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What is the natural history of ^{18}F-FDG uptake in arterial atheroma on PET/CT? Implications for imaging the vulnerable plaque

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ABSTRACT

Purpose: Increased uptake of ^{18}F-fluorodeoxyglucose (^{18}F-FDG) in atherosclerotic plaque on Positron Emission Tomography (PET), predicts vulnerability. Recent studies have shown that the PET signal is reproducible over a 2-week period and as a result drug trials are underway. However, the natural history of these lesions is unknown. The aim of this study is determine the natural history of increased vascular wall uptake of ^{18}F-fluorodeoxyglucose (^{18}F-FDG).

Methods: Following institutional ethics committee approval, we retrospectively examined PET/CT images of patients from our Institution that had at least 4 examinations in the last 5 years. This represented 205 studies in total, from 50 patients (29 men, 21 women, mean age 49.4 ± 12.1 years, mean 5.1 ± 1.7 studies/patient). The mean follow-up was 27.2 ± 11.8 months. The carotids and the aorta were evaluated for increased ^{18}F-FDG uptake with a maximum Standardized Uptake Value (SUV_{max}) >2.5, and >3.0, and calcification. Plots of SUV_{max} and Hounsfield units (HU) were made versus time.

Results: The initial prevalence of increased focal arterial ^{18}F-FDG uptake was 17/50 patients and of arterial calcification 19/50. 132 sites of ^{18}F-FDG uptake in total were observed longitudinally. ^{18}F-FDG vascular uptake did not persist with time. There was no correlation between ^{18}F-FDG uptake and HU. No calcifications developed at sites of focal increased ^{18}F-FDG uptake.

Conclusions: Arterial lesions with increased ^{18}F-FDG uptake represent transient phenomena. This data is important for the interpretation of findings of clinical trials using arterial ^{18}F-FDG uptake as an imaging biomarker to monitor pharmacological intervention.

1. Introduction

The concept of the vulnerable arterial plaque has been increasingly recognized [1]. Successfully imaging such lesions *in vivo* would have a major impact on the diagnosis, prognosis and therapeutic monitoring of cardiovascular disease. There is increasing evidence that ^{18}F-fluorodeoxyglucose (^{18}F-FDG) Positron Emission Tomography (PET) has potential to non-invasively detect and quantify plaque inflammation and instability in humans [2,3] with histological validation that there are raised inflammatory markers at these sites [2,3]. As a continuum of this work, a study was published on near-term (2 weeks) reproducibility of the technique [4] with recommendations for clinical trials using ^{18}F-FDG PET as a potential biomarker to monitor therapeutic intervention [5,6]. However the pattern of uptake, changes in approximately half of patients over longer periods of time [7]. These changes in uptake must be considered when the use of ^{18}F-FDG vascular imaging is suggested to define the efficacy of therapy [8], since the longer term natural history of arterial lesions with increased ^{18}F-FDG uptake on PET is unknown. Indeed, it has been postulated that such uptake in these arterial lesions may be transient [9]. In order to test this clinically critical hypothesis, a longitudinal study has been recommended where it would be predicted that over time plaques that had increased ^{18}F-FDG uptake originally would lose their avidity [9]. However to test this theory prospectively would be ethically difficult, both with respect to the required repeated exposure to ionizing radiation and withholding of treatment from symptomatic patients.

We therefore performed retrospective longitudinal ^{18}F-FDG vascular measurements on patients to evaluate the natural history of avid arterial plaques on PET/computed tomography (CT).

Abbreviations: ^{18}F-FDG^{18}, F-fluorodeoxyglucose; PET, Positron Emission Tomography; CT, computed tomography; CRP, C-reactive protein; MBq, MegaBecquerel; SUV, standardized uptake value; SD, standard deviation; HU, Hounsfield unit.

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2. Materials and methods

2.1. Patients

We retrospectively examined PET/CT images from all the patients presenting to our institution in the last 4 years, who had had a minimum of 4 examinations. There were 50 patients (29 men, 21 women, mean age at presentation 49.4. ± 12.1, with an average of 5.1 ± 1.7 studies per patient). This represented 205 PET/CT studies in total. The local institutional ethics committee approved the research protocol. All the patients were referred for tumour staging, therapy monitoring or re-staging. Their medical charts were reviewed to determine their cardiovascular risk factors, history and subsequent cardiovascular events.

2.2. Image acquisition

Images were acquired 1 h after injecting 370 MBq of ^{18}F-FDG using combined GE Discovery LS PET/CT, Discovery STE or DVCT scanners (GE Healthcare, Chalfont St Giles, UK). Whole-body examinations were performed with the patient supine. CT was performed using 4, 16 or 64 detectors, a pitch of 1.5, and a 3.75–5 mm collimation, depending on the generation of the CT scanner. The CT exposure factors for all examinations were 140 kVp and 80 mA in 0.8 s. Maintaining patient position, a whole-body PET emission scan was performed and covered an area identical to that by CT, viz. from skull base to mid-thigh. All acquisitions were carried out in 2D-mode (5-min/bed position). PET images were reconstructed using CT for attenuation correction. Transaxial emission images of 4.3 mm × 4.3 mm × 4.25 mm were reconstructed using ordered subsets expectation maximization with two iterations and 28 subsets.

2.3. Image analysis

PET/CT images of the full length of the carotids and aorta were reviewed for focal ^{18}F-FDG activity that followed arterial contours on the fused images in 3 orthogonal planes. The intensity of ^{18}F-FDG uptake was quantified by measuring the maximum standardized uptake value (SUV_{max}). A region of interest was placed on each axial image of the same diameter as the vessel under analysis. The maximum pixel activity within the vessel wall was recorded if greater than 2.5 (Fig. 1) and greater than 3.0. These values of 2.5 and 3.0 were chosen after a calculation of blood pool SUV, and noise in the image (see Appendix A). The CT number in Hounsfield units (HU) of the vessel wall at these sites were also recorded. Linear and diffuse patterns of increased ^{18}F-FDG uptake as described in arteritis [3] would not be included for further evaluation. The carotids, aorta and coronary arteries were evaluated visually for sites of vascular calcification.

By examining the appearances of these vascular ^{18}F-FDG avid sites, at the same anatomical position, as defined by the CT portion of the studies, on prior and subsequent studies, plots of SUV_{max} and Hounsfield units versus time were created (Fig. 2).

To determine the variability of the SUV measurements, images from the repeat examinations of 10% of PET/CT studies were re-analyzed, several weeks apart, in a blinded manner.

2.4. Statistical analysis

Data are presented as mean ± standard deviation. The relationship between CT calcifications and increased vascular ^{18}F-FDG uptake was examined with respect to each other, age, sex, cardiovascular risk factors, i.e. hypertension, diabetes, hypercholesterolaemia, smoking history, and coronary artery calcification, and any chemotherapy or radiotherapy, using Fisher's exact test for categorical data, and Pearson's correlation and the unpaired *t*-test for continuous data. To investigate the relationship between the number of FDG avid sites on the first scan with the total number of FDG avid sites on subsequent scans, a Spearman rank correlation was performed. The kappa statistic was calculated to determine inter-observer agreement. Statistical software by GraphPad (San Diego, Ca., USA) was used. *p* values of <0.05 were taken to be statistically significant.

3. Results

A total of 205 studies were reviewed. The mean number of studies per patient was 5.1 ± 1.7. The mean time between studies was 6.5 ± 5.5 months. The mean length of follow-up was 27.2 ± 11.8 months. The clinical characteristics of the study population are presented in Table 1.

At initial presentation, there were 17/50 (34%) patients who had increased vessel wall ^{18}F-FDG uptake and 19/50 (38%) patients who had arterial calcification. There were 5 sites where there was focal ^{18}F-FDG uptake at sites of initial vascular calcification. The number of patients who developed new ^{18}F-FDG avid arterial lesions was 21/50 (42%). The number who developed new arterial calcification was 12/50 (24%). None of these new sites of arterial calcification had increased focal ^{18}F-FDG,when discovered. In total, 132 sites of increased ^{18}F-FDG vascular uptake were observed longitudinally. Linear and diffuse patterns of increased ^{18}F-FDG uptake as described in arteritis were not observed in the study population.

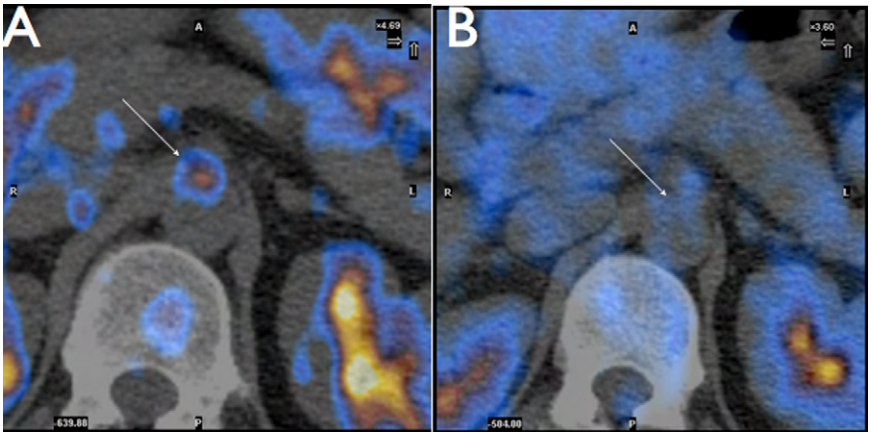

Fig. 1. Fused PET/CT axial images showing (A) focal ^{18}F-FDG uptake in the abdominal aortic wall (arrow), which has diminished with 3 months (B). There is no arterial calcification on the CT.