Association between age, uptake of ^{18}F-fluorodeoxyglucose and of ^{18}F-sodium fluoride, as cardiovascular risk factors in the abdominal aorta

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Abstract

Objective: We aimed to assess the feasibility of quantifying fluorine-18-fluorodexoglucose (^{18}F-FDG) and ^{18}F-sodium fluoride (^{18}F-NaF) uptake in abdominal aorta and examine their association with age and cardiovascular risk factors. **Subjects and Methods:** Our study comprised 123 subjects (48±14 years of age, 62 men) including 78 healthy volunteers and 45 patients with chest pain syndrome, who originally enrolled in the CAMONA study in Odense, Denmark (NCT01724749). All subjects underwent ^{18}F-FDG positron emission tomography/computed tomography (PET/CT) and ^{18}F-NaF PET/CT on separate days, 180min and 90 min after administration of tracers, respectively. The global tracer uptake value (GTUV) in the abdominal aorta was determined as sum of the product of each slice area and its corresponding average standardized uptake value (SUV mean), divided by the sum of those slice areas. In addition, for each subject, the 10 years Framingham risk score (FRS) was calculated. The correlations between ^{18}F-NaF and ^{18}F-FDG GTUV with age and 10 years FRS were assessed in all, healthy and patient subjects. **Results:** There was a significant, positive correlation between subjects' age and ^{18}F-NaF GTUV (r=0.35, P<0.001), but not ^{18}F-FDG GTUV (r=0.06, P= 0.53). Also, there was a significant, positive correlation between 10 years FRS and ^{18}F-NaF GTUV (r=0.30, P< 0.001), but not ^{18}F-FDG GTUV (r=0.01, P=0.95). Individual differences in ^{18}F-FDG and ^{18}F-NaF uptake were large in both healthy subjects and patients. **Conclusion:** In this study, the global uptake of ^{18}F-NaF in abdominal aorta was positively associated with age and 10 years FRS in all subjects, healthy and patient groups, whereas the global uptake of ^{18}F-FDG was not.

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Introduction

Atherosclerosis, which is the main pathologic pathway of cardiovascular disease (CVD), is thought to be due to early age onset of progressive multifactorial processes that occur throughout the entire life. The sequential process of damage and healing in the arterial wall eventually forms calcification as endothelial scar tissue [1, 2], but this process is gradual with no clinical symptoms at early stages. Several noninvasive imaging techniques including ultrasonography, computed tomography (CT) scan and magnetic resonance imaging (MRI) are able to detect calcified plaques and determine potential luminal stenosis. They are, however, typically applied only when symptoms have developed. In addition, although CT can visualize arterial wall macrocalcification, it cannot differentiate between active and inactive parts or predict which plaques are more prone to rupture [3]. Therefore, it may be worth looking for early biological arterial wall and plaque changes when potentially still amenable to treatment [4]. Using molecular PET imaging with probes that target biological processes may be a better way to characterize important phases of the atherosclerotic process at earlier stages. Fluorine-18-fluorodeoxyglucose (^{18}F-FDG) and ^{18}F-sodium fluoride (^{18}F-NaF) are examples of probes which are predominantly used for molecular imaging of inflammation and microcalcification, respectively, in the arterial vessel wall [5, 6]. Fluorine-18-FDG is a glucose analogue that accumulates in cells with high glycolytic activity, including macrophages implicated in plaque inflammation. Fluorine-18-FDG PET has high sensitivity, but low spatial resolution (4-8mm), and, therefore, is complemented by simultaneous CT acquisition to localize the ^{18}F-FDG sig-nal. Fluorine-18-NaF PET is a marker of active mineralization which can be used for identifying arterial wall calcification in the heart, thoracic aorta and carotid arteries before being otherwise detectable by conventional imaging [7, 8].

Unlike active plaques in the coronary arteries, aortic arch or carotid arteries that can cause myocardial infarction and stroke, the plaques in the abdominal aorta do not usually cause

Table 1. Demographic and clinical information of the patient.

	Total (N=123)	Healthy volunteers (n=78)	Patients (n=45)	P value for mean difference between groups
Age, yrs	48.2±14.0	43.5±13.2	56.0±11.4	<0.001
Men	62 (50.4)	41 (52.6)	21 (46.0)	0.58
Body mass index, kg/m^2	26.9±4.4	26.8±4.6	27.2±4.2	0.60
Systolic blood pressure, mm Hg	129.3±6.2	128.3±5.4	131.1±17.5	0.37
Diastolic blood pressure, mm Hg	78.2±9.2	77.5±9.8	79.5±7.8	0.20
Low density lipoprotein, mmol/L	3.2±0.8	3.1±0.8	3.4±0.9	0.04
High density lipoprotein, mmol/L	1.4±0.5	1.4±0.5	1.5±0.4	0.80
Triglycerides, mmol/L	1.1±0.7	1.1±0.7	1.2±0.5	0.47
Plasma glucose, mmol/L	5.6±0.6	5.5±0.5	5.8±0.7	0.02
HbA1c, mmol/mol	34.9±4.0	33.8±4.2	36.8±3.0	<0.001
Smokers	11 (8.9)	3 (3.8)	8 (17.7)	0.02
Active	47 (38.2)	27 (34.6)	20 (44.4)	0.34
Former	65 (52.8)	48 (61.5)	12 (37.7)	0.01
Never				

Values are mean±SD, n (%), HbA1c=Glycated hemoglobin.

major cardiovascular events except abdominal aortic aneurysms [9]. However, inflammation and microcalcification in the wall of the abdominal part of the aorta are elements in an ongoing systemic atherosclerotic process which may characterize patients as being at high-risk. Therefore, in this study, we wanted to examine the feasibility of quantifying global inflammation and microcalcification in the abdominal aorta with ^{18}F-FDG PET/CT and ^{18}F-NaF PET/CT, respectively, and also assess their association with age and cardiovascular risks. Although there is a similar study about CVD risk factors correlation with ^{18}F-FDG and ^{18}F- NaF uptake in the thoracic aorta (10), no other study has examined the uptake of both tracers in the abdominal section of the aorta.

Subjects and Methods

Study population

The participants were selected from the Cardiovascular Molecular Calcification Assessed by ^{18}F-NaF PET/CT" (CAMONA) study, approved by the Danish National Committee on Health Research Ethics, registered at ClinicalTrials.gov (NCT 1724749), and conducted in accordance with the principles of the Declaration of Helsinki. All study participants provided written informed consent. The participants of the CAMONA study comprised of 139 heterogeneous subjects including 89 healthy volunteers and 50 patients referred to cardiac CT angiography for chest pain syndrome [10]. Since we planned to assess and compare results of ^{18}F-NaF PET/CT and ^{18}F-FDG PET/CT scans obtained in the two groups, we excluded subjects who had only one of those scans or in whom one of the two scans was defective. After exclusion, 123 subjects including 78 healthy volunteers (mean age= 43.5±13.2 years, 41 men) and 45 patients (mean age= 56.0±11.4 years, 21 men) were included for further analysis. Healthy volunteers were recruited from the general population by advertisement or from the local blood bank and were defined as individuals without any symptoms of cardiovascular disease, deep vein thrombosis or acute pulmonary embolism within the previous three months, and also without oncologic diseases, autoimmune diseases, immunodeficiency syndromes or any history of alcohol abuse, recreational drug use or pregnancy or any prescribed medication. The patient group comprised cases referred for cardiac CT angiography due to chest pain syndrome. In this group, only patients with an estimated 10 years risk for fatal cardiovascular disease equal to or above 1% were included since they had higher prevalence of cardiovascular risk factors such as hypertension and hyperlipidemia or smoking [10]. All subjects had worked up for a comprehensive coronary artery disease risk assessment, which included history of CVD, smoking habit, blood pressure measurements, and biochemical lipid profile, blood sugar and HbA1c. The demographic and medical information of each patient were extracted from their records (Table 1), and a 10 years Framingham risk score (FRS) was calculated (mean=8.6±8.2, range 0.3-30.0).

PET/CT imaging

All subjects underwent whole body ^{18}F-FDG PET/CT and ^{18}F-NaF PET/CT acquisition on two separate days within two weeks, on average [11, 12]. In short, after an overnight fast of at least 8 hours and a blood glucose measurement ensuring a concentration below 8mmol/L, ^{18}F-FDG PET/CT imaging was performed 180min following the injection of 4MBq/kg of ^{18}F-FDG, whereas ^{18}F-NaF scans were undertaken 90min after injection of 2.2MBq/kg of ^{18}F-NaF. Patients were imaged on one of several PET/CT systems (GE discovery, STE, VCT, RX or 690/710 scanners). Positron emission tomography images were corrected for attenuation, random coincidences, scatter, and scanner dead time. Low-dose CT imaging (140kv, 30-110mA, noise index 25, 0.8seconds per rotation, slice thickness 3.75mm) was performed for attenuation correction and for anatomical orientation.

Image processing

A trained physician blinded to the demographics and clinical background of the subjects quantified tracer uptake by manually delineating regions of interest (ROI) in each axial slice around the periphery of the abdominal aorta on the fused PET/CT image using a DICOM viewer (OsiriX MD Software; Pixmeo SARL, Bernex, Switzerland) (Figure 1). The abdominal aorta was defined from the origin of celiac artery down to the level of bifurcation. The global tracer uptake value (GTUV) of each subject was calculated as the sum of the product of each slice area and its corresponding SUV mean, divided by the sum of all slice areas: GTUV= Σ(Area of the slicexSUVmean)/ΣArea.

Data analysis

Continuous variables were described by means and standard deviations. The paired t-test or Fisher's exact test were used to test for differences between healthy controls and patients and between genders. Correlation coefficients were calculated to test for associations between GTUV values on one side and age or FRS on the other side. Scatterplots and exploratory univariable linear regressions were used for visualization purposes. Level of significance was 5%. Statistical analysis was conducted by means of IBM SPSS software (SPSS Inc., Chicago, IL, USA; Version 22).

Results

Fluorine-18-NaF GTUV was significantly higher among chest pain patients than healthy volunteers (mean=1.43 vs mean=1.26, P=0.01). Fluorine-18-FDG GTUV was also higher in chest pain patients than healthy volunteers; however, this difference was not statistically significant (mean=1.58 vs mean=1.45, P=0.10), (Table 2, Figure 2).

Fluorine-18-NaF GTUV correlated positively with age in both healthy volunteers and chest pain patients (r=0.24, P=0.03 and r=0.39, P<0.001, respectively), whereas ^{18}F-FDG GTUV did not correlate with age in either group (r=0.02, P=0.87 and r=0.03, P=0.84, respectively), (Table 3, Figure 3).

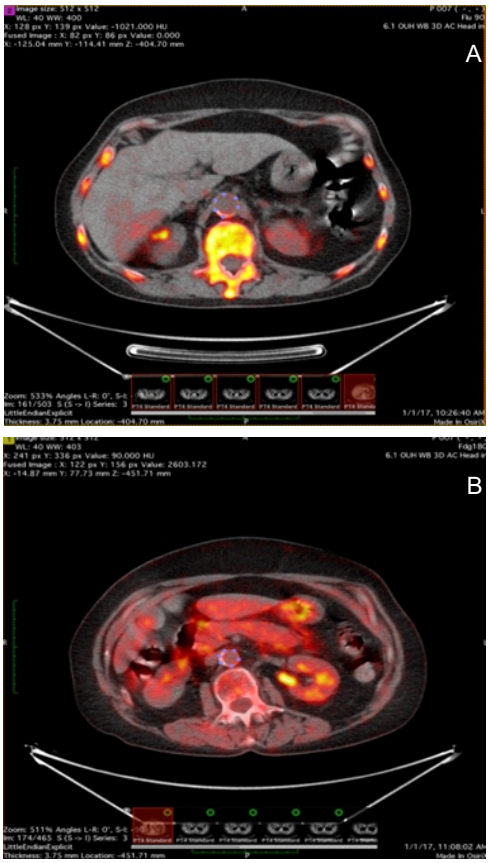

Figure 1. Region of interest (ROI) placement. One transverse slice of fused ^{18}F-NaF PET/CT (A) and ^{18}F-FDG PET/CT (B) images at the level of the abdominal aorta. The ROI is drawn around the abdominal aorta (dotted blue circumference in both A and B), and the software calculates the area of the ROI in mm^2 and the SUVmean within that ROI, which actually represents a volume equal to the product of the ROI area and the slice thickness

Table 2. *Global tracer uptake values for ^{18}F-NaF and ^{18}F-FDG in the abdominal aorta.*

	Total (N=123)	Healthy volunteers (n=78)	Patients (n=45)	P value for mean difference between groups
^{18}F-NaF	1.33± 0.37	1.26± 0.32	1.43± 0.41	0.01
^{18}F-FDG	1.50± 0.41	1.45± 0.27	1.58± 0.58	0.10

Values are mean±SD

Similarly, there was a statistically significant correlation between GTUV for ^{18}F-NaF in all subjects and 10 years FRS (r=0.30, P<0.001). However, no correlation was found between ^{18}F-FDG GTUV and 10 years FRS (r=0.01, P<0.95), (Table 4, Figure 4). In our study, ^{18}F-NaF and ^{18}F-FDG uptake were not affected by gender. (Average ^{18}F-NaF SUV mean uptake in male =1.26±0.15, female=1.38, P=0.70; Average ^{18}F-FDG SUV mean uptake in both male and female = 1.55±0.12, P=1).

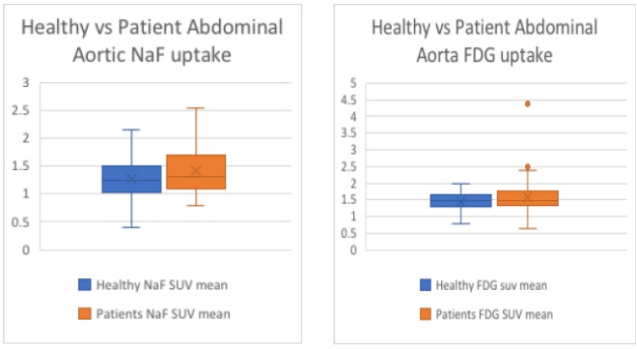

Figure 2. Box plot comparison of global tracer uptake values for ^{18}F-NaF and ^{18}F-FDG in the abdominal aorta in tow groups. GTUV for ^{18}F-NaF was significantly higher among chest pain patients than healthy volunteers (mean=1.43 vs mean=1.26, P=0.01, in left side). GTUV for ^{18}F-FDG was also higher in chest pain patients than healthy volunteers, however, this difference was not statistically significant (mean=1.58 vs mean=1.45, P=0.10 in right side.)

Table 3. *Correlations between global tracer uptake values for ^{18}F-NaF and ^{18}F-FDG in the abdominal aorta and age.*

	Total (N=123)	Healthy volunteers	Patients (n=45)	P value for r in the 3 groups
^{18}F-NaF	r=0.35	r=0.24	r=0.39	<0.001; 0.03; <0.001
^{18}F-FDG	r=0.06	r=0.02	r=0.03	0.53; 0.87; 0.84

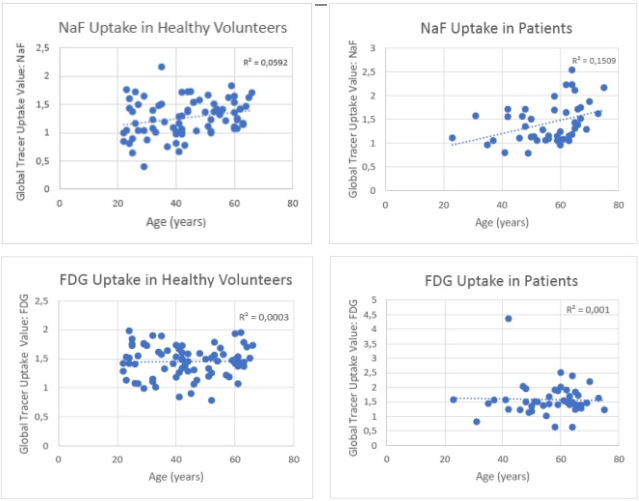

Figure 3. Correlations between global tracer uptake values (GTUV) of ^{18}F-NaF, ^{18}F-FDG and age. Significant correlations were present for ^{18}F-NaF uptake in both healthy volunteers and patients (upper panels) but not for ^{18}F-FDG in these subject groups (lower panels).

Discussion

In this study, in both healthy volunteers and patients with chest pain syndrome, abdominal aortic uptake of ^{18}F-NaF was significantly associated with age and risk factors of CVD, assessed as the 10 years FRS. This could imply that the extent of molecular calcification in the abdominal aortic wall as detected by ^{18}F-NaF PET may play a role for assessing presymptomatic and symptomatic patients suspected of or suffering from atherosclerosis. On the other hand, we did not observe a significant correlation between the uptake of ^{18}F-FDG, which is a marker of inflammation, and age or cardiovascular risk factors in this part of the aorta.

Table 4. *Correlation between global tracer uptake values for ^{18}F-NaF and ^{18}F-FDG in the abdominal aorta and Framingham 10yrs risk score.*

	Total (N=123)	Healthy volunteers	Patients (n=45)	P value for r in the 3 groups
^{18}F-NaF	r=0.30	r=0.28	r=0.31	<0.001;
^{18}F-FDG	r=0.01	r=0.02	r=0.09	0.95; 0.84; 0.53

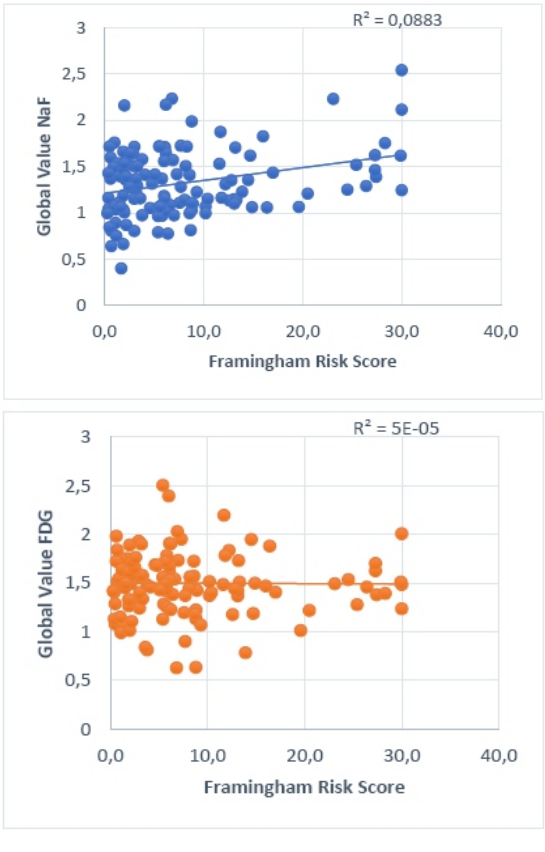

Figure 4. Correlations between global tracer uptake values (GTUV) of ^{18}F-NaF and ^{18}F-FDG and 10 years Framingham risk score (FRS). Significant correlations were present for ^{18}F-NaF uptake in total population (r=0.30, P<0.001) but not for ^{18}F-FDG (r=0.01, P=0.95) in these subject group.

Atherosclerotic plaque formation is a complicated process with multiple sequential stages. Inflammation in the vascu-

lar wall is an important stage in atherogenesis, caused by accumulation of macrophages in response to retention of lipids in the arterial intima. The macrophages in the plaque give rise to different pro-inflammatory cytokines resulting in plaque hypoxia, weakening of the fibrous cap and eventually rupture of the plaque. Plaque rupture and intra-plaque hemorrhage are the major phenomena leading to acute cerebrovascular or cardiovascular events. Plaque calcification is another important stage in the process of atherogenesis. Arterial calcification that can be measured and quantified with the use of multislice CT is a known surrogate measure of the arterial atherosclerotic burden and a marker that can predict the risk of future cardiovascular disease with reasonable certainty.

Almost all the healed rupture plaques contain calcium in their wall. Unlike macrocalcification which can be seen on the conventional CT and is a marker of plaque stability, micro-calcification detected by ^{18}F-NaF PET is beyond the capabilities of conventional CT and associated with increased risk of plaque rupture and cardiovascular events [6, 7, 13-16]. Therefore, the measurement of ^{18}F-NaF uptake as a marker of active calcification may be used to distinguish between active and inactive plaques [8, 17].

In this study, in keeping with what has been observed in other parts of the arterial system [10, 18-20], we observed that the ^{18}F-NaF uptake in the abdominal aorta was associated with higher risk of adverse cardiovascular risk factors, as measured by FRS. Our investigation confirmed Blomberg and co-workers' findings indicating that an unfavorable CVD risk profile is related to noticeable increases in vascular calcification metabolism, but not ongoing arterial inflammation in the thoracic aorta [10]. In addition, our results corroborates findings of Derlin et al. (2011), who demonstrated a correlation between cardiovascular risk factors and uptake of ^{18}F-NaF in the carotid artery [21], as well as of Dweck et al. (2012), who showed a relationship between increased coronary ^{18}F-NaF uptake and angina, higher FRS and higher rates of prior cardiovascular events [8] and, finally, Beheshti et al. (2011), who observed a significantly positive correlation between aortic ^{18}F-NaF uptake and age (Pearson's r=0.97, P= 0.004) [22].

We did not find a similar relation between ^{18}F-FDG uptake and cardiovascular risk factors. This result is in accordance with the Hetterich et al. (2016) study, which showed an increased CT-calcification in the entire aorta at 14 months repeat examination without a similar change in ^{18}F-FDG uptake [19]. Nonetheless, ^{18}F-FDG uptake in the arterial wall may still be a marker of an inflammatory phase in the process of plaque forming. Fluorine-18-FDG is being taken up by the activated pro-inflammatory macrophages which are in abundance within the unstable and ruptured plaques and are thought to contribute to degradation of the fibrous cap by secreting matrix metalloproteinases [6, 23]. In addition, increased uptake of ^{18}F-FDG could be linked to presence of aneurysms and dissection of the aorta, which are diseases related to inflammation of arterial wall tissue [24]. Viewed from this point, increase in arterial ^{18}F-FDG uptake could be related to and predictive of cardiovascular events [25]. Fluorine-18-FDG PET has also been described as a potential tool in monitoring the response to treatment with statins in patients with atherosclerosis [26]. Yun et al. (2001) were the first to report arterial ^{18}F-FDG uptake when they demonstrated an age-dependent uptake in the abdominal aorta, iliac, and proximal femoral arteries [18]. Pasha et al. (2015) showed that the ^{18}F-FDG uptake in the aorta and peripheral arteries correlates positively with age and cardiovascular risk factors in patients diagnosed with melanoma [27], perhaps due to the fact that atherosclerosis and cancer share multiple pathogenic and pathophysiologic processes [28].

A possible explanation for why we could not find a significant correlation between ^{18}F-FDG uptake and age or adverse cardiovascular risk factors and inflammation in the vessel wall is that the inflammatory phase may be shorter than post inflammatory phases. This was con-vincingly demonstrated by Meirelles et al. B (2011) who studied 100 consecutive cancer patients with ^{18}F-FDG PET/CT scans about 7 months apart. These investigators observed that 70% of patients who had aortic ^{18}F-FDG uptake at baseline had an increase on the second scan 55% of the time. Moreover, they reported that calcifications where very seldom present at the same site as ^{18}F-FDG uptake [29]. Therefore, statistically there is less probability that a plaque is being imaged in the inflammatory phase in a high-risk patient [25]. This asynchronous temporal profile of inflammatory phase versus post-inflammatory phase of atherogenesis is important and should be considered in the design of all future studies comparing ^{18}F-FDG and ^{18}F-NaF uptake with CT calcifications.

A limitation of this study was the inability to validate findings from ^{18}F-FDG and ^{18}F-NaF PET imaging with histological data. Because the PET parameters introduced in this study aim to characterize arterial wall changes at the microscopic level, it would, of course be useful to confirm if the inferred changes were actually present histologically. In addition, the interpretation of our results is limited by the cross-sectional study design, which precludes the study of temporal relationships. A longitudinal study to more directly assess the relationship between the inflammation and calcification phases is warranted to reveal the existence of an early corresponding inflammatory phase preceding early arterial wall microcalcification. Lastly, our method of quantification does not correct for the partial volume effect, which causes underestimation of tracer uptake in small regions of interest [30, 31]. Future longitudinal studies with histological data are needed to validate these findings.

In conclusion, ^{18}F-FDG and ^{18}F-NaF uptake in the abdominal aorta could easily be quantified. The global uptake of ^{18}F-NaF in this part of the aorta was positively associated with age and 10 years FRS, whereas the global uptake of ^{18}F-FDG was not. Causes of this apparent discrepancy should be sought in carefully designed prospective studies scheduled to reveal the temporal context and geographical agreement between abnormal uptake of ^{18}F-NaF and ^{18}F-FDG in the wall of the abdominal aorta.

The authors declare that they have no conflicts of interest.

Bibliography

1. Hayden MR, Tyagi SC, Kolb L et al. Vascular ossification-calcification in metabolic syndrome, type 2 diabetes mellitus, chronic kidney disease, and calciphylaxis-calcific uremic arteriolopathy: the emerging role of sodium thiosulfate. *Cardiovasc Diabetol* 2005; 4: 4.

2. Herrington W, Lacey B, Sherliker P et al. Epidemiology of atherosclerosis and the potential to reduce the global burden of atherothrombotic disease. *Circ Res* 2016; 118: 535-46.
3. Matter CM, Stuber M, Nahrendorf M. Imaging of the unstable plaque: how far have we got? *Eur Heart J* 2009; 30: 2566-74.
4. Jander S, Sitzer M, Schumann R et al. Inflammation in high-grade carotid stenosis: a possible role for macrophages and T cells in plaque destabilization. *Stroke* 1998; 29: 1625-30.
5. Chen W, Dilsizian V. Targeted PET/CT imaging of vulnerable atherosclerotic plaques: microcalcification with sodium fluoride and inflammation with fluorodeoxyglucose. *Curr Cardiol Rep* 2013; 15: 364.
6. McKenney-Drake ML, Moghbel MC, Paydary K et al. ^{18}F-NaF and ^{18}F-FDG as molecular probes in the evaluation of atherosclerosis. *Eur J Nucl Med Mol Imaging* 2018; 45(12): 2190-200.
7. Derlin T, Richter U, Bannas P et al. Feasibility of ^{18}F-sodium fluoride PET/CT for imaging of atherosclerotic plaque. *J Nucl Med* 2010; 51: 862.
8. Dweck MR, Chow MW, Joshi NV et al. Coronary arterial ^{18}F-sodium fluoride uptake: a novel marker of plaque biology. *J Am Coll Cardiol* 2012; 59: 1539-48.
9. members ATF, Erbel R, Aboyans V et al. 2014 ESC Guidelines on the diagnosis and treatment of aortic diseases: Document covering acute and chronic aortic diseases of the thoracic and abdominal aorta of the adult The Task Force for the Diagnosis and Treatment of Aortic Diseases of the European Society of Cardiology (ESC). *Eur Heart J* 2014; 35: 2873-926.
10. Blomberg BA, De Jong PA, Thomassen A et al. Thoracic aorta calcification but not inflammation is associated with increased cardiovascular disease risk: results of the CAMONA study. *Eur J Nucl Med Mol Imaging* 2017; 44: 249-58.
11. Blomberg BA, Thomassen A, Takx RA et al. Delayed ^{18}F-fluorodeoxyglucose PET/CT imaging improves quantitation of atherosclerotic plaque inflammation: results from the CAMONA study. *J Nucl Cardiol* 2014; 21: 588-97.
12. Blomberg BA, Thomassen A, Takx RA et al. Delayed sodium ^{18}F-fluoride PET/CT imaging does not improve quantification of vascular calcification metabolism: Results from the CAMONA study. *J Nucl Cardiol* 2014; 21: 293-304.
13. Huang H, Virmani R, Younis H et al. The impact of calcification on the biomechanical stability of atherosclerotic plaques. *Circulation* 2001; 103: 1051-6.
14. Vengrenyuk Y, Carlier S, Xanthos S et al. A hypothesis for vulnerable plaque rupture due to stress-induced debonding around cellular microcalcifications in thin fibrous caps. *Proc Natl Acad Sci USA* 2006; 103(40): 14678-83.
15. Derlin T, Habermann CR, Hahne JD et al. Quantification of ^{18}F-FDG uptake in atherosclerotic plaque: impact of renal function. *Ann Nucl Med* 2011; 25: 586-91.
16. Derlin T, Tóth Z, Papp L et al. Correlation of inflammation assessed by ^{18}F-FDG PET, active mineral deposition assessed by ^{18}F-fluoride PET, and vascular calcification in atherosclerotic plaque: a dual-tracer PET/CT study. *J Nucl Med* 2011; 52: 1020.
17. Joshi NV, Vesey AT, Williams MC et al. ^{18}F-fluoride positron emission tomography for identification of ruptured and high-risk coronary atherosclerotic plaques: a prospective clinical trial. *Lancet* 2014; 383: 705-13.
18. Yun M, Yeh D, Araujo LI Jet al. F-18 FDG uptake in the large arteries: a new observation. *Clin Nucl Med* 2001; 26: 314-9.
19. Hetterich H, Rominger A, Walter L et al. Natural history of atherosclerotic disease progression as assessed by ^{18}F-FDG PET/CT. *Int J Cardiovasc Imaging* 2016; 32: 49-59.
20. Joshi FR, Rajani NK, Abt M et al. Does vascular calcification accelerate inflammation?: a substudy of the dal-PLAQUE trial. *J Amer Coll Cardiol* 2016; 67: 69-78.
21. Derlin T, Wisotzki C, Richter U et al. In vivo imaging of mineral deposition in carotid plaque using ^{18}F-sodium fluoride PET/CT: correlation with atherogenic risk factors. *J Nucl Med* 2011; 52: 362.
22. Beheshti M, Saboury B, Mehta NN et al. Detection and global quantification of cardiovascular molecular calcification by fluoro18-fluoride positron emission tomography/computed tomography-a novel concept. *Hell J Nucl Med* 2011; 14: 114-20.
23. Hansson GK. Inflammation, atherosclerosis, and coronary artery disease. *N Engl J Med* 2005; 352: 1685-95.
24. Golestani R, Sadeghi MM. Emergence of molecular imaging of aortic aneurysm: implications for risk stratification and management. *J Nucl Cardiol* 2014; 21: 251-67.
25. Blomberg BA, Høilund-Carlsen PF. ^{18}F-fluorodeoxyglucose PET imaging of atherosclerosis. *PET clinics* 2015; 10: 1-7.
26. Tahara N, Kai H, Ishibashi M et al. Simvastatin attenuates plaque inflammation: evaluation by fluorodeoxyglucose positron emission tomography. *J Am Coll Cardiol* 2006; 48: 1825-31.
27. Pasha AK, Moghbel M, Saboury B et al. Effects of age and cardiovascular risk factors on ^{18}F-FDG PET/CT quantification of atherosclerosis in the aorta and peripheral arteries. *Hell J Nucl Med* 2015; 18(1): 5-10.
28. Tapia-Vieyra JV, Delgado-Coello B, Mas-Oliva J. Atherosclerosis and cancer; a resemblance with far-reaching implications. *Arch Med Res* 2017; 48: 12-26.
29. Meirelles GSP, Gonen M, Strauss HW. ^{18}F-FDG uptake and calcifications in the thoracic aorta on positron emission tomography/computed tomography examinations: frequency and stability on serial scans. *J Thor Imag* 2011; 26: 54-62.
30. Alavi A, Werner TJ, Høilund-Carlsen PF. PET-based imaging to detect and characterize cardiovascular disorders: Unavoidable path for the foreseeable future. Springer, 2018.
31. Alavi A, Werner TJ, Høilund-Carlsen PF, Zaidi H. Correction for Partial Volume Effect Is a Must, Not a Luxury, to Fully Exploit the Potential of Quantitative PET Imaging in Clinical Oncology. *Mol Imag Biol* 2018; 20: 1-3.