Age-related inflammatory changes in the spine as demonstrated by ^{18}F-FDG-PET: observation and insight into degenerative spinal changes

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Abstract

Our aim was to determine whether the inflammatory component associated with age-related degenerative changes in the spine can be assessed by ^{18}F-fluoro-2-de-oxy-D-glucose positron emission tomography (^{18}F-FDG-PET). *Mean and maximum standardize uptake values* (SUV$_{mean}$ and SUV$_{max}$) of intervertebral discs and spinous processes were measured in 45 patients who had undergone ^{18}F-FDG-PET for any clinical indication. Correlations between age and FDG-PET indices (SUV$_{mean}$ and SUV$_{max}$ of intervertebral discs and spinous processes) were determined. *Pearson's correlation coefficients* between age and intervertebral disc SUV$_{mean}$, between age and intervertebral disc SUV$_{max}$, and between age and spinous process SUV$_{mean}$ were 0.4821, 0.3946, and 0.5017 (P<0.05), indicating moderate positive correlations between these parameters. However, Pearson's correlation coefficient between age and spinous process SUV$_{max}$ was 0.7998 (P>0.05), indicating no correlation between these two parameters. *In conclusion,* intensity of ^{18}F-FDG uptake in the intervertebral discs and spinous processes generally increases with aging, which is likely to reflect associated inflammatory processes.

Introduction

The spine is a flexible, multisegmented column. Its functional role is to maintain stability and an upright position as well as providing mobility at the segmental level [1, 2]. Aging will lead to degenerative changes of all parts of the spine, starting with subtle (multifactorial) biochemical alterations followed by microstructural and finally gross structural changes of the spinal unit. The degenerative cycle with its biomechanical consequences will progressively modify the functional anatomy and generate various pain syndromes, rupture of equilibrium and destabilization [1, 2]. Of interest, this degenerative process starts at the disc level, as early as during the first decade of life [1, 2]. A variety of inflammatory mediators have been implicated in the degeneration of the intervertebral disc including nitric oxide, interleukins, matrix metalloproteinases, prostaglandin E2, tumor necrosis factor alpha, and a group of cytokines [3]. However, the potential role of inflammation in the pathophysiology of disc degeneration has mainly been indicated by means of analysis of *ex vivo* disc specimens [3], while *in vivo* studies supporting this hypothesis are still lacking. Although traditional imaging methods such as conventional X-ray imaging, computed tomography (CT), and magnetic resonance imaging (MRI) are useful to assess late, degenerative structural changes [4], they do not provide (clinically proven) imaging biomarkers of inflammation that may possibly occur early in the pathophysiology of spine degeneration [3]. In contrast, positron emission tomography (PET) using the glucose analogue ^{18}F-fluoro-2-deoxy-D-glucose (^{18}F-FDG) may play an important role in the evaluation of inflammation [5, 6]. At present, ^{18}F-FDG-PET is most frequently employed for the evaluation of cancer, since most malignant cells have an increased glycolytic rate and subsequent high ^{18}F-FDG uptake [7]. However, like malignant cells, inflammatory cells also preferentially metabolize glucose. Several molecular mechanisms have been proposed as the basis for ^{18}F-FDG uptake in inflammatory cells, with overexpression of glucose transporter 1 (GLUT1) receptors in stimulated macrophages, neutrophils, and lymphocytes being

considered as the most likely underlying biological phenomenon responsible for this observation. It is reasonable to conclude that activated inflammatory cells accumulate ^{18}F-FDG with high concentration depending on the degree of stimulation at the site [5, 6]. The purpose of this study was to assess whether ^{18}F-FDG-PET can detect age-related inflammatory changes in the spine.

Materials and methods

Patients

Institutional Review Board approval for retrospective data collection and image analysis along with a Health Information Portability Accountability Act waiver were obtained at the Hospital of the University of Pennsylvania prior to study initiation. A retrospective search was conducted for subjects who had undergone ^{18}F-FDG-PET/CT for any clinical indication and did not have a history of malignancy (based on all imaging reports and follow up visits), spine surgery, recent history of osteomyelitis, and any report of events which may interfere with PET quantification (^{18}F-FDG extravasations, high uptake of ^{18}F-FDG in extremities' muscle, diabetes mellitus). In total, 45 patients (23 men and 22 women; mean age, 56.1 years; age range, 28-81 years; age >55 years: n=22; age ≤55 years: n=23) were included.

^{18}F-FDG-PET

Subjects fasted for 8h prior to the ^{18}F-FDG-PET/CT scan. Fasting serum glucose levels were checked by finger stick to assure glucose levels <150mg/dL prior to ^{18}F-FDG administration. Whole body PET/CT image acquisition (Gemini TF, Philips Healthcare, Bothell, WA) commenced ~60min after intravenous administration of 140μCi or 5.18MBq/kg ^{18}F-FDG. Image reconstruction was performed using a list-mode maximum-likelihood expectation-maximization (ML-EM) algorithm with 33 ordered subsets and 3 iterations. The system model included time-of-flight as well as normalization, attenuation, random, and scatter corrections. Rescaled low-dose CT images were utilized for attenuation correction of PET images. PET and CT images were reconstructed at 5mm nominal slice thickness.

Data analysis

Standard manual standardized uptake value (SUV) measurements were carried out by using dedicated image visualization and analysis software (Extended Brilliance Workstation, Philips Healthcare, Bothell, WA). Regions of interest (ROI) were placed in the intervertebral disc and the spinous processes on the midsagittal slice through these structures in order to measure intervertebral disc and spinous process mean SUV (SUV$_{mean}$) and maximum SUV (SUV$_{max}$). The ROI for the intervertebral disc was placed at the level of the lumbar spine, included the entire superior-inferior length of the disc, and the distance of the upper and lower borders of this ROI from the adjacent vertebral bodies was equal. By adhering to this approach, contamination from bone marrow ^{18}F-FDG uptake in the vertebral bodies was minimized. The ROI for the spinous processes were rectangular or semi-rectangular in shape and were created at three anatomic sites; i.e. at the levels of the cervical, thoracic, and lumbar spine. Each of these ROI contained all bony structures within the assigned region and avoided any adjacent tissues as best as possible. Spinous process SUV$_{mean}$ and SUV$_{max}$ were obtained by averaging the individual values from these three ROI. Examples of intervertebral disc and spinous process SUV measurements are shown in Figures 1 and 2. Of note, no SUV measurements were made in the bone marrow of the vertebral bodies. This decision was made because it could not be completely excluded that the vertebral bodies were free of focal lesions with high ^{18}F-FDG uptake, which could bias SUV measurements.
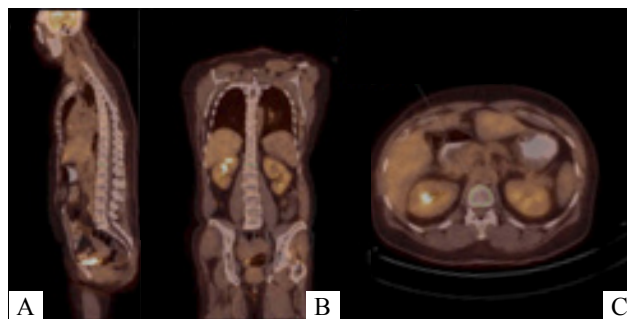

Figure 1. Example of intervertebral disc SUV measurement with ROI shown in the (A) sagittal, (B) coronal, and (C) axial planes.
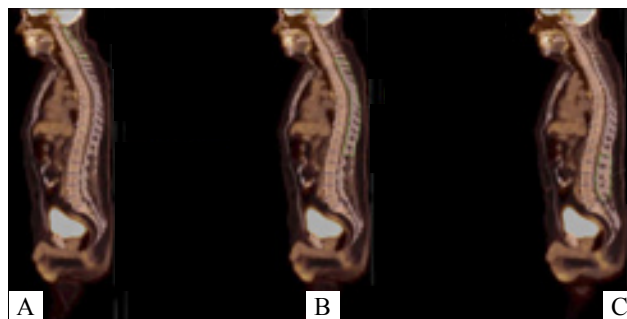

Figure 2. Example of spinous process SUV measurement with ROI shown at the levels of the (A) cervical, (B) thoracic, and (C) lumbar spine in the sagittal plane.

Statistical analysis

Kolmogorov-Smirnov tests were used to check whether age, intervertebral disc and spinous process SUV$_{mean}$ and SUV$_{max}$ were normally distributed. Differences in intervertebral disc and spinous process SUV$_{mean}$ and SUV$_{max}$ between males and females, and between patients over 55 years or age and patients of 55 years of age or less, were assessed using unpaired two-tailed t tests. Correlation between age and (intervertebral disc or spinous process) SUV$_{mean}$, and correlation between age and (intervertebral disc or spinous process) SUV$_{max}$ were assessed using Pearson's correlation coefficient analysis. P values less than 0.05 were considered to indicate a statistically significant difference. Statistical analyses were executed using MedCalc version 10.4.5.0 software (MedCalc, Mariakerke, Belgium).

Results

Kolmogorov-Smirnov tests confirmed that each variable was normally distributed, justifying analysis by means of parametric tests. There were no significant differences in intervertebral disc and spinous process SUV$_{mean}$ and SUV$_{max}$ between males and females (Table 1). However, interver-

Table 1. *Comparison of intervertebral disc and spinous process SUV$_{mean}$ and SUV$_{max}$ (expressed as means with standard deviations) between males and females, with corresponding P values*

Parameter	Males	Females	P value
Intervertebral disc SUV$_{mean}$	0.6673±0.2118	0.6242±0.1782	0.4655
Intervertebral disc SUV$_{max}$	0.8597±0.2223	0.8439±0.2178	0.8109
Spinous process SUV$_{mean}$	0.8169±0.1676	0.7581±0.1101	0.1737
Spinous process SUV$_{max}$	1.4019±0.4071	1.2654±0.1942	0.1615

Table 2. *Comparison of intervertebral disc and spinous process SUV$_{mean}$ and SUV$_{max}$ (expressed as means with standard deviations) between patients over 55 years or age and patients of 55 years of age or less, with corresponding P values*

Parameter	>55 years	≤55 years	P value
Intervertebral disc SUV$_{mean}$	0.7142±0.2086	0.5812±0.1599	0.0204
Intervertebral disc SUV$_{max}$	0.9094±0.2399	0.7971±0.1829	0.0838
Spinous process SUV$_{mean}$	0.8348±0.1515	0.7435±0.1235	0.0317
Spinous process SUV$_{max}$	1.3015±0.3897	1.3674±0.2531	0.5028

Table 3. *Pearson's correlation coefficients between age and intervertebral disc and spinous process SUV$_{mean}$ and SUV$_{max}$, with corresponding P values*

Comparison	Pearson's correlation coefficient*	P value
Age-intervertebral disc SUV$_{mean}$	0.4821 (0.2196-0.6795)	0.0008
Age-intervertebral disc SUV$_{max}$	0.3946 (0.1143-0.6167)	0.0073
Age-spinous process SUV$_{mean}$	0.5017 (0.2441-0.6931)	0.0004
Age-spinous process SUV$_{max}$	0.03888 (-0.2576-0.3287)	0.7998

*95% confidence intervals between parentheses

tebral disc and spinous process SUV$_{mean}$ of patients over 55 years or age were significantly higher (P<0.05) than those of patients of 55 years of age or less, and a trend (P=0.0838) towards a higher intervertebral disc SUV$_{max}$ in patients over 55 years or age compared to patients of 55 years of age or less was observed (Table 2). On the other hand, there was no significant difference (P=0.5028) in spinous process SUV$_{max}$ between the two age categories of patients (Table 2). Pearson's correlation coefficients between age and intervertebral disc SUV$_{mean}$, between age and intervertebral disc SUV$_{max}$, and between age and spinous process SUV$_{mean}$ were 0.4821, 0.3946, and 0.5017 (P<0.05), respectively, indicating moderate positive correlations between these parameters (Table 3, Fig. 3-5). However, Pearson's correlation coefficient between age and spinous process SUV$_{max}$ was 0.7998 (P>0.05), indicating the absence of a correlation between these two parameters (Table 3, Fig. 6).

Discussion

The results of this pilot study indicate that levels of ^{18}F-FDG uptake by the intervertebral discs and spinous processes tend to rise with increasing age, as evidenced by the signifi-

cant differences in intervertebral disc and spinous process SUV$_{mean}$ between patients over 55 years of age and patients of 55 years of age or less, and the (moderate) positive correlations between age and SUV$_{mean}$ of the intervertebral discs and spinous processes. Since ^{18}F-FDG is known to accumulate in inflammatory tissue [5, 6, 8, 9], our results are supportive of the hypothesis that inflammation plays an important role in the age-related degenerative process of the spine [3]. Hence, with this observation as such, ^{18}F-FDG-PET appears to provide *in vivo* pathophysiologic insights into the degenerative process of the spine. Interestingly, although age and intervertebral disc SUV$_{max}$ were also found to be positively correlated, no correlation was found between age and spinous process SUV$_{max}$. This can be explained by the fact that we did not specifically look for focal lesions in the spinous processes; it can be speculated that the spinous process ROI may have included small focal lesions with high ^{18}F-FDG uptake in some young patients, which may have influenced the SUV$_{max}$ but not the SUV$_{mean}$.

Previous studies [10, 11] have reported that increased ^{18}F-FDG uptake can be found in inflammatory bone and joint disorders including osteoarthritis and rheumatoid arthritis. In a study by other researchers [10] in shoulder osteoarthritis, the ^{18}F-FDG uptake pattern was circumferential and dif-
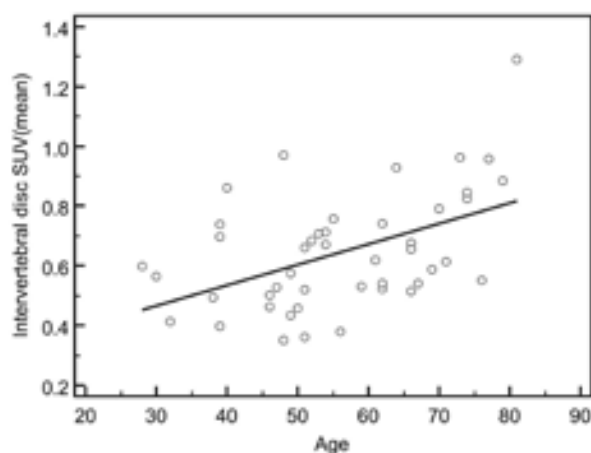
Figure 3. Scatter plot with age in years (x-axis) vs. intervertebral disc SUV_{mean} (y-axis) including regression line. Pearson's correlation coefficient was 0.4821 (P=0.0008).
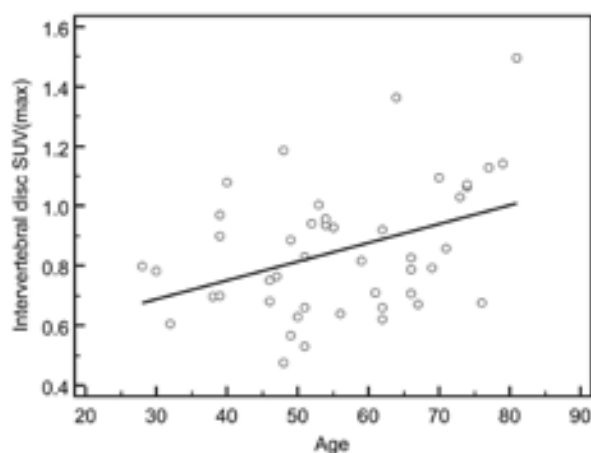

Figure 4. Scatter plot with age in years (x-axis) vs. intervertebral disc SUV_{max} (y-axis) including regression line. Pearson's correlation coefficient was 0.3946 (P=0.0008).
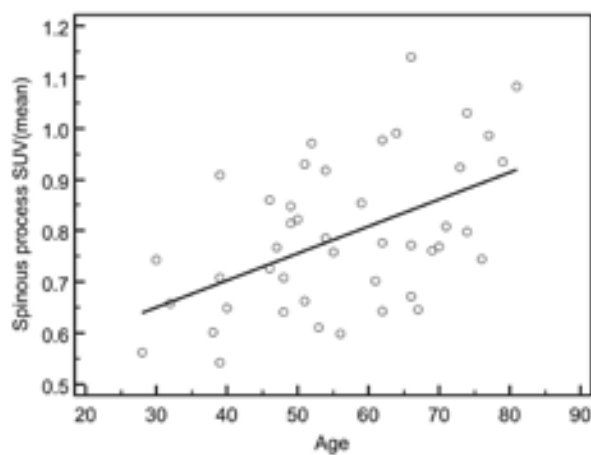

Figure 5. Scatter plot with age in years (x-axis) vs. spinous process SUV_{mean} (y-axis) including regression line. Pearson's correlation coefficient was 0.5017 (P=0.0008).
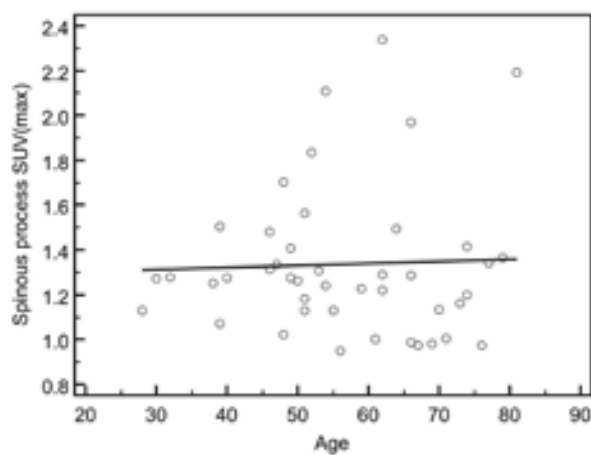

Figure 6. Scatter plot with age in years (x-axis) vs. spinous process SUV_{max} (y-axis) including regression line. Pearson's correlation coefficient was 0.03888 (P=0.0008).

fused, and the authors of this study speculated that this finding reflected the presence of mild synovitis. In another study [11] it was postulated that in the osteoarthritic knee, synovitis and ligament tear may be causes of increased 18F-FDG uptake. In addition, these researchers [11] found 18F-FDG accumulation around osteophytes, which was thought to reflect upregulated metabolism of osteochondral tissue in osteophytes and/or soft tissue inflammation around osteophytes. 18F-FDG accumulation was also found in bone marrow lesions, presumably bone marrow edema [11]. Other studies [12, 13] have shown that 18F-FDG-PET can be used to detect spondylodiscitis, which is an inflammatory process of the intervertebral disc space. All these studies [10-13] support the concept that inflammation associated with bone and joint degeneration, including degeneration of the spine, can be visualized with 18F-FDG-PET. Also of interest is a recent study by other researchers [14], who investigated the changes of 18F-FDG uptake in large arteries with aging as visualized by 18F-FDG-PET imaging. These researchers [14] reported that the prevalence and intensity of 18F-FDG uptake in large arteries generally increases with aging. Importantly, increased 18F-FDG uptake was thought to likely represent the presence of active inflammatory process of atherosclerotic plaque. Although the subject of the previous study [14] was different from that of the present study, its findings are important, because they indicate that 18F-FDG-PET may be used as a biomarker for assessing inflammatory changes during aging. To the best of our knowledge, the present study is the first to use 18F-FDG-PET to assess age-related inflammatory changes in the spine. It would be of great interest to conduct further, prospective studies in which the same individuals will undergo repeated 18F-FDG-PET examinations over time. Such studies are needed to confirm the role of inflammation in the degenerative process of the spine, to assess the time relationship between inflammatory changes as assessed by 18F-FDG-PET and the occurrence of symptoms and structural changes, and to determine whether 18F-FDG-PET findings can be used for preventive therapeutic strategies.

The present study had several limitations. First, because of its retrospective, cross-sectional design and relatively small sample size, larger prospective follow-up studies are warranted. Second, the relationship between 18F-FDG uptake, back symptoms, and structural changes was not assessed. Nevertheless, this was beyond the scope of this pilot study,

which only aimed to assess whether inflammatory changes in the spine, as assessed with ^{18}F-FDG-PET, occur during aging, if any. This study forms the basis to conduct more rigorous studies on this subject. Third, although strict in- and exclusion criteria were applied to minimize the risk of including patients with (malignant or infectious) spinal disease, this risk could not be completely excluded.

Future prospective studies are required to confirm the present results, to increase our understanding of the role of inflammation in the degeneration of the spine, and to determine the possibility of ^{18}F-FDG-PET-directed preventive therapeutic strategies.

In conclusion, intensity of ^{18}F-FDG uptake in the intervertebral discs and spinous processes generally increases with aging, which is thought to reflect inflammatory processes.

The authors declare that they have no conflicts of interest.

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