental Table 2), results were comparable, showing even more stable standardized beta's

Table 2 Presence of calcification according to calcification score in individual patients and median (IQR) SUVmax scores in all vascular segments

Vascular segment	0	1	2	3	4	Indeterminate*	SUVmax
Aortic arch	41	24	16	11	1	4	2.62 (0.65)
Descending aorta	59	27	9	0	0	3	2.60 (0.66)
Abdominal aorta	17	20	20	9	25	8	2.76 (0.73)
Iliac arteries	25	22	18	7	17	10	2.72 (0.73)

Calcification score: 0 = absent, 1 ≤ 10%, 2 = 10–25%, 3 = 25–50%, 4 ≥ 50%

*Could not be reliably assessed. IQR = interquartile range; SUV = standardized uptake value

Fig. 3 Box plots (including median and interquartile range) showing the association between calcification and SUVmax in the aortic arch (a), descending aorta (b), abdominal aorta (c), and iliac artery (d)

for determinants of vascular wall ^{18}F -FDG uptake without and with adjustment for the presence of calcification.

Discussion

In this study we observed a weak positive association between calcification and vascular wall ^{18}F -FDG uptake, particularly in the aortic arch, abdominal and descending aorta.

This finding is consistent with previous studies showing either a weak or no association between vascular ^{18}F -FDG

uptake and calcification. A positive association was suggested in a small group of patients who recently suffered an ischemic stroke [18]. In addition, a limited degree of co-localization of vascular ^{18}F -FDG uptake and calcification was found in one small and one larger retrospective study in cancer patients [15, 17]. Neither study reported quantitative correlations between calcification and ^{18}F -FDG uptake. Finally, a recently published study in both healthy volunteers and patients with chest pain ($n = 139$) showed no correlation between ^{18}F -FDG uptake in the thoracic aorta and calcification [16].

To our knowledge, this is the first study to investigate whether calcification, as a marker of global atherosclerotic burden, affects the identification of determinants of vascular wall ^{18}F -FDG uptake. Consistent with the weak association between vascular ^{18}F -FDG uptake and calcification, adjustment for the degree of calcification in multivariate regression had no substantial or consistent impact on statistical determinants of vascular wall ^{18}F -FDG uptake. Our findings thus argue against the notion that vascular wall ^{18}F -FDG uptake is simply a reflection of global atherosclerotic burden.

Our study had both strengths and limitations. We prospectively included adult patients with variable levels of cardiovascular risk. As opposed to most previous studies, multiple arterial segments were investigated by multiple observers. A limitation is the relatively small sample size. Also, we only studied the effect of a select number of potential determinants of vascular wall ^{18}F -FDG uptake, i.e. well-established cardiovascular risk factors. We cannot fully exclude the possibility that adjustment for the degree of calcification affects alternative predictors of vascular wall ^{18}F -FDG uptake. Finally, we did not exclusively select patients with established cardiovascular disease or patients with a high-risk profile. However, our exploratory analysis in subgroups with high and low cardiovascular risk showed similar results.

In conclusion, the association between vascular ^{18}F -FDG uptake and global burden of atherosclerosis, as reflected by calcification, is weak, and appears insufficient to affect the identification of determinants of vascular

Table 3 Independent determinants of SUVmax in univariate and multivariate analysis

	Univariate	Beta coefficient	Multi variate analysis*	Standardized beta coefficient	Multivariate analysis†	Standardized beta coefficient
Aortic arch	Age	(0.305)‡	Age	(0.271)‡	Age	(0.132)
	BMI	(0.501)‡	BMI	(0.404)‡	BMI	(0.423)‡
	DM	(0.260)§				
	SBP	(0.247)§				
	Triglyce rids	(0.243)§ (−0.177)?				
Descendi ng aorta	HDL				Calcification	(0.297)‡
	Age	(0.351)‡	Age	(0.299)‡	Age	(0.274)§
	BMI	(0.395)‡	BMI	(0.319)‡	BMI	(0.312)‡
	DM	(0.214)§				
	SBP	(0.289)‡				
Abdomi nal aorta	Triglycerids	(0.201)?				
	Age	(0.364)‡	Age	(0.339)‡	Age	(0.263)§
	BMI	(0.487)‡	BMI	(0.398)‡	BMI	(0.429)‡
	DM	(0.289)‡				
	Statin use	(0.236)§				
Iliac arteries	SBP	(0.242)§				
	Triglycerids	(0.254)§			Calcification	(0.228)?
	Age	(0.344)‡	Age	(0.285)‡	Age	(0.278)§
	BMI	(0.427)‡	BMI	(0.359)‡	BMI	(0.352)‡
	DM	(0.274)‡				
	SBP	(0.317)‡				
	HDL	(−0.179)?				
	Triglyce rids	(0.238)§				

DM diabetes mellitus, SBP systolic blood pressure, BMI body mass index, HDL high density lipoprotein, DBP diastolic blood pressure

*Calcification not included

†Calcification included

?p < 0.1

§p < 0.05

‡p < 0.01

¹⁸F-FDG uptake, suggesting that ¹⁸F-FDG uptake should not be adjusted for the extent of atherosclerotic burden.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

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