Quantitative Evaluation of Normal Spinal Osseous Metabolism with $^{18}$F-NaF PET/CT

Cyrus Ayubcha, 1 Mahdi Zirakchian Zadeh (M.D.), 2 Mette Jensen Stochkendahl (P.h.D), 3,4 Abdullah Al-Zaghal (M.D.), 1 Jan Hartvigsen (P.h.D), 3,4 Chamith S. Rajapakse (P.h.D), 1,5 William Raynor, 1 Thomas Werner (M.S.E), 1 Anders Thomassen (P.h.D), 6 Hongming Zhuang (M.D.), 2 Poul F. Høilund-Carlsen (M.D.), 6,7 Abass Alavi (M.D.) 1

1. Department of Radiology, Perelman School of Medicine, University of Pennsylvania, PA, USA
2. Department of Radiology, Children’s Hospital of Philadelphia, PA, USA
3. Department of Sports Science and Clinical Biomechanics, University of Southern Denmark, Odense, Denmark
4. Nordic Institute of Chiropractic and Clinical Biomechanics, Odense, Denmark
5. Department of Orthopaedic Surgery, Perelman School of Medicine, University of Pennsylvania, PA, USA
6. Department of Nuclear Medicine, Odense University Hospital, Odense, Denmark
7. Department of Clinical Research, University of Southern Denmark, Odense, Denmark

Corresponding Author: Abass Alavi Department of Radiology Perelman School of Medicine University of Pennsylvania, PA, USA Telephone: 215-662-3069 Fax: 215-349-5843 E-mail: abass.alavi@uphs.upenn.edu
Abstract

Objective: To describe osseous metabolic activity with respect to age and weight in the spine as expressed through 18-F-sodium fluoride (NaF) uptake in a healthy male population.

Methods: Whole body NaF-PET/CT scans of healthy male subjects (22-71 years, 50-145 kg, n = 47) were analyzed using a global assessment methodology to derive mean standardized uptake values (SUV\text{mean}). Individual regions of the spine (cervical, thoracic and lumbar) along with the aggregate whole spine were assessed and compared as potential functions of age and body weight.

Results: Subjects of older age did not have higher NaF uptake than younger subjects (whole spine, \( p = 0.93 \); cervical, \( p = 0.12 \); thoracic, \( p = 0.93 \); lumbar, \( p = 0.42 \)), whereas increasing body weight was associated with greater tracer uptake (whole spine \( p = 0.003 \); cervical \( p = 0.01 \); thoracic \( p = 0.002 \); lumbar \( p = 0.004 \)). The thoracic (average SUV\text{mean} = 4.864 \pm 1.338) and lumbar (average SUV\text{mean} = 4.939 \pm 1.284) spines each had significantly elevated (\( p < 0.0001 \)) uptake as compared to the cervical spine (average SUV\text{mean} = 3.969 \pm 1.024).

Conclusion: We assessed the metabolic activity of the spine’s osseous tissues with NaF-PET using a global assessment approach in healthy males. Our study illustrated evidence of differences in spinal metabolism as related to weight, but not age. Our study offers a foundation for future larger studies in symptomatic populations.

Keywords: Spine, NaF-PET, Degeneration, Weight, Normal Subjects, Lumbar, Thoracic, Cervical, Global Analysis, Positron Emission Tomography
**Introduction**

Lower back pain (LBP) and neck pain (NP) are prevalent symptoms experienced by populations worldwide. Nearly 28% of adults in the United States have experienced LBP in the last three months [1]; neck and back pain are often persistent or recurrent [2]. Low back pain as a symptom may accompany several diseases; however, 90% of low back pain is categorized as non-specific in that it is impossible to reliably identify the etiology of the pain [3,4]. Various spinal structures may potentially contribute to nonspecific spine pain. Investigations with standard clinical assays or conventional structural imaging techniques have failed to effectively define the source of such pain [5]. Present management of non-specific back pain therefore does not rely upon structural diagnostic imaging [6].

Recently, greater emphasis has been placed on functional imaging of the spine, in the hope that metabolic inquiries may provide new insight into the metabolic activities of the spine. Specifically, positron emission tomography (PET) presents such an opportunity to observe metabolic processes occurring in the spine. PET with 18-F-sodium fluoride (NaF-PET) allows for the imaging of metabolic activity in osseous tissues [7]. Previously, NaF has been clinically popularized as a PET radiotracer in assessing bone metastases related to breast and prostate cancer [15-17]. Data derived from NaF-PET can be assessed with respect to other factors (e.g. age and weight) and offer an enhanced understanding of osseous metabolic processes (e.g. degeneration and osteoporosis) in the spine [8-12].

Understanding spinal metabolism in a normal population with respect to potentially influencing factors may lead to an enhanced understanding of the spine. Specifically, age and weight have both been scientifically determined to cause elevated inflammation and degeneration in the spine [13-16]; moreover, such degeneration has been present in a significant number of those with nonspecific pain [15]. Accordingly, this study aims to describe osseous metabolic activity in the spine as expressed through NaF uptake in a normal male population, and correlate the uptake with age and weight.
Materials and Methods

Materials and Image Acquisition:

This study utilized the whole-body PET scans of healthy male subjects from the CAMONA study [17]. All procedures performed in this study were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration including its later amendments or comparable ethical standards. CAMONA was approved by the Danish National Committee on Biomedical Research Ethics and registered at ClinicalTrials.gov (NCT01724749). The present study included all healthy male subjects (n=47, average age: 44±14 years, age range: 22-71 years, weight range: 50-145 kg, average BMI: 26 ± 4.1 kg/m²) present in the CAMONA study. All subjects had normal lipid levels, fasting plasma glucose levels, Hb1Ac and estimated glomerular filtration rates. Subjects with oncologic disease, autoimmune disease, immunodeficiency syndromes, alcohol abuse, illicit drug use, cardiovascular disease, or any prescription medication were not included. In light of the two variables of interest (age and weight), a linear correlation analysis confirmed that the group exhibited no significant relationship between their ages and weights; this allowed each variable to be independently assessed.

Figure 1 & Figure 2

Further, the CT or PET images were scrutinized by a trained radiologist to detect spinal abnormalities (i.e., vertebral fracture, ankylosing spondylitis, scoliosis or any other abnormalities) as additional grounds for exclusion. However, no subject was excluded on these grounds. NaF-PET/CT imaging was performed on integrated PET/CT systems (Discovery 690/710, STE, VCT, and RX; GE Healthcare) at Odense University Hospital, Denmark. NaF-PET/CT images were collected 90 minutes after intravenous injection of 2.2 MBq of 18-F-NaF per kilogram of body weight. PET images were corrected for attenuation, scatter, random coincidences, and scanner dead time.

Figure 3

Image Processing:

Data from the PET/CT images was analyzed using OsiriX software; Pixmeo SARL; Bernex, Switzerland (version 7.04); co-registration of the PET/CT allowed us to spatially map functional information with respect to anatomy. CT images were used to identify the C1 to L5 vertebral region, which was isolated with a maximum intensity projection deletion tool; the regional analysis similarly isolated individual spinal regions: lumbar (L1-L5), thoracic (T1-T12) and cervical (C1-C7). This method comprised all relevant spinal structures, including vertebral bodies, spinal canal, intervertebral discs, spinal processes and facet joints, however, transverse processes were
excluded. A 2D/3D segmentation tool, based on a region growing threshold algorithm, allowed for segmentation of the desired region. The parameters of the threshold algorithm (lower/upper bounds) were defined by Hounsfield units as acquired from the CT; this study’s technique utilized a (85/1500) threshold limit. The vertebra’s cortical bone was used as a landmark for the seeding point to promote the application of the segmentation algorithm in three dimensions. The final segmented region of interest (ROI) was manually altered to better capture the regions with additions and deletions (brush ROI) to the automatically segmented area. Based on the ROIs, software generated metrics were obtained per axial slice (3.75mm thickness).

Global Assessment Computation and Statistical Analysis:

The global assessment method was applied to the whole spine and per region. Pixel values of uptake within the two-dimensional axial ROI were averaged to determine a SUV\textsubscript{mean} per axial slice. Individual axial slices’ SUV\textsubscript{means} were multiplied by the respective axial area of the ROI (pixel area) to derive the total uptake per axial ROI. Accordingly, the total uptake of each axial ROI was summed across all slices to calculate the total uptake in the structure. Further, the axial ROI areas per slice were summed to derive the total volume of the structure. The total uptake of the structure was divided by the structure’s volume to determine the SUV\textsubscript{mean} of said structure.

Statistical analyses were performed utilizing this SUV\textsubscript{mean} of the entire volume per respective structure. Bivariate statistical analyses were utilized to both compare appropriate spinal regions (two-sample paired t-tests) and observe trends with respect to populations variables (linear correlations with respect to age, weight, and SUV\textsubscript{mean}). All analyses were performed using R Software and R Studio. The terms \( p \) and \( r \) are used to represent \( p \) value and Pearson’s correlation coefficient, respectively. \( p < 0.05 \) was deemed significant.

Results

Correlations between subjects’ SUV\textsubscript{mean} and age, with respect to each region of the spine, were statistically insignificant (whole spine \( p = 0.93, r = 0.01 \), cervical \( p = 0.12, r = 0.23 \), thoracic \( p = 0.93, r = 0.01 \), lumbar \( p = 0.42, r = -0.12 \))

Figure 4 & Figure 5 & Figure 6
Subjects’ particular SUV$_{\text{mean}}$ were correlated with weight; all three regions and the whole spine illustrated significant positive trends in uptake with increasing weight (whole spine $p = 0.003$, $r = 0.43$, cervical $p = 0.01$, $r = 0.36$, thoracic $p = 0.002$, $r = 0.43$, lumbar $p = 0.004$, $r = 0.42$).

**Figure 7**

A two-sample paired t-test found that the thoracic (average SUV$_{\text{mean}} = 4.864 \pm 1.338$, $p = < 0.0001$) and lumbar (average SUV$_{\text{mean}} = 4.939 \pm 1.284$, $p = < 0.0001$) spines each had significantly higher uptake than the cervical spine (average SUV$_{\text{mean}} = 3.969 \pm 1.024$). While lumbar expressed marginally greater average SUV$_{\text{mean}}$, the lumbar and thoracic regions were statistically similar ($p = 0.35$).

**Discussion**

Our study utilized the stated methodology to examine the relationship between age or weight and osseous metabolism. We found a statistically significant positive correlation between NaF uptake and increasing weight, which was reproduced in each region of the spine. We observed statistically insignificant correlations in relation to age.

Various proposed biological processes may theoretically be captured by our results. NaF radiotracer interacts solely with the bone’s hydroxyapatite matrix; this nonspecific nature allows various metabolic processes, including degenerative bone remodeling and age-dependent metabolic diseases related to osteoporosis, to simultaneously influence the magnitude of NaF uptake. Normal aging populations suffer degenerative changes of the intervertebral disc, known as degenerative disc disorder (DDD) [18,19]. The absence of functioning discs imposes physiologically abnormal amounts of pressure on the bone and may even allow physical friction between vertebrae [18,19]; degeneration-related effects in osseous tissues arise from pressure-stimulated mechanotransduction remodeling [20,21]. Increased mechanical load derived from degenerative changes may lead to increased metabolic activity, where spinal bone responds to pressure through the mechanotransduction pathway to stimulate remodeling via coordinated osteoblastic-osteoclastic activity [20,21]. Such leads to significantly increased metabolic activity in the way of bone remodeling and bone formation, often in the form of osteophytes [18,22]. As a consequence, natural degeneration with age is expected to promote NaF uptake [12]. However, this expected elevation of uptake with age via degenerative bone remodeling and formation would potentially be counteracted by
the diminished metabolic maintenance of the bone with normal aging [8-11]. Lessened metabolic activity in bone maintenance leads to lower bone mineral density, which is the accepted clinical marker for osteoporosis [23]. Moreover, compared to normal vertebrae, osteoporotic vertebrae have lower perfusion [24], which would lead to decreased SUV [25]. Such a counteraction may underlie the minimal correlation derived in our age analysis.

In our study, heavier subjects illustrated greater SUV\textsubscript{mean} in all three regions of the spine. This supports the concept of weight influencing degeneration related metabolic activity in osseous spinal tissues. Models have predicted that increased weight would lead to greater mechanical load on the vertebral bodies [26] and thus greater bone remodeling via mechanotransduction [20,21]. Additionally, increased mechanical load stimulates DDD [19]; this weight-related disc degeneration in heavier populations would contribute to further increase the mechanical load and thus promote additional remodeling activity.

Pressure based mechanisms may also explain the elevated average SUV\textsubscript{mean} in the lumbar and thoracic spines as compared to the cervical spine in our study. The spine is a multi-segmented structure where each successive caudal vertebra is burdened with increased net mechanical load as each vertebra supports weight above its respective axial position [27]. Also, the thoracic, but more so the lumbar vertebrae, support a majority of the weight when lifting objects [28,29]. However, the natural curvature of the spine diverts pressure to focal points in the thoracic curves [30]. In totality, the mentioned factors could theoretically sum to similarly increased mechanical stress on the lumbar and thoracic spines, which may explain the reported variations in average SUV\textsubscript{mean}.

Our study is unique to most PET studies in the use of a global assessment methodology. Common procedures regarding PET calls for subjective qualitative assessment of the region in question. However, quantitative methodologies are more objective and often align with clinical diagnoses [31,32]. Among known methods of quantification, the global assessment method has been determined to be a comprehensive and reproducible approach [31,33,34]. Most previous PET studies of the spine have relied upon SUV\textsubscript{max} and punch biopsy [7,8,11,35], however, our study uses the global assessment methodology and SUV\textsubscript{mean}. By utilizing all points of uptake in the desired region, global assessment derives a more robust value [31,33,34]. Further, the use of SUV\textsubscript{mean} as opposed to SUV\textsubscript{max}, which only uses a single data point in the region, has similar advantages [31,33,34].
Other studies have used NaF-PET to investigate the spine, however, this study is novel in its assessment of healthy subjects. Most studies confirmed PET as an appropriate diagnostic modality in qualitatively diagnosing specific disorders in the spine, such as spinous process injuries, localized facet inflammation or spondylolysis [36,37]. Win et al. used NaF-PET to correlate tracer uptake in individual vertebrae with age and weight [11]. Their study only had 11 subjects and each subject had various preexisting malignancies that prompted their scans. Further, their study used punch-biopsy and SUV$_{\text{max}}$ to examine individual vertebrae. Their particular study found that weight increased NaF uptake, though their trend was insignificant likely due to insufficient sample size. However, Win et al. reported a decrease in SUV$_{\text{max}}$ with age, which may relate to osteoporotic change [11]; their trend can be rationalized by their purposeful selection of only “normal” vertebral regions. So, their exclusion of more metabolically active regions (potentially related to spinal degeneration) that were included in our global analysis technique may explain the conflicting trend between our studies.

Our study has some limitations of note. Variations within the linear trends may be attributed to uncontrollable environmental factors that could influence the bone and its metabolism (e.g. occupation, diet, exercise etc.). While these factors are complicating, they are unlikely to significantly alter the broad relationships previously expressed. Moreover, our study included only healthy male subjects. Given that osteoporotic processes act counter to the degenerative process to decrease uptake, women’s postmenopausal accelerated bone loss would variably confound age or weight-related degeneration unevenly. Male rates of depressed osseous metabolic activity are lower as compared to females [38,39], and thus, such effects are less variable and less significant in our population. Additionally, this study includes no information regarding the clinical back pain history of our subjects. Accordingly, a clinical translation of this modality and methodology to those with non-specific back pain can be accomplished with a larger study of the target population.

Conclusions

This study has established a methodology to assess the metabolic activity of the spine’s osseous tissues with NaF-PET. Further, our study illustrated evidence of differences in spinal metabolism as related to weight, but not age. The presumed metabolically degenerative effects of weight on osseous spinal tissues observed provide broad precedent for potential etiologies of weight related back symptomology. Our study offers a foundation for future studies in diseased populations.
Figures and Legends:

Figure 1: Diagram graphically portraying the selection criteria for the subjects in this study.

Figure 2: Distribution of weight and age within the subject group. There is no significant relationship (Slope = -0.18, R = 0.01) and thus no confounding interaction between the two variables.

Figure 3: An axial image of a patient’s PET-CT scan. Whereas the red-yellow color scheme represents the degree of NaF activity, the green shading illustrates an exemplary region of interest, as applied by the mentioned methodology, to an axial image of the spine.

Figure 4: Positive correlation between uptake and weight in the cervical spine.

Figure 5: Positive correlation between uptake and weight in the thoracic spine.

Figure 6: Positive correlation between uptake and weight in the lumbar spine.

Figure 7: Bar graph showing the average SUV_{mean} of the anatomical subdivision of the spine in the studied population.
Notes

Funding: This study was funded by the MD/PhD ‘Alexandre Suerman’ programme, University Medical Center Utrecht, Utrecht, The Netherlands, the Anna Marie and Christian Rasmussen’s Memorial Foundation, University of Southern Denmark, Odense, Denmark, and the Jørgen and Gisela Thrane’s Philanthropic Research Foundation, Broager, Denmark.

Conflict of Interest: No conflicts of interest to disclose.

Ethical approval: All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. This study is part of the CAMONA protocol. CAMONA was approved by the Danish National Committee on Biomedical Research Ethics and registered at ClinicalTrials.gov (NCT01724749).

Informed consent: Informed consent was obtained from all individual participants included in the study.
References


CAMONA Study Subjects
n = 139

Characteristics:
Lack of oncologic disease, immunodeficiency syndromes, illicit drug use, alcohol abuse, autoimmune disease, and prescription medications.

Excluded: n = 92
Exclusion Criteria Order:
1. Females: n = 66
2. Elevated Cardiovascular Risk Factors: n = 26
3. Complicating Spinal Disorders: n = 0

Eligible Participants
n = 47
Figure 4

Cervical

$SUV_{mean}$ vs. $Weight (kg)$

Weight (kg)

$SUV_{mean}$
Figure 5
Figure 6

Lumbar

$SUV_{mean}$ vs. $Weight(kg)$
Figure 7

Cervical
Thoracic
Lumbar

SUV
mean

Cervical
Thoracic
Lumbar