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Case Report

^{18}F-NaF PET/CT for early detection of osteoporosis in the lumbar spine: two case reports

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Abstract: Osteoporosis is a highly prevalent skeletal disease involving a pathophysiology of altered bone turnover. Positron emission tomography (PET)/computed tomography (CT) imaging with ^{18}F-sodium fluoride (NaF) can visualize metabolic alterations in bone that precede clinical manifestations or structural alterations and thus may serve a role in the early detection and monitoring of osteoporosis. We present two non-oncological case reports demonstrating different metabolic changes in early and advanced disease stages as assessed by ^{18}F-NaF PET/CT that cannot be appreciated by conventional structural imaging alone, supporting a potential clinical application of ^{18}F-NaF PET/CT for early detection and monitoring of osteoporosis in the lumbar spine.

Keywords: Osteoporosis, lumbar spine, ^{18}F-sodium fluoride (NaF), positron emission tomography (PET), computed tomography (CT)

Introduction

Osteoporosis is a systemic skeletal disease characterized by reduced bone mineral density and altered bone microstructure that predisposes patients to low-impact fragility fractures [1, 2]. The global prevalence of osteoporosis is estimated to be greater than 200 million, affecting more than 70% of people over the age of 80 [3, 4]. Given the progressive nature of this disease, the early detection of osteoporosis is critical for initiating timely therapeutic interventions and optimizing patient management [5].

Dual-energy x-ray absorptiometry (DXA) remains the most frequently used imaging modality to quantify changes in bone mineral density [6]. It is a standard method for measuring bone mineral density (BMD), used to diagnose osteoporosis and assess fracture risk. The results are expressed as a T-score, which compares a person's bone density to that of a healthy young adult, with a T-score of -2.5 or below indicating osteoporosis [7]. While DXA enables detection of structural osteoporotic deterioration, this imaging approach does not capture microscopic changes in bone metabolism that potentially hold clinical relevance in identifying early-stage pathology or disease progression [8]. Imaging the pathophysiological changes that underlie the development of osteoporosis may improve methods of quantifying bone degeneration, fracture risk, and response to treatment.

^{18}F-sodium fluoride (^{18}F-NaF) positron emission tomography (PET)/computed tomography (CT) is a molecular imaging modality capable of detecting active metabolic activity in bone [9]. The dissociated fluoride ion binds exposed hydroxyapatite crystal *in vivo*, thereby providing a quantitative measure of osteoblastic and osteoclastic activity [10]. While conventionally used to evaluate skeletal tumors, ^{18}F-NaF has gained interest in the imaging of bone degeneration that precedes the onset of structural alterations visible on conventional imaging.

Below we present two non-oncological case reports demonstrating the potential of ^{18}F-NaF PET/CT to identify early metabolic alterations of the lumbar spine, showcasing its utility in the early detection and monitoring of osteoporosis.

Case 1

A 25-year-old female with a body mass index (BMI) of 28.1 kg/m^2, no history of cardiovascular disease (CVD), a smoking history of 5 pack-years, and active alcohol consumption was recruited from the Cardiovascular Molecular Calcification Assessed by ^{18}F-NaF PET CT (CAMONA) clinical trial (NCT01724749) [11] as a healthy volunteer. The subject underwent ^{18}F-NaF PET/CT imaging 90 minutes after radiotracer injection (**Figure 1**). The mean standardized uptake value (SUVmean) for ^{18}F-NaF in the trabecular region of each lumbar vertebral body (VB) was assessed by manual delineation of a region of interest (ROI) using OsiriX MD software (Pixmeo, Bernex, Switzerland). Specifically, the ROI was created by applying the oval function the center of the trabecular bone region throughout the consecutive axial PET/CT slices of L1 to S1 vertebrae. The size of the ROI was kept constant and placed to avoid cortical bone, vertebral arch, and facet joints. The average SUV of all voxels in the ROIs was then calculated to determine ^{18}F-NaF SUVmean for each VB. To determine lumbar spine density, the same ROIs was used

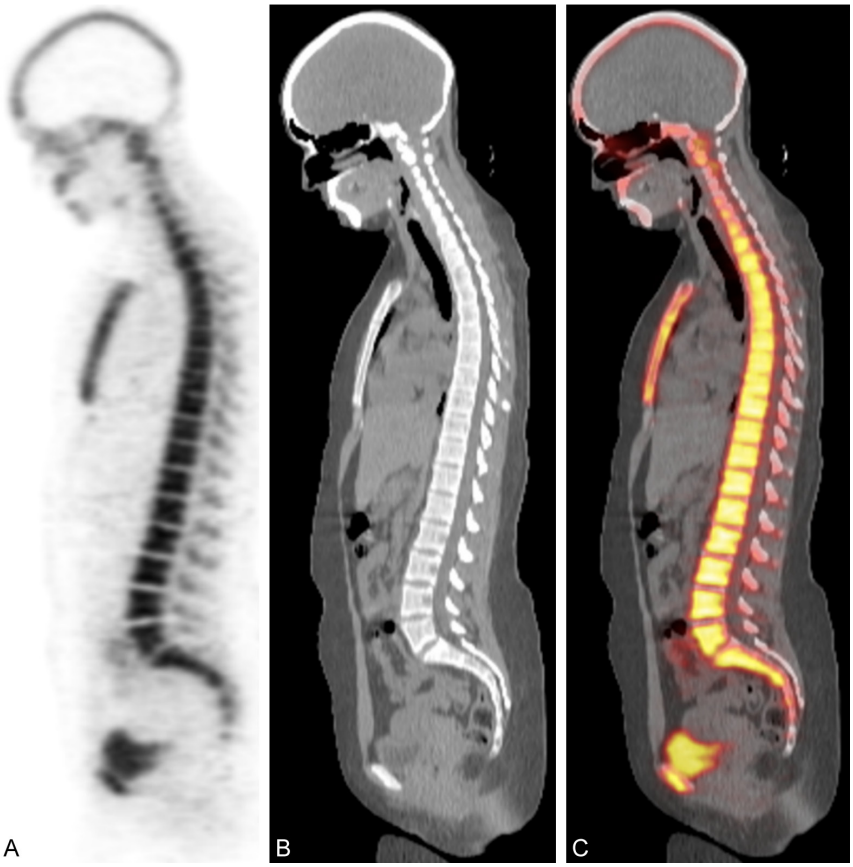

Figure 1. Sagittal views of ^{18}F-NaF PET (A), CT (B), and combined ^{18}F-NaF PET/CT (C) for Case 1.

Table 1. ^{18}F-NaF SUVmean and CT radiodensity values for Case 1

Vertebral Level	^{18}F-NaF SUVmean	Radiodensity (HU)
L1	10.76	213
L2	12.63	237
L3	13.88	229
L4	13.95	200
L5	14.04	191
S1	7.64	301

to calculate the average CT Hounsfield unit (HU) value in each VB. The following thresholds were used to distinguish lumbar osteoporosis with 88.5% specificity and 60.8% sensitivity: L1 ≤ 110 HU or L2 ≤ 100 HU or L3 ≤ 85 HU or L4 ≤ 80 HU [12].

The subject's lumbar spine ^{18}F-NaF SUVmean and radiodensity on CT were among the highest noted in the entire cohort of patients assessed (**Table 1**). The high HU values suggest no structural abnormalities.

Case 2

A 67-year-old female with a BMI of 22.7 kg/m^2, history of CVD and a high Framingham Risk Score of 25.4%, smoking history of 8 pack-years, and active alcohol consumption was recruited from the CAMONA clinical trial. She was enrolled as an "at-risk" patient for CVD and underwent ^{18}F-NaF PET/CT imaging 90 minutes after radiotracer injection (**Figure 2**).

This patient's ^{18}F-NaF SUVmean values and CT radiodensity in the lumbar spine were among the lowest in the entire cohort of subjects who were assessed (**Table 2**). The low HU values are consistent with osteoporotic degeneration in all vertebrae but L4, which was borderline normal [12].

Discussion

These case reports demonstrate the utility of ^{18}F-NaF PET/CT imaging in evaluating progressive osteoporotic changes of the lumbar spine. Case 1, a 25-year-old female with minimal osteoporotic risk factors, demonstrated elevated ^{18}F-NaF uptake and high lumbar spine density, indicating robust bone turnover and active remodeling prior to structural alterations. In Case 2, a 67-year-old female exhibited markedly low ^{18}F-NaF uptake, likely reflecting trabecular bone loss as evidenced by reduced CT radiodensity. Decreased trabecular bone volume reduces the availability of hydroxyapatite for fluoride binding, resulting in low ^{18}F-NaF uptake [9].

The subjects' risk factors for osteoporosis are pertinent to the observed findings. The subject in Case 1 was also positive for several osteoporotic risk factors, supporting the finding of elevated ^{18}F-NaF SUVmean. Her young age may explain the absence of structural changes on CT. The subject in Case 2 was an elderly female with a history of CVD, smoking, and alcohol use - factors known to elevate the risk of developing osteoporosis. Aging and female sex can predispose to bone loss due to the decline in estrogen levels post-menopause, which accelerates trabecular bone resorption [13]. A history of CVD has been associated with osteoporosis due to common pathophysiological mechanisms and shared risk factors [14]. Smoking and alcohol consumption both decrease bone mineral density through alterations in bone formation and resorption [15, 16]. Information on the use of bone-active medications was not recorded for either patient, which may also influence patterns of radiotracer uptake [17].

Several studies have investigated the use of ^{18}F-NaF PET to detect degenerative changes in the spine and other regions susceptible to osteoporosis. In a study of 32 pre- and post-menopausal women, Kurata et al. observed an inverse correlation between ^{18}F-NaF maximum standardized uptake value (SUVmax) in the lumbar spine and age.

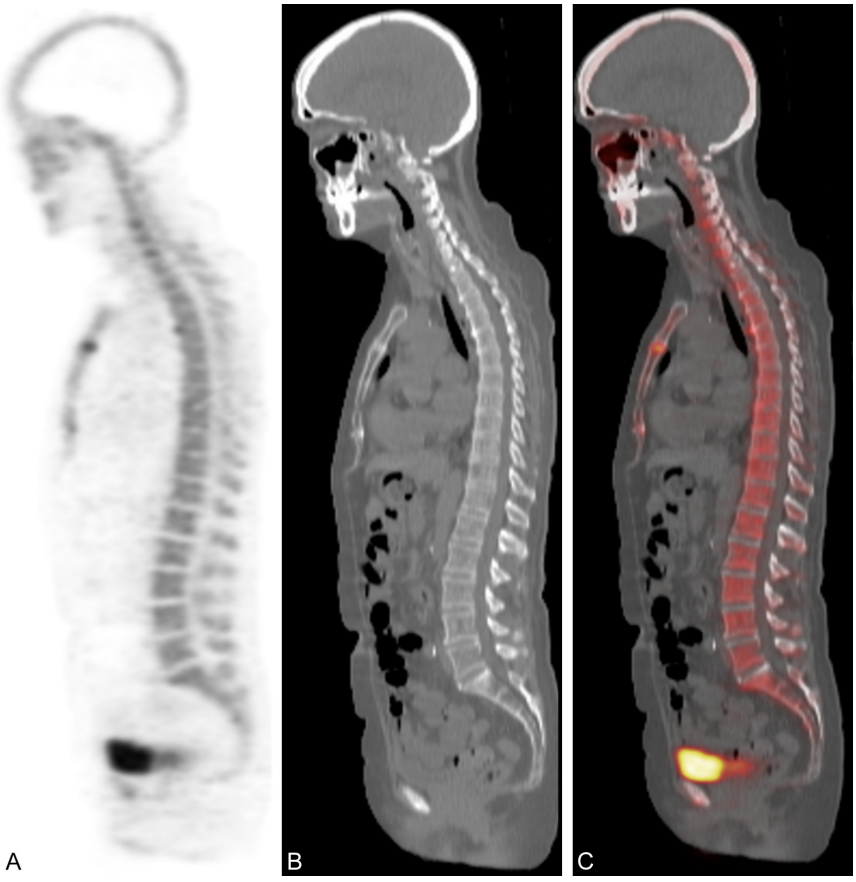

Figure 2. Sagittal views of ^{18}F-NaF PET (A), CT (B), and combined ^{18}F-NaF PET/CT (C) for Case 2.

Table 2. ^{18}F-NaF SUVmean and CT radiodensity values for Case 2

Vertebral Level	^{18}F-NaF SUVmean	Radiodensity (HU)
L1	5.91	105
L2	6.46	83
L3	7.43	83
L4	7.04	81
L5	6.58	104
S1	5.35	67

A direct correlation between ^{18}F-NaF SUVmax in the humeral shaft and age was also noted [18]. Rhodes et al. calculated the Bone Metabolism Score (BMS) as the ratio of ^{18}F-NaF SUV in the femoral neck to that of the total bone, demonstrating inverse correlations between BMS and age [19]. The findings in our cases add to a growing body of evidence indicating a promising clinical application of ^{18}F-NaF PET/CT as a biomarker of osteoporosis.

While DXA remains the gold standard for imaging osteoporosis, this modality has limitations including a low sensitivity for estimating fracture risk [20-22]. Quantitative CT has also been utilized to screen osteoporosis, as attenuation values correlate with traditional bone mineral density measurements [23]. DXA and other structural imaging approaches, however, cannot detect the molecular changes occurring in bone that precede the onset of structural pathology (e.g., vertebral fractures) or clinical symptoms. ^{18}F-NaF PET/CT may thus serve a complementary role as a measure of bone metabolism to enhance methods of identifying osteoporosis. As suggested by our cases, clinical applications of ^{18}F-NaF PET/CT could involve early detection of the vulnerable patient as well as monitoring progression of disease. The Fracture Risk Assessment Tool (FRAX) calculates the 10-year risk of osteoporotic fractures in patients based on DXA-derived bone mineral density and clinical factors [24]. Incorporating metabolic measurements from ^{18}F-NaF PET/CT may provide a comprehensive assessment of bone quality and improve the predictive accuracy of FRAX.

Moreover, ^{18}F-NaF PET/CT may have a practical role as an opportunistic screening tool for the oncological patient population. In a study of 105 males with prostate cancer who underwent ^{18}F-NaF PET/CT imaging, Chesnais et al. identified decreased ^{18}F-NaF SUVmean and SUVmax in the thoracic spine of patients with fractures relative to those without fractures [25]. However, no differences in CT HU of the cervical, thoracic, lumbar, or sacral regions were found. A separate study by Huang et al. found a direct correlation between ^{18}F-NaF uptake and DXA-derived bone mineral density in the lumbar spine of 199 oncological patients [26]. ^{18}F-NaF PET/CT may thus provide a quantitative measure of the degree of osteoporosis including early phase osteoporosis that is not yet apparent on CT.

The case reports presented in this study provide a descriptive evaluation of ^{18}F-NaF PET/CT's promising role as a biomarker for osteoporosis. While the limited sample size precludes definitive assessments, we provide a proof-of-concept for future investigations to generate hypotheses on the application of this radiotracer for monitoring disease progression. Furthermore, the subjects analyzed in the CAMONA trial were primarily evaluated for cardiovascular disease: our analysis of bone quality was exploratory, and few subjects in the entire patient population met the criteria for osteoporosis. A future study of patients with a high risk of developing osteoporosis (e.g., elderly women) is warranted to provide further detail on ^{18}F-NaF PET/CT's clinical utility.

Conclusion

^{18}F-NaF PET/CT imaging reveals metabolic changes affecting the bone microstructure of patients at risk for

osteoporosis. This modality may serve a future role as an early diagnostic measure of osteoporosis and biomarker of disease progression. Further research, particularly longitudinal studies that can assess the relationship between ^{18}F-NaF uptake in the spine and patient outcomes, is needed to validate the clinical application of this modality.

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Disclosure of conflict of interest

None.

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