

# Association of vascular fluoride uptake with vascular calcification and coronary artery disease

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**Objective** The feasibility of a fluoride positron emission tomography/computed tomography (PET/CT) scan for imaging atherosclerosis has not been well documented. The purpose of this study was to assess fluoride uptake of vascular calcification in various major arteries, including coronary arteries.

**Methods** We retrospectively reviewed the imaging data and cardiovascular history of 61 patients who received whole-body sodium [<sup>18</sup>F]fluoride PET/CT studies at our institution from 2009 to 2010. Fluoride uptake and calcification in major arteries, including coronary arteries, were analyzed by both visual assessment and standardized uptake value measurement.

**Results** Fluoride uptake in vascular walls was demonstrated in 361 sites of 54 (96%) patients, whereas calcification was observed in 317 sites of 49 (88%) patients. Significant correlation between fluoride uptake and calcification was observed in most of the arterial walls, except in those of the abdominal aorta. Fluoride uptake in coronary arteries was demonstrated in 28 (46%) patients and coronary calcifications were observed in 34 (56%) patients. There was significant correlation between history

of cardiovascular events and presence of fluoride uptake in coronary arteries. The coronary fluoride uptake value in patients with cardiovascular events was significantly higher than in patients without cardiovascular events.

**Conclusion** sodium [<sup>18</sup>F]fluoride PET/CT might be useful in the evaluation of the atherosclerotic process in major arteries, including coronary arteries. An increased fluoride uptake in coronary arteries may be associated with an increased cardiovascular risk. *Nucl Med Commun* 33:14–20 © 2011 Wolters Kluwer Health | Lippincott Williams & Wilkins.

Nuclear Medicine Communications 2012, 33:14–20

**Keywords:** atherosclerosis, bone scan, sodium [<sup>18</sup>F]fluoride, positron emission tomography, vascular calcification

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Received 21 June 2011 Revised 2 August 2011 Accepted 18 August 2011

## Introduction

Cardiovascular disease remains the leading cause of morbidity and mortality in the world [1]. The major pathophysiologic change of cardiovascular disease is atherosclerosis in critical arteries. Atherosclerosis is a slow, progressive, and cumulative process that results in atheromatous plaque formation in vascular walls and eventually leads to narrowing of the arterial lumen, occlusion, or aneurysm formation. The development of atherosclerotic plaque is characterized by subendothelial fatty material accumulation, a chronic inflammatory process, and vascular calcification [2,3]. To predict and prevent any deadly cardiovascular events, extensive studies have been conducted to evaluate the risk of cardiovascular disease. Over the past decade, many cardiovascular studies focused on the calcification process in atherosclerosis [4–7].

Calcification in atherosclerosis occurs through an active process that resembles bone formation and is controlled by complex enzymatic and cellular pathways [8,9]. Coronary artery calcification parallels atherosclerosis progress and is strongly and linearly correlated with the

total atherosclerotic burden [10]. Coronary calcification can be measured by computed tomography (CT) studies and is one of the most important predictors of future cardiovascular events. The level of coronary artery calcium can also help to reclassify asymptomatic individuals into high-risk or low-risk categories [4]. Currently, sodium [<sup>18</sup>F]fluoride positron emission tomography (PET)/CT is the most sensitive imaging modality to detect active bone formation [11]. Recently, Derlin *et al.* [12] reported the feasibility of sodium [<sup>18</sup>F]fluoride PET/CT for imaging atherosclerotic calcification in major arteries, including carotid, aorta, iliac, and femoral arteries. They also found that the mineral deposition in the carotid plaque detected by sodium [<sup>18</sup>F]fluoride PET/CT significantly correlates with atherogenic risk factors [13]. Although atherosclerosis is a systemic disease, and evaluation of vascular calcification may potentially predict cardiovascular events, studies have shown that direct assessment of coronary arteries is superior to surrogate imaging for evaluating the risk of cardiovascular events [14]. Some recent studies have demonstrated that evaluation of coronary arteries by PET is feasible [15–22]. Most of these studies investigated

fluorodeoxyglucose (FDG) uptake in coronary arteries. However, the clinical significance of [ $^{18}\text{F}$ ]fluoride uptake in coronary arteries has not been documented.

In this study, we evaluated sodium [ $^{18}\text{F}$ ]fluoride uptake in major arteries, including coronary arteries, in 61 patients. The relationship between [ $^{18}\text{F}$ ]fluoride uptake and cardiovascular history and/or multiple risk factors was also evaluated.

## Materials and methods

This study has been approved by the institutional review board of the Greater Los Angeles VA Healthcare System.

### Patients

We retrospectively reviewed sodium [ $^{18}\text{F}$ ]fluoride PET/CT bone studies conducted at Veterans Affairs Greater Los Angeles Healthcare System from April 2009 to June 2010. There were 58 male patients and three female patients. Detailed clinical histories and the presence of cardiovascular risk factors, such as hypertension, diabetes, hypercholesterolemia, smoking history, obesity, and history of cardiovascular events, were obtained for all patients. The clinical characteristics of the patients are summarized in Table 1.

### Positron emission tomography/computed tomography protocols and imaging reconstruction

PET/CT scans were performed using a Philips Gemini TF 64-channel time-of-flight PET/CT scanner (Philips Healthcare, Andover, Massachusetts, USA) with spatial resolution of 4.5 mm at West Los Angeles VA Medical Center. Sodium [ $^{18}\text{F}$ ]fluoride was injected intravenously at a dose of  $10 \pm 2$  mCi ( $370 \pm 74$  MBq). Participants were comfortably seated in a private, quiet, cozy room. Forty minutes after the injection, patients were subjected to a low-dose CT scan of the whole body without contrast at 50 mA, 120 kV<sub>p</sub>, 0.5 s/rotation, a pitch of covering 0.83 mm, and a slice thickness of 5 mm [23,24]. The

subsequent PET data were acquired continuously for 90 s and at 180 mm per bed position with 50% overlap between consecutive bed positions using a matrix of  $140 \times 140$ , followed by reconstruction corrected for attenuation using low-dose CT scans. No cardiac or respiratory gating was performed.

### Imaging and statistical analyses

CT and PET images were coregistered by the Philips Extended Brilliance workstation (Philips Healthcare). CT, PET, and fused PET/CT images were evaluated visually and semiquantitatively simultaneously using the same workstation. All images were analyzed by two independent nuclear medicine physicians blinded to all patients' clinical information. Inter-reader reproducibility was excellent and was evaluated using an intraclass correlation coefficient (0.89). Vascular calcification was identified as positive on CT images if the target was visually detectable with a greater than 130 Hounsfield units. CT-attenuated PET images were evaluated for fluoride uptake in major arteries. Background activity was based on the standardized uptake value (SUV) of the blood pool, which was calculated from the mean SUVs of three circular regions of interest (ROIs) placed in the left atrium, mid lumen of the aortic arch, and abdominal aorta at the level of the celiac trunk on axial images. The sizes of ROIs were 2 cm in diameter for the left atrium and 1 cm for the aortic arch and the abdominal aorta. Maximum SUVs (SUV<sub>max</sub>) from target arteries were obtained by manually placing an individual circular ROI of 1 cm diameter in the target artery wall. All three orthogonal images were assessed for focal lesions in major arteries with an increased fluoride uptake. Positive fluoride uptake was identified if the target lesion was visually detectable with a greater than or equal to 1.5 target-to-background ratio in all three orthogonal image planes. For either CT or PET evaluation, the arterial territory was categorized as positive if at least one lesion was detected and agreed upon by both readers. The percentages of positive studies on both CT and PET of each arterial territory were calculated. Correlation between fluoride uptake and CT calcification was analyzed by Fisher's exact test. Correlation of PET results and the number of cardiovascular risk factors were analyzed by the Wilcoxon rank-sum test. Significance was defined as *P* value of less than 0.05 in two-tailed studies.

## Results

Patients' age and reasons for sodium [ $^{18}\text{F}$ ]fluoride PET/CT imaging are summarized in Table 1. Most patients were men with a median age of 66 years (27–91 years). The majority of patients (69%) had more than one risk factor for coronary artery disease.

### Arterial sodium [ $^{18}\text{F}$ ]fluoride uptake and calcification

Arterial wall sodium [ $^{18}\text{F}$ ]fluoride uptake and calcification were evaluated in major arteries, including carotid

**Table 1** Patients' clinical characteristics

Characteristics	Number (%)
Total number	61
Male	58 (95)
Age	Range: 27–91 years; median: 66
Number of cardiac risk factors <sup>a</sup>	
0	11 (18)
1	8 (13)
2	17 (28)
3	18 (30)
4	5 (8)
5	1 (2)
Reasons for bone scan	
Evaluation of bone metastases in prostate cancer	38 (63)
Evaluation of bone metastases in other cancers	14 (23)
Benign bone lesions <sup>b</sup>	9 (15)

<sup>a</sup>Cardiac risk factors include hypertension, diabetes, hypercholesterolemia, smoking history, and obesity.

<sup>b</sup>Benign bone lesions include Paget's disease, suspected fracture, prosthesis evaluation, and heterotrophic ossification.

arteries, the thoracic ascending (including aortic arch) aorta, the thoracic descending aorta, the abdominal aorta, femoral arteries, and major branches of coronary arteries. Iliac arteries were not evaluated because of frequently observed urinary and occasional bowel uptake in the pelvis, which interferes with the accurate assessment of iliac vessels. For coronary arteries, four major branches were evaluated. An example of fluoride uptake in femoral arteries is shown in Fig. 1. Orthogonal views of fluoride uptake in the aorta and coronary arteries are shown in Figs 2 and 3.

Fig. 1



Whole-body positron emission tomography image demonstrates remarkable fluoride uptake in both femoral arteries.

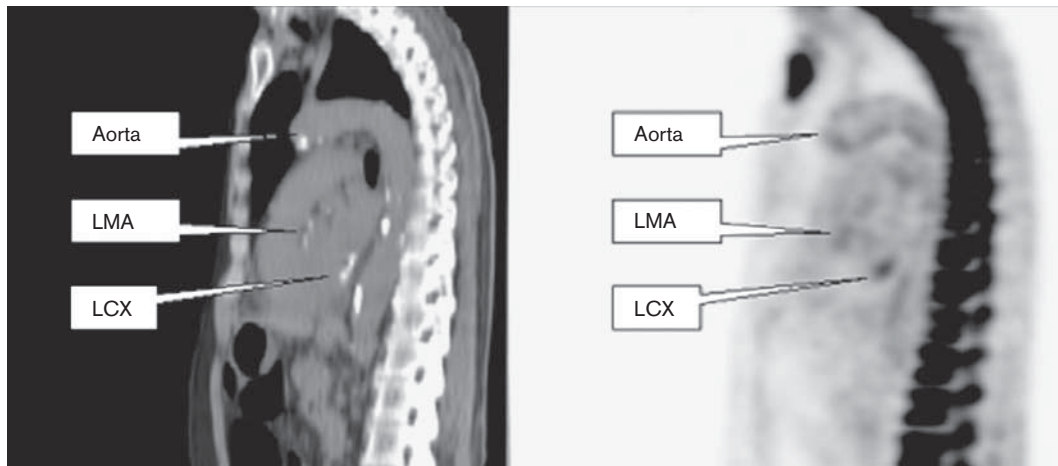
Both fluoride uptake and calcification were common in major arteries as summarized in Table 2. In general, fluoride uptakes in vascular walls were observed in 361 vascular territories of 59 (97%) patients, and calcifications were observed in 317 vascular territories of 49 (88%) patients. Only two patients did not demonstrate fluoride uptake in any of the vasculatures (one patient aged 27 and one aged 61). In thoracic aortas, the abdominal aorta, and femoral arteries, fluoride uptake was observed more frequently compared with calcification. In contrast, calcification was more common than fluoride uptake in carotid and coronary arteries (Table 2). Except for the abdominal aorta, fluoride uptake and calcification were significantly correlated in the same vascular territories, as evaluated by Fisher's exact test. It should be noted that the fluoride uptake and calcification were not necessarily overlapped in the exact same anatomic locations. At calcification sites that did not demonstrate prominent overlapping fluoride uptake, fluoride uptake was frequently observed in the adjacent area within the same arterial territories (Fig. 2).

#### Relationship between coronary fluoride uptake and cardiovascular risk factors

The coronary arteries were also investigated for fluoride uptake. Four major branches of coronary arteries, including left main artery (LMA), left anterior descending (LAD), left circumflex (LCA), and right coronary artery (RCA) were evaluated. Fluoride uptake was more frequently observed in the LAD and LCAs. A similar pattern was also identified in coronary artery calcification. In each individual coronary branch, calcification was more frequently observed than fluoride uptake (Table 2). Among 10 patients who had significant three-vessel coronary calcifications, 80% demonstrated fluoride uptake in at least one coronary branch (data not shown).

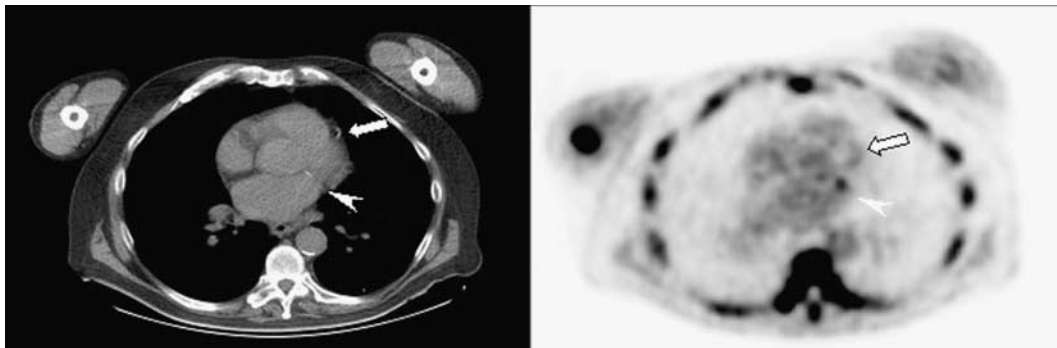
Cardiovascular risk factors including hypertension, obesity, diabetes, hypercholesterolemia, smoking history, and history of coronary artery disease were reviewed in all patients (Table 3). The majority of the patients (69%) had more than one cardiovascular risk factor; however, neither the individual cardiovascular risk factor nor the number of risk factors was significantly correlated with coronary fluoride uptake (Table 3). Nine patients had a history of cardiovascular events. Among them, eight demonstrated identifiable coronary fluoride uptake. There was significant correlation between coronary calcification and fluoride uptake in this group evaluated by Fisher's exact test (Table 3). All nine patients also demonstrated coronary calcification on CT images. We also compared the  $SUV_{max}$  in coronary arteries between patients with and without a history of cardiovascular events. The average coronary  $SUV_{max}$  in patients with a history of cardiovascular events was 1.70, significantly higher than 1.39 for patients without a history of cardiovascular events ( $P = 0.029$ , two-tailed Student's

Fig. 2



Sagittal computed tomography (left) and positron emission tomography (right) images show aortic and coronary calcification and fluoride uptake. Calcification and fluoride uptake in the aorta do not always overlap. LCX, circumflex coronary artery; LMA, left main coronary artery.

Fig. 3



Computed tomography (left) and positron emission tomography (right) images show coronary calcification and fluoride uptake in the left anterior descending coronary artery (arrow) and the circumflex coronary artery (arrow head).

*t*-test). No correlation was observed between cardiovascular risk factors and fluoride uptake in other vascular territories (noncoronary).

### Discussion

Vascular calcification, in particular coronary calcification, has been shown to predict vascular events [25–27]. Recent utilization of multidetector CT has made the assessment of coronary calcium feasible and reproducible [7,28]. However, CT can only evaluate structural change, which usually represents later stages of the disease's process. Given the assumption that fluoride uptake represents dynamic atherosclerotic calcification, we would expect that fluoride uptake occurs at the stage before the formation of detectable calcium deposition. Consistent with this theory, Derlin *et al.* [12] reported that only 12% of the calcification sites demonstrated

prominent overlapping fluoride uptake, whereas 12% of fluoride-positive lesions did not show concordant calcification. In our study, fluoride uptake and CT calcification are significantly correlated in the same arterial territories, except in the abdominal aorta. This is because of the extremely high positive rate (97%, only one patient demonstrated negative uptake) for fluoride uptake in the abdominal aorta. Fluoride uptake either overlaps with calcification or locates adjacent to the detectable calcium deposits, suggesting that fluoride uptake and detectable calcification represent different stages of the atherosclerotic process.

In large arteries, such as the thoracic aorta, abdominal aorta, and femoral arteries, fluoride uptake is more commonly observed than calcification. This finding is different from results published by Derlin *et al.* [12],

**Table 2** Prevalence of fluoride uptake and calcifications in major arteries

Artery	SUV <sub>max</sub> of fluoride		TBR mean ± SD	Fluoride uptake only (%)	Calcification only (%)	Neither (%)	Both (%)	Fluoride uptake (%)	Calcification (%)	P value <sup>a</sup>
	Mean ± SD	Range								
Left carotid	1.39 ± 0.72	0.7–4.3	1.39 ± 0.66	1 (2)	8 (13)	31 (51)	21 (34)	23 (38)	29 (48)	<0.001
Right carotid	1.38 ± 0.83	0.7–5.2	1.37 ± 0.66	3 (5)	11 (18)	30 (49)	17 (28)	21 (34)	26 (43)	<0.001
Aorta										
Thoracic ascending (including arch)	1.98 ± 0.73	0.7–4.5	2 ± 0.72	20 (33)	0 (0)	5 (8)	36 (59)	56 (92)	36 (59)	0.020
Thoracic descending	1.57 ± 0.62	0.7–3.2	1.57 ± 0.56	23 (38)	0 (0)	20 (33)	18 (30)	41 (67)	18 (30)	0.001
Abdominal	2.45 ± 1.01	0.7–4.3	2.45 ± 0.97	18 (32)	0 (0)	2 (4)	41 (67)	59 (97)	41 (67)	0.123
Left femoral	2.16 ± 0.98	0.7–4.7	2.16 ± 0.89	12 (20)	1 (2)	10 (18)	38 (62)	50 (82)	39 (64)	<0.001
Right femoral	2.23 ± 1.08	0.7–5.8	2.24 ± 0.95	12 (21)	0 (0)	12 (20)	37 (61)	50 (82)	37 (61)	<0.001
Any Coronary arteries				4 (7)	10 (18)	23 (38)	24 (39)	28 (46)	34 (56)	<0.001
Left main	1.20 ± 0.51	0.7–2.7	1.18 ± 0.33	8 (14)	6 (10)	41 (67)	6 (11)	14 (25)	20 (33)	
LAD	1.14 ± 0.40	0.7–2.3	1.12 ± 0.24	2 (4)	17 (30)	25 (41)	17 (28)	19 (31)	34 (56)	
LCX	1.32 ± 0.71	0.7–6.5	1.31 ± 0.37	5 (9)	8 (14)	34 (56)	14 (23)	19 (31)	22 (36)	
RCA	1.10 ± 0.39	0.7–2.3	1.08 ± 0.21	1 (2)	7 (11)	45 (74)	8 (14)	9 (16)	15 (25)	

LAD, left anterior descending coronary artery; LCX, circumflex coronary artery; RCA, right coronary artery. TBR, target-to-background ratio.

<sup>a</sup>Evaluated by Fisher's exact test.

**Table 3** Correlation between cardiovascular risk factors and coronary fluoride uptake

Patient characteristics	PET +	PET –	P value
High cholesterol	19	15	0.121
Diabetes	10	6	0.151
Hypertension	24	21	0.079
Smoking history	8	12	0.591
Morbid obesity	5	6	1
Number of risk factors	2.26	1.90	0.361
Known cardiovascular events <sup>a</sup>	8	1	0.009

Statistical analyses were conducted by Fisher's exact test and by the Wilcoxon rank-sum test.

PET, positron emission tomography.

<sup>a</sup>Cardiovascular events include myocardial infarction, coronary bypass surgery, and coronary angioplasty.

which demonstrated that fluoride uptake is less frequently observed than calcification in all major arteries. The discrepancy may be due to different PET/CT scanners. In our study, we used a time-of-flight PET/CT scanner with better spatial resolution (4.5 mm vs. 8 mm) and higher sensitivity. In addition, differences in patient populations may also contribute to the discrepancy. Most of our patients were older male veterans with multiple cardiovascular risk factors. Consistent with this, our data demonstrated notably higher incidents of calcification compared with the data published by Derlin *et al.* [12]. Recently, they also reported that fluoride uptake in carotid arteries significantly correlated with cardiovascular risk factors. We found that 43 (right) and 48% (left) of patients have carotid calcifications, whereas 34 (right) and 38% (left) of patients have fluoride uptake, compared with 32 (right) and 37% (left) with calcification and 25 (right) and 28% (left) with fluoride uptake according to the results from Derlin *et al.* [13]. However, we did not observe any correlation between carotid fluoride uptake and cardiovascular risk factors, probably because of the limited number of patients in our study.

In contrast to the results of the aorta and femoral arteries, fluoride uptake was less commonly observed than calcification in coronary arteries. This phenomenon could be due to the following reasons: (a) the limited spatial resolution of PET reduces the sensitivity to detect fluoride uptake in smaller arteries; (b) the combination of cardiac and respiratory motions further reduces the sensitivity of PET in the evaluation of coronary arteries; (c) the proximal coronary arteries are surrounded by vascular structures that are highly susceptible to calcification. These include aorta, pulmonary artery, and heart valves. All these structures may affect the interpretation of fluoride uptake in coronary arteries; and (d) the partial volume effect on the small size of the ROIs is also a possible reason.

Coronary motion is greatest in the RCA, followed by circumflex coronary artery, LAD, and LMA in descending order [29]. Our study demonstrated that fluoride uptake was more frequently observed in LAD and circumflex coronary artery than in the RCA and LMA. Motion artifact reduces the sensitivity to detect fluoride uptake in the RCA. The short length of LMA and its short distance to the aorta, which frequently demonstrates fluoride uptake, may attribute to the low frequency of fluoride uptake in the LMA. Despite the feasibility of fluoride PET evaluation of coronary calcification, coronary imaging with fluoride PET/CT remains challenging because of small artery size, motion artifact, and interference of surrounding vasculature calcifications. All of these factors will potentially cause either false-negative or false-positive results. The recent development of cardiac-respiratory gating technology in PET scans may increase the accuracy of coronary imaging [30–32]. In addition to the technical difficulties in evaluating coronary arteries, the limited number of patients and the unvarying nature of the patient population in this study may be skewed and may not apply to the general population.

We found that fluoride uptake in coronary arteries is significantly correlated with a patient's history of cardiovascular events, and the uptake value in patients with cardiovascular events was significantly higher than that in patients without cardiovascular events. These results further support the fact that higher fluoride uptake in coronary arteries indicates increased cardiovascular risk. Recently, several studies have demonstrated the feasibility of FDG-PET/CT in detecting plaque inflammation in coronary arteries [15–22]. Nevertheless, fluoride PET/CT detects active mineral deposition, which represents the distinct pathophysiologic process of atherosclerosis. Derlin *et al.* [33] reported that uptake of FDG and sodium fluoride in vessel wall alterations was rarely coincident, supporting the suggestion that these two studies evaluate different functional and morphologic changes of the atherosclerotic process. The FDG uptake and fluoride uptake of atherosclerotic plaques could have complementary roles in evaluating the cardiovascular risk of patients. The combination of sodium [<sup>18</sup>F]fluoride PET and CT is a promising imaging modality that provides both metabolic and anatomic information in evaluating vascular calcification. However, large-scale studies are needed to evaluate the clinical significance of fluoride PET/CT for imaging atherosclerosis.

## Conclusion

Our study demonstrates that vascular calcification and fluoride uptake are significantly correlated in the same arterial territory, although not necessarily overlapping in the same anatomic locations. An increased fluoride uptake in coronary arteries may be associated with an increased cardiovascular risk. Combined anatomic and metabolic imaging with sodium [<sup>18</sup>F]fluoride PET/CT offers a promising, noninvasive method to evaluate atherosclerosis.

## Acknowledgements

### Conflicts of interest

There are no conflicts of interest.

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