Atherosclerosis 260 (2017) 41–46

Contents lists available at ScienceDirect

Atherosclerosis

journal homepage: www.elsevier.com/locate/atherosclerosis

Atherosclerotic plaque metabolism in high cardiovascular risk subjects – A subclinical atherosclerosis imaging study with ^{18}F-NaF PET-CT

Manuel de Oliveira-Santos [a, b, c, *], Miguel Castelo-Branco [b, c], Rodolfo Silva [b], Andreia Gomes [b], Nuno Chichorro [b, c], Antero Abrunhosa [b, c], Paulo Donato [b, c], João Pedroso de Lima [c], Mariano Pego [a], Lino Gonçalves [c], Maria João Ferreira [a, b, c]

[a] University Hospitals of Coimbra, Cardiology, Praceta Prof. Mota Pinto, 3000-075, Coimbra, Portugal
[b] Institute of Nuclear Sciences Applied to Health - Faculty of Medicine of the University of Coimbra, Azinhaga de Santa Comba, 3000-548, Coimbra, Portugal
[c] Faculty of Medicine of the University of Coimbra, Rua Larga, 3004-504, Coimbra, Portugal

ARTICLE INFO

Article history:
Received 2 November 2016
Received in revised form
7 March 2017
Accepted 8 March 2017
Available online 10 March 2017

Keywords:
Sodium fluoride
Atherosclerosis
Positron-emission tomography
Molecular imaging
Cardiovascular diseases

ABSTRACT

Background and aims: Atherosclerotic plaque molecular imaging with ^{18}F-sodium fluoride (NaF) in positron emission tomography with computed tomography (PET-CT) provides potential discrimination between active unstable microcalcification and established dormant calcification. We aimed to study ^{18}F-NaF atherosclerotic plaque uptake in high cardiovascular (CV) risk participants and its associations with CV risk factors, coronary calcium score and thoracic fat volume.

Methods: High CV risk hypertensive individuals from a single centre were prospectively scanned with ^{18}F-NaF-PET-CT in the coronary, aortic and carotideal arteries. Atherosclerotic plaque ^{18}F-NaF uptake was expressed as Corrected Uptake per Lesion (CUL): maximum standard uptake value in each vascular territory subtracted by mean blood pool activity.

Results: Mean age was 64 years, 56% male and 96% Caucasian (n = 25). Ninety six per cent of the subjects showed ^{18}F-NaF uptake in the aorta (CUL 0.9 ± 0.3), 40% in the carotid arteries (median CUL 0.0, IQR 0.0–0.7) and 64% in the coronary arteries (0.4, IQR 0.0–0.6). Individuals with ≥ five risk factors (60%) had increased overall ^{18}F-NaF uptake (1.1 ± 0.3 *vs.* 0.7 ± 0.3, $p < 0.01$), which was positively correlated with predicted fatal CV risk - SCORE (r = 0.49, $p = 0.01$). There was no correlation between ^{18}F-NaF uptake in the coronary arteries and calcium score ($p = 0.87$). Thoracic fat was moderately correlated with overall CUL (r = 0.41, $p = 0.04$).

Conclusions: In a high CV risk group, ^{18}F-NaF atherosclerotic plaque uptake was related to the burden of CV risk factors and thoracic fat volume, but there was no association between coronary uptake and calcium score.

1. Introduction

Cardiovascular disease (CVD) is the main cause of mortality in developed countries; its prevention is challenging. The methods to identify high-risk individuals range from clinical assessment of risk factors to non-invasive imaging of the atherosclerotic plaque [1]. Advances in molecular imaging of the atherosclerotic plaque enhanced the study of its pathophysiology, in particular with positron emission tomography with computed tomography (PET-CT). The marker ^{18}F-sodium fluoride (NaF) has been studied in arterial plaque imaging as an *in vivo* marker of on-going calcification [2–4]. The ^{18}F ions deposit in the bone by exchange of hydroxyl group on the surface of the hydroxyapatite matrix to form fluoroapatite, which implies that this tracer detects areas of active calcification and osteogenic remodelling [5]. Thus, ^{18}F-NaF labelled PET-CT can non-invasively detect microcalcification in active unstable atherosclerosis [6].

Coronary imaging with ^{18}F-NaF labelled PET-CT was recently described and proposed to be able to discriminate between active and inactive coronary calcification, possibly identifying high-risk patients [7]. Joshi et al. tested this hypothesis and reported that coronary plaque ^{18}F-NaF uptake in stable angina patients correlated

* Corresponding author. University Hospitals of Coimbra, Cardiology, Praceta Prof. Mota Pinto, 3000-075, Coimbra, Portugal.
E-mail address: oliveirasantos@uc.pt (M. Oliveira-Santos).

http://dx.doi.org/10.1016/j.atherosclerosis.2017.03.014
0021-9150/

with high-risk features shown invasively with intravascular ultrasound. Accordingly, the *culprit* plaques of myocardial infarction displayed greater ^{18}F-NaF uptake and ^{18}F-NaF was superior to ^{18}F-FDG in identifying high-risk plaques [8]. Although this data are suggestive that PET-CT ^{18}F-NaF coronary imaging may identify vulnerable patients for vascular events, prospective studies are required to show whether it can be used to predict CVD complications [9].

The proportion of coronary, aortic and carotideal plaques with ^{18}F-NaF uptake in individuals with no clinically apparent CVD, but with high CV risk, has not been reported. We aimed to assess the proportion of ^{18}F-NaF positive coronary, aortic and carotideal plaques in high CV risk individuals and explore their correlation with traditional CV risk factors, coronary artery calcium score and thoracic fat volume in high CV risk subjects.

2. Materials and methods

2.1. Population

Patients followed at the Arterial Hypertension outpatient clinic of *Centro Hospitalar e Universitário de Coimbra* were prospectively screened and selected if they met *all* of the following inclusion criteria: a) older than 40 years; b) provided written informed consent; c) considered to be at high or very high CV risk according to the European Society of Cardiology guidelines [1] (any of: predicted fatal CV event at 10 years $\geq$ 5% (SCORE tables for low-risk countries); chronic kidney disease with glomerular filtration rate (GFR) under 60 mL/min (Modification of Diet in Renal Disease equation - MDRD); diabetes mellitus (type 1 or 2); markedly elevated single risk factors).

We excluded patients with previous CV events, malignant neoplasms in the past five years, chronic inflammatory disease and pregnant women or in child bearing age without contraceptive use. Patients with previous statin therapy stopped treatment for two weeks before enrolment as previously described [10], for better assessment at baseline.

The protocol was approved by the Ethics Committee of Faculty of Medicine of the University of Coimbra and written according to Good Clinical Practice Guidelines and the Declaration of Helsinki.

2.2. Baseline examination

After obtaining the signed informed consent, the clinician performed a clinical questionnaire and standard physical examination, followed by peripheral blood drawing. CV risk was estimated according to SCORE equations [1] and the American Heart Association pooled cohort risk equation [11]. Patients' medical history and CV risk factors were recorded, as well as physical examination findings, including age, race, gender, smoking status (current, past, quantification with pack-years), diabetes mellitus (type 1, 2, pre-diabetes), family history of premature coronary heart disease (first degree: men < 55 and women < 65 years old), relevant past medical history, blood pressure, heart rate, weight and height. Levels of total cholesterol, high and low-density lipoprotein cholesterol (HDL and LDL), triglycerides, creatinine, creatine kinase, alanine amino-transferase, aspartate amino-transferase, gamma-glutamyl transpeptidase, alkaline phosphatase, glycated hemoglobin, fasting glucose, high-sensitivity C-reactive protein and haemoglobin were determined. Hyperlipidemia was defined as either one of: total cholesterol above 190 mg dL^{-1}, LDL above 115 mg dL^{-1}, HDL under 40 mg dL^{-1} in men and 46 mg dL^{-1} in women, triglycerides above 150 mg dL^{-1}, patients under lipid lowering treatment.

2.3. ^{18}F-NaF labelled PET-CT

Patients underwent whole body ^{18}F-NaF-PET-CT for identification of coronary, carotideal, thoracic and abdominal aorta arteries plaques and quantification of ^{18}F-NaF uptake between May 2014 and June 2015.

The protocol consisted in the administration of 185 MBq ^{18}F-NaF intravenously, followed by an attenuation correction CT scan and PET imaging after 60 min (Gemini GXL Philips 16 PET/CT system). The coronary imaging protocol consisted of a cardiac-gated PET-CT with a 10 min electrocardiogram-gated acquisition with attenuation correction. An iterative reconstruction of cardiac PET scans was performed in multiple phases with the diastolic phase between 50 and 75% used for analysis. To assess aorta and carotid vessels, a whole-body acquisition was performed (the bounding box was defined by the base of the skull, the coccygeal bone, the sternum, the spinous process of L5 and the sacroiliac joints).

Two-dimensional regions of interest were drawn around all major epicardial coronary vessels and around the major vessels on three millimetres axial slices. Quantification of ^{18}F-NaF uptake was performed by measuring the maximum standard uptake value (SUV) in the region of interest (the decay-corrected tissue concentration of the tracer divided by the injected dose per bodyweight). The lesion SUV was then corrected for blood pool activity (the average of five mean SUV in the mid lumen of superior vena cava) by calculating the difference between lesion and superior vena cava SUV (corrected uptake per lesion - CUL) [12]. Scans were reviewed and analysed by experienced observers blinded to the clinical diagnosis.

Quantification of coronary calcium score was performed by one experienced blinded reader with an off-line workstation with a dedicated software for calcium scoring – GE Healthcare Advantage Workstation 4.2. Thoracic fat volume was assessed in CT using and automated software: a predefined threshold of −190 to −30 Hounsfield units was applied to identify the voxels consisting of fat. These voxels were summed to obtain the volume in millilitres. The superior limit for thoracic fat measurements was defined by the bifurcation of pulmonary artery, the inferior by the end of pericardial sac, the anterior by the sternum and the posterior by the ribs and vertebral column [13]. After manually tracing the region of interest in CT sections, the software automatically interpolated between the traced sections using the thresholds already described.

2.4. Statistical analysis

Continuous data were described using the mean ± standard deviation or median (interquartile range) according to the normality of the distribution, and compared with Student T test or Mann-Whitney *U* test, respectively. Correlations were analysed with Pearson or Spearman correlation tests according to the normality. Categorical variables were described as counts (percent). We performed a reliability analysis of two independent observers for radiotracer uptake and thoracic fat volume using intraclass correlation coefficient (Cronbach's Alpha). The analysis was performed with SPSS Statistics for Macintosh software, version 20.0 (IBM).

3. Results

The demographic and clinical characteristics of the 25 patients are depicted in Table 1, and the biochemical parameters in Table 2.

The 10-year expected CV risk according to SCORE was 4.3 ± 2.9% and 28.8 ± 18.9% with the ACC/AHA pooled cohort equation. Median thoracic fat volume was 173.1 (110.7–200.4) mL and coronary calcium score 0.0 (0.0–11.0).

Table 1
Demographic and clinical characteristics.

Age (years)	63.9 ± 8.6
Male sex – no. (%)	14 (56.0)
Caucasian – no. (%)	24 (96.0)
Weight (Kg)	85.1 ± 21.9
Body mass index (Kg.m^{-2})	29.6 (26–37)
Waist circumference (cm)	103.5 (95–122)
Systolic blood pressure (mmHg)	157.4 ± 26.8
Diastolic blood pressure (mmHg)	80.0 (70–90)
Heart rate (beats per minute)	65 (60–70)
Medical history – no. (%)	
Type 2 diabetes	17 (68.0)
Hyperlipidemia	18 (72.0)
Hypertension	25 (100.0)
Current smoker	2 (8.0)
Past smoker	3 (12.5)
Family history of CHD	4 (16.0)
Metabolic syndrome (IDF)	20 (80.0)
Abdominal obesity (>94/80 cm)	24 (96.0)
Obesity (BMI> 30 kg m^2)	13 (52.0)
CKD	6 (24.0)
Medication – no. (%)	
ACE inhibitor	10 (40.0)
Angiotensin-receptor blocker	15 (60.0)
Beta-blocker	19 (76.0)
Calcium-channel blocker	20 (80.0)
Diuretic	20 (80.0)
Aldosterone antagonist	7 (28.0)
Statin	17 (68.0)
Fibrate	1 (4.0)
Metformin	13 (52.0)
DPP-4 inhibitors	10 (40.0)
Antithrombotic	6 (24.0)

CHD, coronary heart disease; CKD, chronic kidney disease; ACE inhibitors, angiotensin-converting-enzyme inhibitors; DPP-4 inhibitors, dipeptidyl peptidase 4 inhibitors.

Table 2
Biochemistry parameters.

Total cholesterol (mg.dL^{-1})	207.4 ± 39.1
Low-density lipoprotein cholesterol (mg.dL^{-1})	141.7 ± 30.3
High-density lipoprotein cholesterol (mg.dL^{-1})	48.6 ± 10.3
Triglycerides (mg.dL^{-1})	113.0 (85–172)
Fasting glucose (mg.dL^{-1})	115.0 (95–131)
Glycated hemoglobin (%)	6.0 (5.6–6.2)
Glycated hemoglobin in diabetic subgroup (%)	6.0 (6.0–7.2)
High-sensitivity C-reactive protein (mg.dL^{-1})	0.32 (0.14–0.94)
Creatinine (mg.dL^{-1})	1.0 (0.76–1.00)
Glomerular filtration rate (mL.min^{-1})	86.3 ± 29.9
Creatine kinase (U.L^{-1})	109.0 (81–147)
Alanine amino-transferase (U.L^{-1})	25.0 (18–33)
Aspartate amino-transferase (U.L^{-1})	25.0 (20–29)
Gamma-glutamyl transpeptidase (U.L^{-1})	45.0 (24–78)
Alkaline phosphatase (U.L^{-1})	82.0 (66–97)
Haemoglobin (g.dL^{-1})	14.0 [13–15]

Table 3
Maximum corrected-uptake-per-lesion (CUL).

Location	Maximum CUL
Ascending aorta	0.6 (0.5–0.8)
Aortic arch	0.7 ± 0.3
Descending aorta	0.7 ± 0.4
Aortic artery	0.9 ± 0.3
Carotid arteries	0.0 (0.0–0.7)
Coronary arteries	0.4 (0.0–0.6)
Any location maximum	0.9 ± 0.4

The maximum CUL in each vascular territory is shown in Table 3. We identified ^{18}F-NaF-positive plaques when maximum SUV was higher than superior vena cava maximum SUV. Ninety six per cent of the subjects showed ^{18}F-NaF uptake in the aorta, 40% in the carotid arteries and 64% in the coronary arteries (Fig. 1).

Considering the maximum ^{18}F-NaF uptake in any location, individuals with five or more risk factors (60%; defined as hypertension, dyslipidemia, type 2 diabetes, GFR<60, obesity, abdominal obesity, family history of CHD, current smoker) had increased CUL compared to those with lower risk factors burden (1.1 ± 0.3 *vs.* 0.7 ± 0.3, $p < 0.01$) (Fig. 2). Again, maximum CUL in any location was positively correlated with SCORE (R = 0.49, $p = 0.01$). We did not find significant correlation between the measures of radiotracer uptake and lipid profile or high-sensitivity C-reactive protein.

Regarding coronary calcium score, it was correlated to the risk of fatal CV event predicted by SCORE (r = 0.55, $p < 0.01$), but there was no correlation with plaque ^{18}F-NaF uptake. In particular, of the 17 individuals with zero calcium score, 12 had significant ^{18}F-NaF uptake in the coronary arteries. For those with a calcium score between 11 and 100 (five subjects), three showed significant uptake. Only one of the two individuals with calcium score >100 had fluoride uptake. Thus, there was no correlation between ^{18}F-NaF uptake in the coronary arteries and calcium score ($p = 0.87$).

On the other hand, thoracic fat was moderately correlated with maximum CUL in any of the vascular territories (r = 0.41, $p = 0.04$) (Fig. 3).

The intraclass correlation coefficient for two independent observations was 0.99 (95% confidence interval 0.99–0.99) for radiotracer uptake and 0.99 (95% confidence interval 0.79–0.99) for thoracic fat volume analysis.

4. Discussion

In this work, we performed imaging of the coronary, carotideal and aortic arteries of individuals with high CV risk, but no clinically apparent CVD, with ^{18}F-NaF PET-CT. With this exploratory analysis of 25 subjects under treatment for arterial hypertension, we report a significant proportion of arterial plaque ^{18}F-NaF uptake, mainly in the aorta (96%), followed by the coronaries (64%) and carotid arteries (40%). These features were already published in retrospective analysis of bone scans in oncological patients, with somewhat lower proportions of fluoride uptake (60% total in large vessels, 35% in the carotid arteries) [3,14].

We analysed the ^{18}F-NaF uptake per lesion, and corrected it to blood pool activity by subtracting the superior vena cava SUV from lesion SUV - CUL. We used maximum SUV rather that mean SUV due to its higher reproducibility. Previous studies used predominantly the ratio of maximum SUV to mean blood pool activity SUV (tissue-to-background ratio – TBR); however, this method has been criticized for being too dependent on blood pool activity variations [15]. This was also the choice in the CAMONA study, a prospective study of vascular calcification activity with ^{18}F-NaF PET-CT, which proposed the method we are currently using, for being less dependent on blood activity [12].

In this primary prevention population with high CV risk, we detected an association between ^{18}F-NaF uptake and the burden of CV risk factors, as well as the SCORE risk estimator. The use of a dichomotous variable (more than five CV risk factors) has a cost by implying loss of information, instead of a policotomic approach, but has the benefit of preserved statistical power. There were no correlations with individual risk markers, such as cholesterol levels or high-sensitivity C-reactive protein.

This association is consistent with data from oncologic patients, namely with positive correlations between radiotracer uptake in large vessels both with CV risk factors and the Framingham CV risk score [2,4], but also with coronary uptake [7,16]. This connection with CV risk markers is in line with the concept ^{18}F-NaF PET-CT

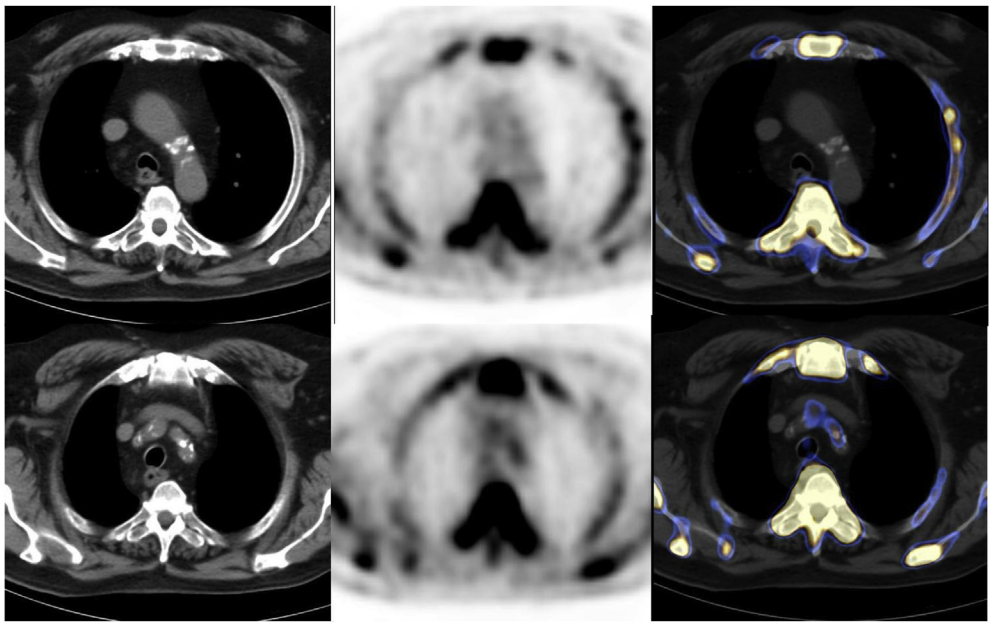

Fig. 1. Fusion ^{18}F-NaF-PET-CT images, depicting calcified plaques with no uptake (top) and with ^{18}F-NaF uptake (bottom).

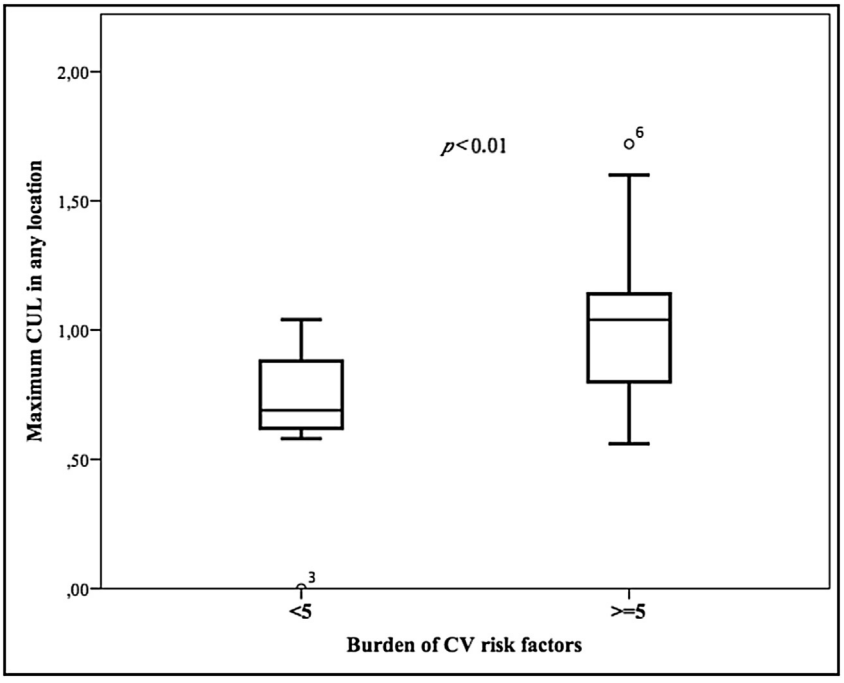

Fig. 2. ^{18}F-NaF uptake in any location (CUL) according to the number of CV risk factors.

arterial plaque imaging is one of the most promising methods to detect unstable plaques [17]. In fact, this radiotracer detects areas of active micro-calcification, thus offering molecular information on plaque's metabolism, contrasting to the sole detection of established macro-calcification from CT studies [18]. As suggested by recent studies, micro-calcification activity is probably correlated with clinical instability [8]. However, larger prospective studies are necessary to assess the prognostic implications of ^{18}F-NaF uptake in CV risk estimation. We found no correlation between coronary artery calcium score and coronary ^{18}F-NaF uptake, probably due to the fact that these methods identify different pathophysiological stages (the latter targeting active pathology) in the atheroma calcification process.

To our knowledge, we report for the first time a positive correlation between ^{18}F-NaF uptake and thoracic fat volume. There are data linking the volume and distribution of epicardial fat to obstructive coronary heart disease [19–21], CV clinical outcomes [22], myocardial ischemia [23] and also coronary plaque vulnerability [24]. Hypothetically, as ^{18}F-NaF marks micro-calcification in metabolically active plaques, possibly unstable, it might as well correlate with thoracic fat volume, which is associated with atherosclerosis and pro-inflammatory state.

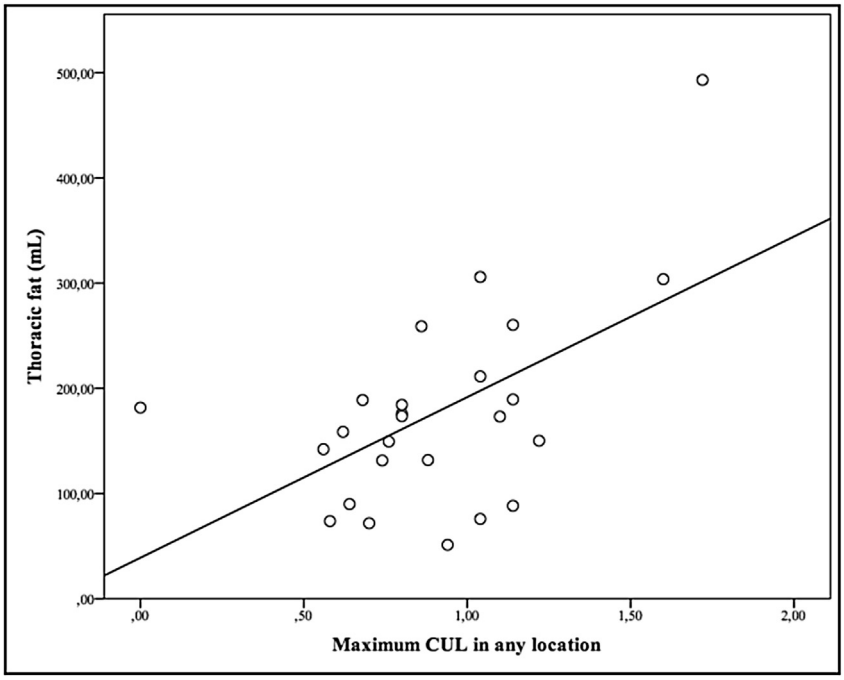

Fig. 3. Correlation between thoracic fat volume and ^{18}F-NaF uptake in any location (r = 0.41, p = 0.04).

Risk stratification systems to tailor primary prevention strategies in cardiovascular diseases are not perfect, and we still need to find methods to identify high risk patients who benefit from aggressive lipid lowering therapy. Potentially, this technology could be used in the future to select CV naive individuals who are candidates for high intensity statin therapy, as it provides both anatomical and functional information on the active atheroma burden.

We identify some limitations of the present study: the relatively small number of subjects and the multiple measures performed in this exploratory analysis may limit the inferences on external validity of the results, which need confirmation in larger populations. Secondly, we acknowledge the limited spatial resolution of the PET system and the methods for radiotracer uptake quantification should still be optimized; further work should lead to improved standardization.

In a study of individuals with high CV risk, but no clinically apparent CVD, under treatment for arterial hypertension, we found a significant proportion of atherosclerotic plaques in the coronary, carotideal and aortic arteries with ^{18}F-NaF uptake. There was an association between ^{18}F-NaF uptake and the burden of CV risk factors and thoracic fat volume, but not with coronary artery calcium score. The ^{18}F-NaF PET-CT is a potentially valuable tool in CV risk stratification.

Conflict of interest

The authors declared they do not have anything to disclose regarding conflict of interest with respect to this manuscript.

Financial support

Funding sources: Institute of Nuclear Sciences Applied to Health (ICNAS) - Faculty of Medicine of the University of Coimbra.

Author contributions

MOS, MCB and MJF designed the study, performed the experiments, analysed the results and interpreted the data. MJF is the chief investigator. LG, MP and JPL participated in the study design and patient recruitment. RF, PD and AG collected the data and analysed it. NC and AA interpreted the data. MOS drafted the first and subsequent versions of this report with key input form MCB, MJF and LG, and revisions from all other authors, who reviewed and approved the final submitted report.

Acknowledgments

We acknowledge the contribution of Rui Ferreira (ICNAS) in data analysis and the support of ICNAS staff.

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