Original Article

Application of ^{18}F-NaF-PET/CT in assessing age-related changes in the cervical spine

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Background: Cervical spondylosis is the degeneration of cervical spine often associated with aging and neck pain. As the degenerative changes are coupled with altered osteoblastic activity, imaging modalities sensitive to such molecular changes could be valuable for clinical assessment, disease prophylaxis, and monitoring early therapy response. In this study, we examined the role of ^{18}F-sodium fluoride-positron emission tomography/computed tomography (^{18}F-NaF-PET/CT) in detecting age-associated changes in the cervical spine of an adult population with broad age spectrum.

Methods: In this retrospective cross-sectional study, we analyzed ^{18}F-NaF-PET/CT scans of 88 control volunteers (43 females, 45 males) with age ranging from 21 to 75 years (mean =44.6, standard deviation, 14.0) divided into younger (21–45 years) and older (46–75 years) age groups. A semi-automated global assessment technique was used to measure ^{18}F-NaF uptake in C2-C4 and C5-C7 vertebrae of the subjects. Furthermore, a CT-based scoring system was devised to measure the degree of structural degeneration.

Results: There was a significant difference in ^{18}F-NaF uptake of the younger and older groups at the C5-C7 vertebrae for both females (younger: mean =4.13, 95% CI: 3.72–4.55; older: mean = 4.80, 95% CI: 4.40–5.20; P=0.005) and males (younger: mean =3.66, 95% CI: 3.24–4.09; older: mean =4.22, 95% CI: 3.80–4.64; P=0.009), but not at the C2-C4 vertebrae. Furthermore, there was a positive correlation between the degree of degeneration and ^{18}F-NaF uptake at both C2-C4 and C5-C7 spinal segments of both sexes.

Conclusions: Aging is associated with increased ^{18}F-NaF uptake in the cervical spine, which may be associated with osteoblastic activity coupled with degeneration. Our study alludes to the potential role of ^{18}F-NaF-PET/CT in evaluating age-related degeneration and osteoarthritis of the spine.

Keywords: Positron emission tomography/computed tomography (PET/CT); sodium fluoride; aging; cervical spine; cervical spondylosis

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Introduction

Degenerative cervical spondylolysis, or cervical arthritis, is the deterioration of the cervical spine and its associated structures with increasing age (1). While cervical degeneration can be asymptomatic, symptomatic cervical spondylosis can present as chronic neck pain and/or neurological abnormalities that can seriously undermine quality of life (2). The cervical level with greatest incidence of abnormal findings and deterioration is the C5-C6 vertebrae, followed by C6-C7 (3-5). While magnetic resonance imaging (MRI) has been the imaging modality of choice for assessing neck pain and age-related degenerative changes in the spine, incorporation of additional imaging modalities may enhance clinical correlation, prompt diagnoses for disease prophylaxis, and monitoring of early therapy response (6,7).

^{18}F-sodium fluoride (NaF)-positron emission tomography (PET) is an emerging molecular imaging modality with potential to evaluate neck pain and degenerative changes in the spine (8-11). Specifically, ^{18}F ions are incorporated into hydroxyapatite present in osseous or calcifying parts of the body, reflecting regional blood flow and osteogenic activity. ^{18}F-NaF binds minimally to protein and clears rapidly in the plasma, allowing for the precise and fast acquisition of image with low background uptake already within 45 to 60 min after administration (12,13). The role of ^{18}F-NaF-PET in diagnosis and clinical management of malignant bone diseases, benign osseous conditions, and atherosclerosis has been well-studied previously (14-16). While ^{18}F-NaF-PET has been employed to assess the sources of neck pain (8), its use for measuring age-related degenerative changes in the spine has not been fully explored.

In this study, we examine the potential of ^{18}F-NaF-PET/CT for monitoring age-associated changes in the cervical spine of an adult population with broad age spectrum. We hypothesize that increased ^{18}F-NaF uptake may be observed with aging at the cervical spine, especially the C5-C7 segment given its susceptibility to wear-and-tear degeneration. Using a semi-automated global assessment technique to calculate the global mean standardized uptake value (SUVmean), we measure and compare ^{18}F-NaF uptake in the C2-C4 and C5-C7 vertebrae levels with respect to age and sex. Additionally, we investigate the relationship between the degree of structural vertebrae degeneration visible in CT scans and the association of the degeneration with ^{18}F-NaF uptake. We present the following article in accordance with the STROBE reporting checklist (available at https://qims.amegroups.com/article/view/10.21037/qims-21-1174/rc).

Methods

Subjects

This is a retrospective cross-sectional study examining the age-related changes of the cervical spine in an adult population with broad age spectrum. The CAMONA study was conducted from 2012 to 2016 in accordance with the Declaration of Helsinki (as revised in 2013) and approved by the Danish National Committee on Health Research Ethics, registered at ClinicalTrials.gov (NCT01724749). All study participants provided written informed consent. All participants provided written informed consent. Specifically, we analyzed and measured the ^{18}F-NaF standard uptake value (SUV) in the C2-C7 segments of control subjects from the study Cardiovascular Molecular Calcification Assessed by ^{18}F-NaF PET CT (CAMONA) performed at the Odense University Hospital (OUH), Denmark (NCT01724749).

To describe briefly, the CAMONA study enrolled total of 139 subjects—50 subjects with history of cardiovascular diseases (CVD) and 89 control volunteer subjects to explore molecular calcification using ^{18}F-NaF PET/CT. Age was recorded as part of the study. Enrollment as a control volunteer required no history of CVD, immunodeficiency, autoimmune diseases, history of alcohol or drug abuse, history of malignant cancer, indication for mental illness, active smoking, and pregnancy. A diverse age spectrum from 20–29, 30–39, 40–49, 50–59, and 60 years older were recruited in both male and female cohorts to ensure balanced representation of all ages and eliminate selection bias that could arise from the overrepresentation of certain age groups. Information on neck pain, previous neck trauma, skeletal issues, or occupation was not recorded as part of our study.

In total, our cross-sectional study examined scans of 88 control volunteers with age ranging from 21 to 75 years; one control volunteer scan was excluded because the ^{18}F-NaF-PET/CT images with appropriate time point was unavailable in our research center data base (*Figure 1A*). Additionally, 50 subjects with CVDs were excluded to eliminate any potential confounding bias and variables that may arise from the possible association of degenerative changes with CVD risk factors. In addition to linear

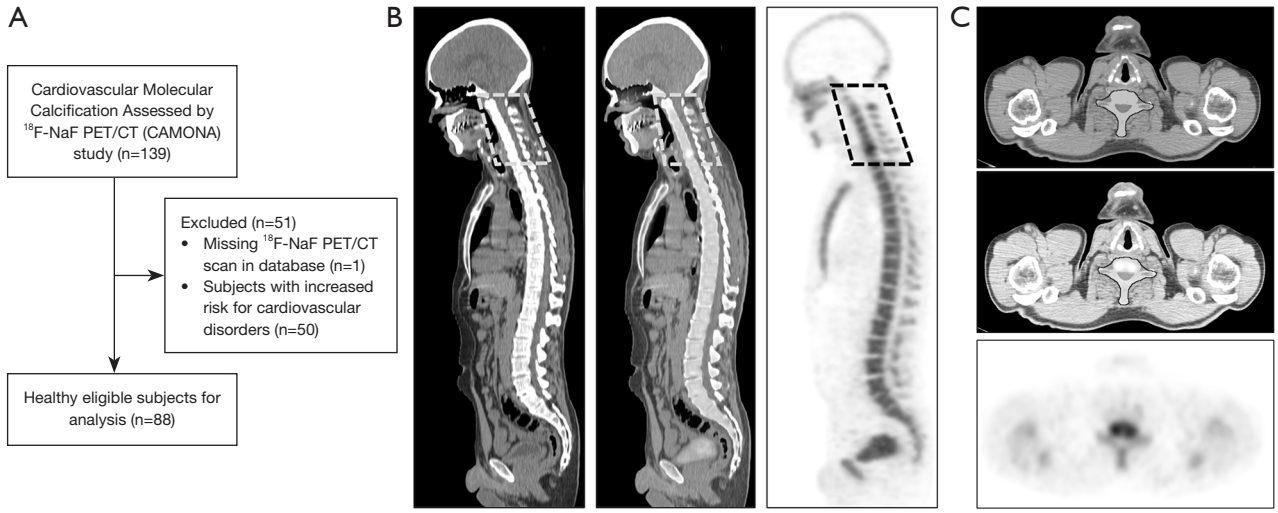

Figure 1 Study design, methodology, and ROI. (A) Flow chart delineating the selection of eligible study subjects for the data analysis. (B) Sagittal CT, fused ^{18}F-NaF-PET/CT, and PET scans (left to right) of the region of interest in the cervical spine dilatated in dashed rectangle. (C) Transverse CT, fused ^{18}F-NaF-PET/CT, and PET sections (top to bottom) showing the semi-automated CT-based segmentation on the ROI of cervical spine. NaF, sodium fluoride; PET, positron emission tomography; CT, computed tomography; ROI, region of interest.

regression analysis, we divided the patients into two groups based on their age (younger: 21–45 years, older: 46–75 years) to best assess the degree to which ^{18}F-NaF uptake changes with aging. Age of 45 years was determined as the designated boundary to compare younger and older because the menopausal status of women was unknown and to ensure comparable number of subjects between the groups (17).

Study design and image analysis

^{18}F-NaF PET/CT scans of the subjects were performed on integrated PET/CT scanners (Discovery 690/710, STE, VCT and RX; GE Healthcare, Chicago, Illinois, USA) with comparative resolutions at OUH following protocol previously outlined by Blomberg *et al.* (18). To summarize, PET scans were acquired 90 min after intravenous administration of 2.2 MBq of ^{18}F-NaF per kilogram of body weight. Whole-body PET images were obtained in 3-dimentional mode, and an iterative reconstruction algorithm (VUE Point; GE Healthcare) was used to generate coronal, transverse, and sagittal slices. Corrections were performed for attenuation, scatter, random coincidence, and scanner dead time. Low-dose CT imaging was performed to correct attenuation. The design of our imaging protocol was constructed in accordance with the practice guidelines of the Society of Nuclear Medicine (19).

OsiriX software version 12.0 (Pixmeo, Bernex, Switzerland) was used to define regions of interest (ROIs) and perform analysis (*Figure 1B*). We identified the ROIs with 3D maximum intensity projection of the CT images and then used the scissor tool to exclude areas outside the ROI. For the analysis of C2-C4 vertebrae, the superior border was defined as the superior articular facet of C2 and the inferior border as the lower end plate of C4 vertebral body and its spinous process. Similarly for the analysis of C5-C7 vertebrae, the superior border was defined as the upper endplate of C5 vertebral body and its spinous process while the inferior border as the lower end plate of C7 vertebral body its spinous process.

Hounsfield unit (HU) threshold-based segmentation algorithm on OsiriX, with lower and upper thresholds of 150 and 1,500 HU, respectively, was used to segment the vertebrae. A morphological closing algorithm was applied to extend the ROI to the entirety of the vertebral bodies. Our ROI included vertebral structures such as the spinal and transverse processes, vertebral body, and lamina as well as vertebral and transverse foramina (*Figure 1C*). Global SUVmean was calculated as the average standardized uptake value (SUV) of all voxels included in each ROI defined on the fused PET/CT image.

Table 1 Study group demographics

Characteristics	Female (n=43)	Male (n=45)	P value	Total (n=88)
Age group				
20–45 years (younger)	21	25		46
46–75 years (older)	22	20		42
Mean ± SD (years)	44.7±14.3	44.5±13.8	0.95	44.6±14.0
BMI (kg/m^2), mean ± SD	25.5±3.22	27.6±5.18	0.03	26.5±4.43
BP (mmHg), mean ± SD				
Systolic	129.9±18.7	130.8±17.9	0.82	130.4±18.2
Diastolic	77.8±9.6	78.3±9.2	0.82	78.0±9.4
Smokers (n)				
None	17	26		43
Former	21	16		37
Current	5	3		8

SD, standard deviations; BMI, body mass index; BP, blood pressure.

Degeneration score system

To determine the severity of the cervical degeneration, we devised a scoring system based on the structural changes visible on CT images, which have been reported in previously published literature (20-23). Specifically, we scored the spine based on the degree of degeneration seen at the vertebral body and facet joints using sagittal, coronal, and transverse views at the individual levels from C2-C3 to C6-C7 vertebrae. For the vertebral body, 0 point was given if the vertebral body contained no osteophytes, no endplate sclerosis with normal disc height; 1 point for vertebral body with mild osteophytosis and endplate sclerosis with normal disc height; 2 points for given vertebral body with a moderate degree of osteophytosis and endplate sclerosis with mild loss of intervertebral disc height; 3 points for vertebral body with severe osteophytosis, endplate sclerosis with severe loss of intervertebral disc height. For the facet joint, 0 point was given for normal joint without narrowing or osteophytosis; 1 point for mild narrowing and joint surface irregularity; 2 points for moderate narrowing and joint surface irregularity with osteophytosis; 3 points for severe narrowing and osteophytosis. Points derived from the vertebral body and facet joints scores were combined to derive the Degeneration Score with minimum and maximum values of 0 and 6, respectively. Average scores of C2-C3 and C3-C4 were used to investigate the relationship between the Degeneration Score and ^{18}F-NaF uptake at the C2-C4 level. Similarly, average of C5-C6 and C6-C7 scores were used to derive association with ^{18}F-NaF uptake at the C5-C7 level.

Statistical analysis

All statistical tests were performed using GraphPad Prism 8 (San Diego, CA, USA). Mann-Whitney test was performed to compare the ^{18}F-NaF uptake between younger and older groups each at the level of C2-C4 or C5-C7 vertebrae by sex. To determine the correlation between global SUVmean and age or Degeneration Score, Spearman correlation test was performed. P value less than 0.05 ($P<0.05$) was taken as statistically significant. Graph bars represent the mean, and the 95% confidence interval (CI) and plus-minus signs indicate values of standard deviations (SD).

Results

In total, 88 subjects (43 females and 45 males), mean age 44.6±14.0 years and body mass index (BMI) 26.5±4.43 kg/m^2 were analyzed (*Table 1*). The results of the key data are summarized in *Table 2*.

In females, there was no difference in the ^{18}F-NaF uptake between younger (20–45 years) and older (46–75 years) groups at the C2-C4 vertebrae (younger: mean =3.59, 95%

Table 2 Correlation of [18]F-NaF-SUVmean and with age in females and males

Variables	Female			Male		
	SUVmean (95% CI)	P value	Spearman R	SUVmean (95% CI)	P value	Spearman R
C2-C4	3.84 (3.58–4.10)	0.06	0.29	3.34 (3.05–3.63)	0.04	0.31
C5-C7	4.48 (4.18–4.77)	0.002	0.47	3.91 (3.61–4.21)	0.0003	0.52

NaF, sodium fluoride; SUVmean, mean standardized uptake value; CI, confidence intervals.

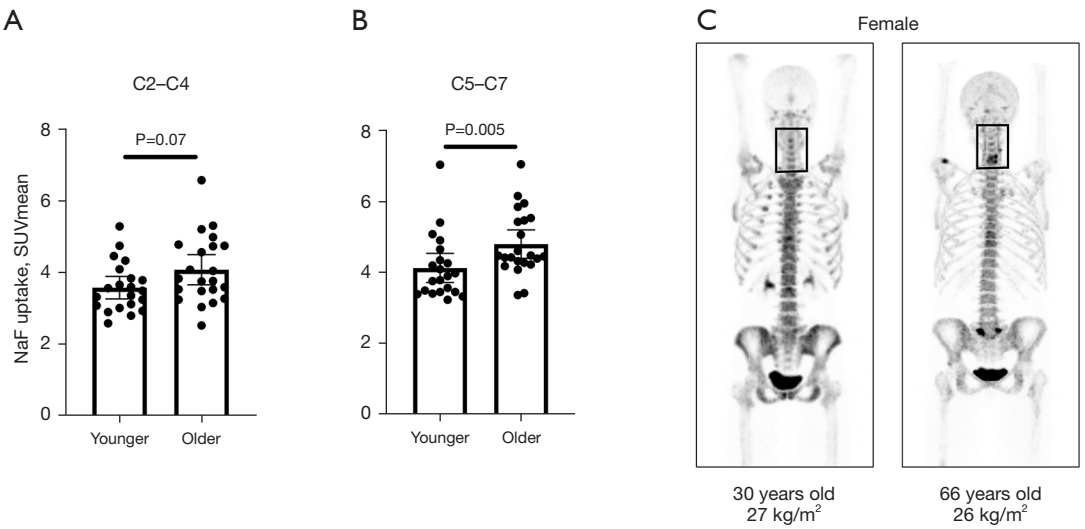

Figure 2 Comparison of [18]F-NaF uptake in the C2-C4 and C5-C7 vertebrae in females. (A) While there is no difference in [18]F-NaF uptake between younger and older age groups in the C2-C4 vertebrae, (B) older group exhibits greater uptake in the C5-C7 vertebrae. (C) 3D Maximum intensity projections of BMI matched females, highlighting greater differential [18]F-NaF uptake in the cervical spine ROI (black) of a 66 years old subject than in that of 30 years old subject. NaF, sodium fluoride; SUVmean, mean standardized uptake value; BMI, body mass index; ROI, region of interest.

CI: 3.27–3.90; older: mean =4.08, 95% CI: 3.67–4.50; P=0.07; *Figure 2A*). However, the older group displayed greater [18]F-NaF uptake than the younger group at the C5-C7 vertebrae (younger: mean =4.13, 95% CI: 3.72–4.55; older: mean =4.80, 95% CI: 4.40–5.20; P=0.005; *Figure 2B,2C*). The results were similar for males, with no significant difference at the C2-C4 vertebrae (younger: mean =3.24, 95% CI: 2.80–3.69; older: mean =3.46, 95% CI: 3.10–3.83; P=0.14; *Figure 3A*) but a significant difference at the C5-C7 vertebrae (younger: mean =3.66, 95% CI: 3.24–4.09; older: mean =4.22, 95% CI: 3.80–4.64; P=0.009; *Figure 3B,3C*). Additionally, linear correlation revealed a stronger positive correlation between age and [18]F-NaF uptake at the C5-C7 vertebrae than the C2-C4 in both females (C2-C4: P=0.06, r=0.29; C5-C7: P=0.002, r=0.47; *Figure 4A*) and males (C2-C4: P=0.04, r=0.31; C5-C7: P=0.0003, r=0.52; *Figure 4B*).

The analysis of structural deterioration using CT images (*Figure 5*) revealed highest Degeneration Score at the C5-C6 (females: mean =1.28, 95% CI: 0.83–1.73; males: mean =1.24, 95% CI: 0.76–1.73) level followed by C6-C7 (females: mean =1.12 , 95% CI: 0.71–1.53; males: mean =0.96, 95% CI: 0.55–1.36) and then C4-C5 (females: mean =0.70, 95% CI: 0.39–1.01; males: mean =0.69, 95% CI: 0.36–1.02) in both females (*Figure 5A*) and males (*Figure 5D*). There was a positive correlation between the Degeneration Score and [18]F-NaF uptake at both C2-C4 (female: P=0.02, r=0.35; *Figure 5B*; males: P=0.04, r=0.31; *Figure 5E*) and C5-C7 (females: P=0.0009, r=0.49; *Figure 5C*; males: P=0.0007, r=0.49; *Figure 5F*) in both sexes, with

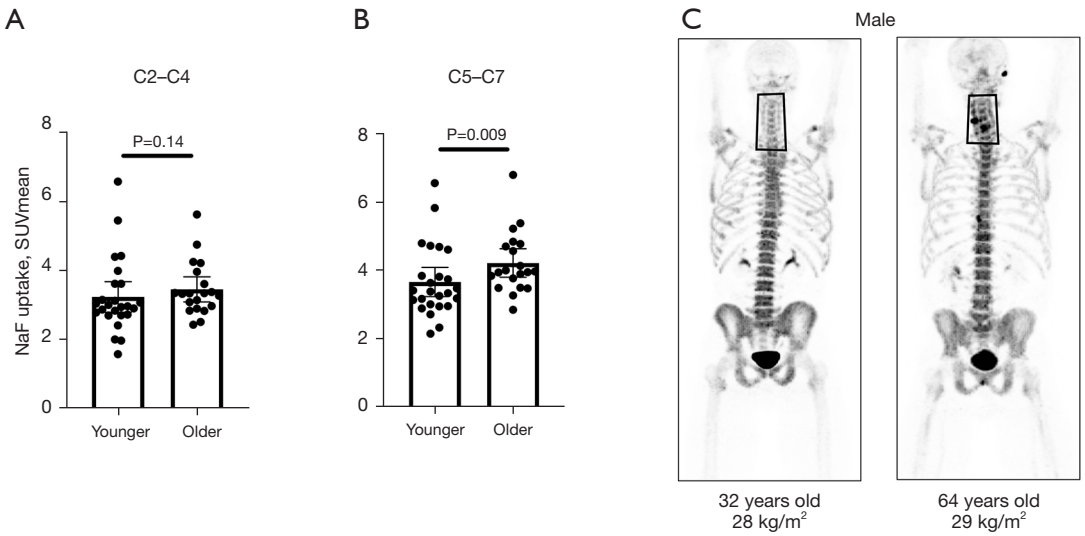

Figure 3 ^{18}F-NaF uptake in the C2-C4 and C5-C7 by age group in males. (A) The older age group has ^{18}F-NaF uptake in the C2-C4 spinal segment comparable to that of the younger group, (B) but has greater uptake in the C5-C7 level. (C) 3D maximum intensity projections of BMI matched males, highlighting greater difference in ^{18}F-NaF uptake between C2-C4 and C5-C7 segments (in black) of a 64 years old subject than in that of 32 years old subject. NaF, sodium fluoride; SUVmean, mean standardized uptake value; BMI, body mass index.

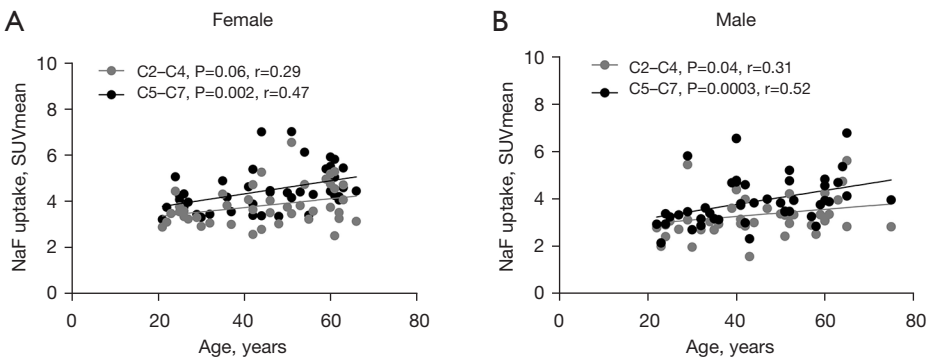

Figure 4 ^{18}F-NaF uptake increases with age in the cervical spine. Positive linear correlation between age and ^{18}F-NaF uptake in the cervical spine in both (A) females and (B) males at the C5-C7 vertebrae. NaF, sodium fluoride; SUVmean, mean standardized uptake value.

stronger associations at the C5-C7 vertebrae.

Discussion

In our study, we found significantly greater ^{18}F-NaF uptake in the older group than the younger at the level of C5-C7 vertebrae, but not at C2-C4, suggesting that the most vulnerable parts of the cervical spine exhibit greater ^{18}F-NaF accumulation indicative of age-related degenerative changes. High ^{18}F-NaF uptake may correspond to increased osteoblastic activity within osteoarthritic lesions (*Figure 6*) such as that seen in osteophyte formation (24,25). This finding may allude to the common observation that the lower region of the cervical spine is at the greatest risk for deterioration (26). For example, a study examining MRI images of patients with neck pain revealed that degenerative findings were most common at levels C5-C6 and C6-C7 and increased with age, which remain consistent with our findings from the analysis of cervical degeneration (5). A case-control study radiographically examining the cervical spine of people who carried loads on their head similarly revealed most degeneration at the level C5-C6, followed by

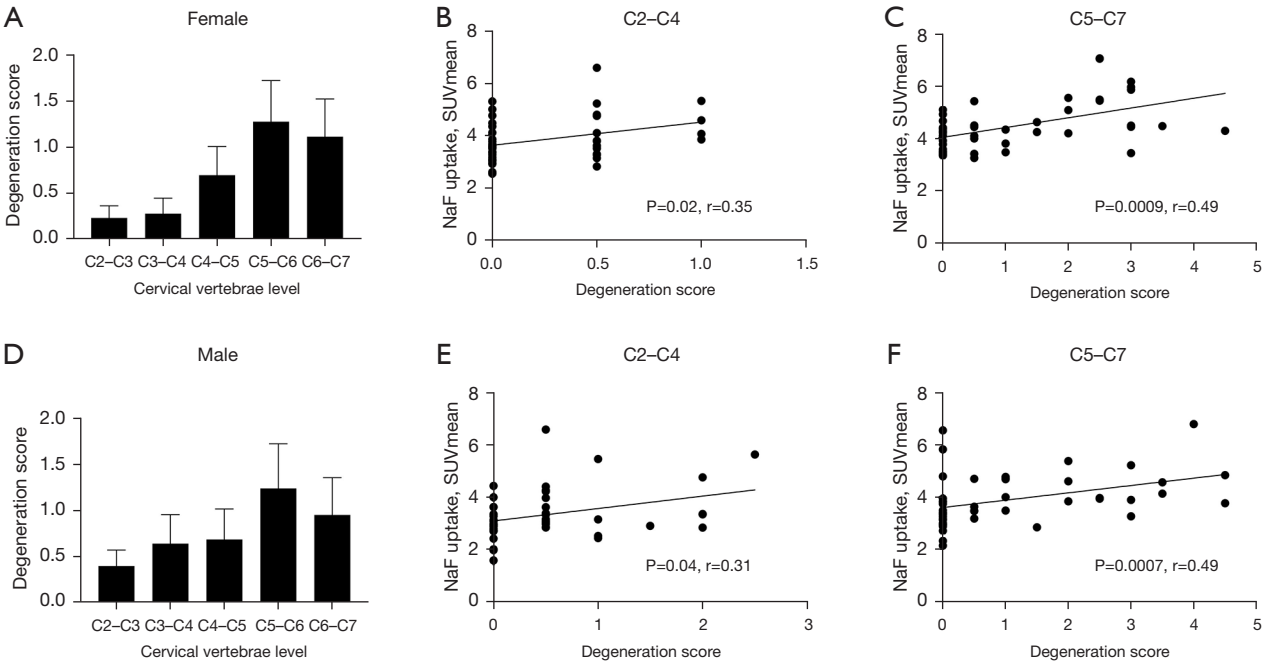

Figure 5 Cervical Degeneration Score and its association with ^{18}F-NaF uptake at the C2-C4 and C5-C7 vertebrae. Average Degeneration Score at each spinal segments from C2 to C7 in females (A) and males (D), with highest Degeneration Score at the C5-C6. There is a positive correlation between Degeneration Score and 18F-NaF uptake at both (B) C2-C4 and (C) C5-C7 of females and for (E) C2-C4 and (F) C5-C7 of males. NaF, sodium fluoride; SUVmean, mean standardized uptake value.

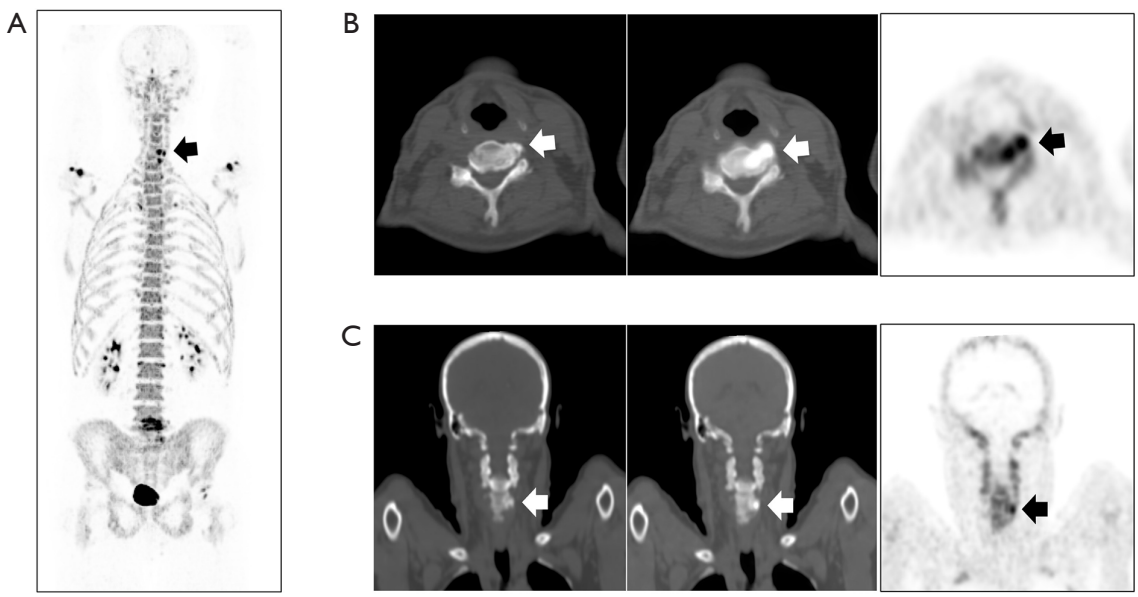

Figure 6 Degenerative or osteoarthritic lesion at the C6 vertebrae of a 60-year-old male, indicated with white/black arrows. (A) Maximum intensity projection of ^{18}F-NaF-PET scan. (B) Transverse and (C) coronal projections of CT, fused ^{18}F-NaF-PET/CT, and ^{18}F-NaF-PET scans of the corresponding lesion. NaF, sodium fluoride; PET, positron emission tomography; CT, computed tomography.

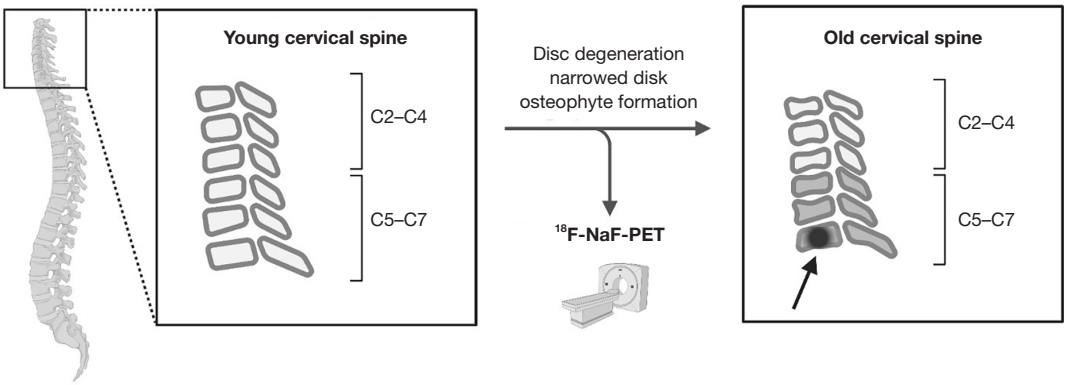

Figure 7 Proposed schematic model for the basis of using ^{18}F-NaF-PET imaging in detecting age-related degeneration in the cervical spine. Cervical degenerations are associated with abnormal structural changes such as osteophyte formation, which is preceded by increased osteoblastic activity that can be identified with molecular imaging. Black arrow indicates to focal NaF uptake within the vertebrae. The figure was created with BioRender.com. NaF, sodium fluoride; PET, positron emission tomography.

C6-C7 and C4-C5 (27).

Our study suggests that increased ^{18}F-NaF uptake in the lower cervical spine could be a common, benign finding in a general adult population of broad age spectrum. In fact, occurrence of degenerative changes in the cervical spine without any symptoms is well known (28). While the relationships between age, ^{18}F-NaF uptake, degenerative changes, and neck pain remain to be further explored, the potential of ^{18}F-NaF-PET in assessing neck pain has also been previously reported. A retrospective study of 58 patients with neck pain found that in 49 cases, ^{18}F-NaF-PET/CT scans were clinically helpful by either confirming or identifying areas of pain (8).

Our finding of an increased ^{18}F-NaF uptake in the older adults also highlights the importance of recognizing false-positive and non-specific findings in ^{18}F-NaF-PET. It has been previously emphasized that high ^{18}F-NaF uptake in spinal segments prone to degenerative changes is a common benign finding in cancer patients who undergo ^{18}F-NaF-PET for the assessment of skeletal metastases (29,30). Our work further expands on the fact that ^{18}F-NaF-avid lesions may be prevalent in the lower regions of the cervical spines from C5 to C7 in older adults regardless of sex, which is important to be aware of when interpreting ^{18}F-NaF-PET images in older subjects (*Figure* 7).

Additionally, our study alludes to the potential of ^{18}F-NaF-PET in monitoring therapeutic progress in the treatment of bone diseases, including arthropathies (15). For instance, SUV values and index scores derived from ^{18}F-NaF-PET/CT scans has been shown to correlate with treatment responses in patients with ankylosing spondylitis (31,32). In studies examining metabolic bone diseases such as osteoporosis, therapy with bisphosphonates has been shown to significantly decrease ^{18}F-NaF uptake and plasma clearance of ^{18}F-NaF to the bone (33,34). Further similar investigation on whether therapeutic interventions for osteoarthritis could correlate with decreases ^{18}F-NaF uptake associated with spinous degeneration could be the crucial next step in harnessing ^{18}F-NaF-PET as a biomarker of treatment efficacy.

We found positive linear correlations between age and ^{18}F-NaF uptake in the cervical vertebrae. This study contradicts with previous ^{18}F-NaF-PET studies by Win *et al.* (35) and Ayubcha *et al.* (36) finding no association between age and ^{18}F-NaF uptake in the cervical spine. However, analysis protocol by Win *et al.* excluded areas with degenerative changes, and the number and age range of subjects they examined were limited with total of 11 patients in the range of 42 to 89 years old (35). As our study aimed to examine the potential of ^{18}F-NaF-PET in detecting age-related changes including degenerative ones, we examined all regions of the cervical spine with a larger number of subjects (n=88) and wider age range (21–75 years old). Meanwhile, Ayubcha *et al.* excluded transverse processes as part of the ROI, used different lower threshold for segmentation (85 HU), and combined all the cervical spines (C1-C7) together for analysis (36). Since we sought to explore the potentially heterogenous effect of aging on the cervical spine, we separately analyzed the cervical spine from C2-C4 and C5-C7 including transverse

processes, which may explain the differing result.

We found that the Degeneration Score of the cervical spine statistically correlated with the corresponding ^{18}F-NaF uptake in our study population, especially at the C5-C7 spinal intervals, highlighting the potential role of ^{18}F-NaF in quantifying and serving as a biomarker of the degree of structural deterioration. Regardless, implementation of ^{18}F-NaF-PET/CT in clinical settings will require studies that directly correlates ^{18}F-NaF uptake with the degree of pain, structural degeneration, and early therapy response. Indeed, our own study revealed subjects that received low Degeneration Score despite having a relatively high ^{18}F-NaF uptake and vice versa, indicating that the tracer uptake does not always correlate with the degree of cervical degeneration. Regions of low degeneration with high ^{18}F-NaF uptake may reflect areas of increased bone turnover that have not yet undergone degenerative changes, while regions of high degeneration with low ^{18}F-NaF uptake may denote areas that have already completed degenerative processes.

In our study, we used SUVmean instead of SUVmax because SUVmean better reflects heterogenous changes within a ROI rather than SUVmax, which only reflects the value of the hottest voxel and therefore does not reflect information from multiple lesions within the same ROI. Furthermore, SUVmax is known to exhibit decreased accuracy, caused by a higher sensitivity to noise and tendency to overestimate activity in areas of heterogeneous uptake (37). Future studies examining degenerative processes of the spine could explore the possibility of thresholding areas of focally increased uptake, thereby excluding areas of the vertebral body that would be subject to metabolic phenomena and would otherwise influence the SUVmean calculated by including the uptake in both the vertebral body and vertebral processes.

Our study has several limitations. First, it was not designed to prospectively assess degenerative changes in the spine; therefore, we do not have relevant MRI images or pertinent information on the history of neck pain. Furthermore, we only examined the cervical spine, but there may be other regions of the body with similar age-related changes in ^{18}F-NaF uptake that warrant investigation. For example, degenerative changes in weight bearing levels of lumbar spine such as L4-L5 and L5-S1 are commonly associated with aging (38,39). Lastly, we did not record the post-menopausal status of women subjects as a part of the study; it would have been elucidating to compare the ^{18}F-NaF uptake of pre-menopausal and post-menopausal women to assess the effect of estrogen deficiency on the cervical bone metabolism.

Conclusions

Using a semi-quantitative approach, we found an increased ^{18}F-NaF uptake at the cervical spine with age, particularly at the C5-C7 level, in an adult population of broad age spectrum. Increased ^{18}F-NaF uptake may reflect age-related deterioration and associated changes in bone turnover. Our study suggests that ^{18}F-NaF-PET/CT may have the potential to serve as a biomarker of changes associated with age and degeneration. Further investigation on the direct relationship of ^{18}F-NaF uptake with structural degeneration, age, and presence of neck pain will be a critical next step for the incorporation of ^{18}F-NaF-PET in the management of neck pain and degenerative bone disorders.

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Footnote

Reporting Checklist: The authors have completed the STROBE reporting checklist. Available at https://qims.amegroups.com/article/view/10.21037/qims-21-1174/rc

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://qims.amegroups.com/article/view/10.21037/qims-21-1174/coif). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The CAMONA study was approved by the Danish National Health Committee on Health Research Ethics, registered at ClinicalTrials.gov (NCT01724749) and conducted in accordance with the Declaration of Helsinki (as revised in 2013). All participants provided written informed consent.

References

1. Theodore N. Degenerative Cervical Spondylosis. N Engl J Med 2020;383:159-68.
2. Binder AI. Cervical spondylosis and neck pain. BMJ 2007;334:527-31.
3. Matsumoto M, Fujimura Y, Suzuki N, Nishi Y, Nakamura M, Yabe Y, Shiga H. MRI of cervical intervertebral discs in asymptomatic subjects. J Bone Joint Surg Br 1998;80:19-24.
4. Lehto IJ, Tertti MO, Komu ME, Paajanen HE, Tuominen J, Kormano MJ. Age-related MRI changes at 0.1 T in cervical discs in asymptomatic subjects. Neuroradiology 1994;36:49-53.
5. Jensen RK, Jensen TS, Grøn S, Frafjord E, Bundgaard U, Damsgaard AL, Mathiasen JM, Kjaer P. Prevalence of MRI findings in the cervical spine in patients with persistent neck pain based on quantification of narrative MRI reports. Chiropr Man Therap 2019;27:13.
6. Green C, Butler J, Eustace S, Poynton A, O'Byrne JM. Imaging modalities for cervical spondylotic stenosis and myelopathy. Adv Orthop 2012;2012:908324.
7. Modic MT, Masaryk TJ, Mulopulos GP, Bundschuh C, Han JS, Bohlman H. Cervical radiculopathy: prospective evaluation with surface coil MR imaging, CT with metrizamide, and metrizamide myelography. Radiology 1986;161:753-9.
8. Byrnes TJ, Xie W, Al-Mukhailed O, D'Sa A, Novruzov F, Casey AT, House C, Bomanji JB. Evaluation of neck pain with (18)F-NaF PET/CT. Nucl Med Commun 2014;35:298-302.
9. Ovadia D, Metser U, Lievshitz G, Yaniv M, Wientroub S, Even-Sapir E. Back pain in adolescents: assessment with integrated 18F-fluoride positron-emission tomography-computed tomography. J Pediatr Orthop 2007;27:90-3.
10. Lim R, Fahey FH, Drubach LA, Connolly LP, Treves ST. Early experience with fluorine-18 sodium fluoride bone PET in young patients with back pain. J Pediatr Orthop 2007;27:277-82.
11. Mabray MC, Brus-Ramer M, Behr SC, Pampaloni MH, Majumdar S, Dillon WP, Talbott JF. (18)F-Sodium Fluoride PET-CT Hybrid Imaging of the Lumbar Facet Joints: Tracer Uptake and Degree of Correlation to CT-graded Arthropathy. World J Nucl Med 2016;15:85-90.
12. Blomberg BA, Thomassen A, Takx RA, Vilstrup MH, Hess S, Nielsen AL, Diederichsen AC, Mickley H, Alavi A, Høilund-Carlsen PF. Delayed sodium 18F-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. Irkle A, Vesey AT, Lewis DY, Skepper JN, Bird JL, Dweck MR, Joshi FR, Gallagher FA, Warburton EA, Bennett MR, Brindle KM, Newby DE, Rudd JH, Davenport AP. Identifying active vascular microcalcification by (18)F-sodium fluoride positron emission tomography. Nat Commun 2015;6:7495.
14. Araz M, Aras G, Küçük ÖN. The role of 18F-NaF PET/CT in metastatic bone disease. J Bone Oncol 2015;4:92-7.
15. Park PSU, Raynor WY, Sun Y, Werner TJ, Rajapakse CS, Alavi A. 18F-Sodium Fluoride PET as a Diagnostic Modality for Metabolic, Autoimmune, and Osteogenic Bone Disorders: Cellular Mechanisms and Clinical Applications. Int J Mol Sci 2021;22:6504.
16. Raynor WY, Borja AJ, Hancin EC, Werner TJ, Alavi A, Revheim ME. Novel Musculoskeletal and Orthopedic Applications of 18F-Sodium Fluoride PET. PET Clin 2021;16:295-311.
17. Rhodes S, Batzdorf A, Sorci O, Peng M, Jankelovits A, Hornyak J, An J, Noël PB, Høilund-Carlsen PF, Alavi A, Rajapakse CS. Assessment of femoral neck bone metabolism using 18F-sodium fluoride PET/CT imaging. Bone 2020;136:115351.
18. Blomberg BA, de Jong PA, Thomassen A, Lam MGE, Vach W, Olsen MH, Mali WPTM, Narula J, Alavi A, Høilund-Carlsen PF. 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.
19. Segall G, Delbeke D, Stabin MG, Even-Sapir E, Fair J, Sajdak R, Smith GT; SNM. SNM practice guideline for sodium 18F-fluoride PET/CT bone scans 1.0. J Nucl Med 2010;51:1813-20.
20. Kumagai G, Ono A, Numasawa T, Wada K, Inoue R, Iwasaki H, Iwane K, Matsuzaka M, Takahashi I, Umeda T, Nakaji S, Ishibashi Y. Association between roentgenographic findings of the cervical spine and neck symptoms in a Japanese community population. J Orthop Sci 2014;19:390-7.
21. Kushchayev SV, Glushko T, Jarraya M, Schuleri KH, Preul MC, Brooks ML, Teytelboym OM. ABCs of the degenerative spine. Insights Imaging 2018;9:253-74.

22. Rydman E, Bankler S, Ponzer S, Järnbert-Pettersson H. Quantifying cervical spondylosis: reliability testing of a coherent CT-based scoring system. BMC Med Imaging 2019;19:45.
23. Walraevens J, Liu B, Meersschaert J, Demaerel P, Delye H, Depreitere B, Vander Sloten J, Goffin J. Qualitative and quantitative assessment of degeneration of cervical intervertebral discs and facet joints. Eur Spine J 2009;18:358-69.
24. Maruotti N, Corrado A, Cantatore FP. Osteoblast role in osteoarthritis pathogenesis. J Cell Physiol 2017;232:2957-63.
25. Bastawrous S, Bhargava P, Behnia F, Djang DS, Haseley DR. Newer PET application with an old tracer: role of 18F-NaF skeletal PET/CT in oncologic practice. Radiographics 2014;34:1295-316.
26. Tao Y, Galbusera F, Niemeyer F, Samartzis D, Vogele D, Wilke HJ. Radiographic cervical spine degenerative findings: a study on a large population from age 18 to 97 years. Eur Spine J 2021;30:431-43.
27. Jäger HJ, Gordon-Harris L, Mehring UM, Goetz GF, Mathias KD. Degenerative change in the cervical spine and load-carrying on the head. Skeletal Radiol 1997;26:475-81.
28. Boden SD, McCowin PR, Davis DO, Dina TS, Mark AS, Wiesel S. Abnormal magnetic-resonance scans of the cervical spine in asymptomatic subjects. A prospective investigation. J Bone Joint Surg Am 1990;72:1178-84.
29. Panagiotidis E, Lam K, Mistry A, Seshadri N, Vinjamuri S. Skeletal Metastases and Benign Mimics on NaF PET/CT: A Pictorial Review. AJR Am J Roentgenol 2018;211:W64-74.
30. Kulshrestha RK, Vinjamuri S, England A, Nightingale J, Hogg P. The Role of 18F-Sodium Fluoride PET/CT Bone Scans in the Diagnosis of Metastatic Bone Disease from Breast and Prostate Cancer. J Nucl Med Technol 2016;44:217-22.
31. Kim K, Son SM, Goh TS, Pak K, Kim IJ, Lee JS, Kim SJ. Prediction of Response to Tumor Necrosis Value-α Blocker Is Suggested by 18F-NaF SUVmax But Not by Quantitative Pharmacokinetic Analysis in Patients With Ankylosing Spondylitis. AJR Am J Roentgenol 2020;214:1352-8.
32. Lee SJ, Kim JY, Choi YY, Lee S, Joo YB, Kim TH. Predictive value of semi-quantitative index from F-18-fluoride PET/CT for treatment response in patients with ankylosing spondylitis. Eur J Radiol 2020;129:109048.
33. Uchida K, Nakajima H, Miyazaki T, Yayama T, Kawahara H, Kobayashi S, Tsuchida T, Okazawa H, Fujibayashi Y, Baba H. Effects of alendronate on bone metabolism in glucocorticoid-induced osteoporosis measured by 18F-fluoride PET: a prospective study. J Nucl Med 2009;50:1808-14.
34. Frost ML, Cook GJ, Blake GM, Marsden PK, Benatar NA, Fogelman I. A prospective study of risedronate on regional bone metabolism and blood flow at the lumbar spine measured by 18F-fluoride positron emission tomography. J Bone Miner Res 2003;18:2215-22.
35. Win AZ, Aparici CM. Factors Affecting Uptake of NaF-18 by the Normal Skeleton. J Clin Med Res 2014;6:435-42.
36. Ayubcha C, Zirakchian Zadeh M, Stochkendahl MJ, Al-Zaghal A, Hartvigsen J, Rajapakse CS, Raynor W, Werner T, Thomassen A, Zhuang H, Høilund-Carlsen PF, Alavi A. Quantitative evaluation of normal spinal osseous metabolism with 18F-NaF PET/CT. Nucl Med Commun 2018;39:945-50.
37. Houshmand S, Salavati A, Hess S, Werner TJ, Alavi A, Zaidi H. An update on novel quantitative techniques in the context of evolving whole-body PET imaging. PET Clin 2015;10:45-58.
38. Kurata S, Shizukuishi K, Tateishi U, Yoneyama T, Hino A, Ishibashi M, Inoue T. Age-related changes in pre- and postmenopausal women investigated with 18F-fluoride PET--a preliminary study. Skeletal Radiol 2012;41:947-53.
39. Saleem S, Aslam HM, Rehmani MA, Raees A, Alvi AA, Ashraf J. Lumbar disc degenerative disease: disc degeneration symptoms and magnetic resonance image findings. Asian Spine J 2013;7:322-34.

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