^{18}F–Sodium Fluoride PET/CT and PET/MR Imaging of Bone and Joint Disorders

Mohsen Beheshti, MD, FEBNM, FASNC[a,b,*]

KEYWORDS

• ^{18}F-NaF • PET/CT • PET/MR imaging • Malignant bone disease • Benign bone disease

KEY POINTS

- The most common auspicious indications of Sodium Fluoride F 18 (^{18}F-NaF) PET/CT in benign bone diseases are insufficiency fractures, occult fractures, osteoarthritis, osteoid osteoma, failed back surgery, child abuse, and evaluation of joint prosthesis as well as metabolic bone diseases.
- ^{18}F-NaF PET/CT is highly accurate modality clearly superior to ^{99m}Tc–methylene diphosphonate planar imaging or single-photon emission CT/CT for staging and restaging of malignant bone disease.
- ^{18}F-NaF PET/CT seems to be promising in differentiating benign from malignant bone lesions, particularly when using dynamic quantitative approaches.
- There are currently no available data supporting the superiority of ^{18}F-NaF PET/MR imaging to ^{18}F-NaF PET/CT for the assessment of bone diseases in the routine clinical practice. With the development and more availability of PET/MR imaging, however, this modality may yield new applications for the widespread use of ^{18}F-NaF in clinical management of malignant diseases, particularly in prostate and breast cancer patients.

INTRODUCTION

Sodium Fluoride F 18 (^{18}F-NaF) is a positron-emitting radiotracer that was first introduced in 1962 for skeletal scintigraphy. Its clinical use was limited, however, at that time mainly due to a short half-life of 109.74 minutes and tracer characteristics that were less ideal for conventional gamma cameras. Thus, it had been largely replaced in the late 1970s by ^{99m}Tc-labeled diphosphonates, which showed optimal characteristics for conventional gamma-based scintigraphy.

With the improvements of PET/CT scanners, high-resolution imaging of bone became a reality; therefore, ^{18}F-NaF was reintroduced for clinical and research investigations in assessment of benign and malignant bone diseases.

^{18}F-NaF is a bone-seeking agent that directly incorporates into the bone matrix, converting hydroxyapatite to fluoroapatite.[1] ^{18}F-NaF is rapidly cleared from the plasma due to small protein-bound proportion with a first-pass extraction rate of 100%, with only 10% remaining in plasma 1 hour after injection.[2,3] Thus, it provides desirable characteristics of high and rapid bone uptake, accompanied by very rapid blood clearance, resulting in a high bone-to-background ratio and

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[a] Department of Nuclear Medicine and Endocrinology, PET - CT Center LINZ, Ordensklinikum, St Vincent's Hospital, Seilerstaette 4, Linz A-4020, Austria; [b] Department of Nuclear Medicine and Endocrinology, Paracelsus Medical University, Muellner Hauptstrasse 48, Salzburg A-5020, Austria

* Corresponding author. Department of Nuclear Medicine and Endocrinology, PET - CT Center LINZ, Ordensklinikum, St Vincent's Hospital, Seilerstaette 4, Linz A-4020, Austria.

E-mail address: mohsen.beheshti@ordensklinikum.at

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high-quality images of the skeleton in less than 1 hour after tracer intravenous administration.

Although only a few studies have compared ^{18}F-NaF with ^{99m}Tc–methylene diphosphonate (MDP) for evaluation of bone and joint disorders, ^{18}F-NaF PET seems more sensitive than conventional bone scanning, showing a higher contrast between normal and abnormal tissue and with the potential for the assessment of small bony structures especially in the spine.[4–11]

This article reviews the available literature and summarizes the clinical experience with ^{18}F-NaF PET/CT in benign and malignant bone diseases.

^{18}F–SODIUM FLUORIDE PET/COMPUTED TOMOGRAPHY IN BENIGN BONE DISEASE

Metabolic Bone Disease

^{18}F-NaF PET/CT provides a novel tool for assessing bone metabolism that complements the conventional methods. Unlike biochemical markers, which globally measure the integrated response to therapy in the whole skeleton, ^{18}F-NaF PET can differentiate the changes occurring at sites of clinically relevant osteoporotic fractures, such as the spine and hip. Effective bone plasma flow (K_1), from which bone blood flow can be estimated, can be obtained by measuring the fluoride plasma clearance to bone mineral (K_i) using dynamic PET acquisitions at the specific anatomic sites within the field of view of the PET scanner. After the dynamic images, static acquisitions can be performed to estimate Ki at additional bony sites by taking 2 and 4 venous blood samples to derive the input function.[12] In addition, standardized uptake value (SUV) can be used for semiquantitative analysis. Measurements of K_i, however, are more complicated to perform than SUV. Nevertheless, they have the advantage that they are specific to the bone metabolic activity at the site of measurement whereas SUV might be influenced by multiple biological and technical factors.

Using the quantitative and semiquantitative approaches, ^{18}F-NaF PET/CT has been used in different metabolic bone diseases. In author's experience, ^{18}F-NaF PET/CT can be helpful for the evaluation of bone involvement in hyperparathyroidism. It is also a sensitive modality for detecting the areas of increased bone remodeling or insufficiency fractures. Moreover, the CT part provides useful information regarding the extension of brown tumors and bone stability.

In an experimental trial, ^{18}F-NaF PET/CT was used for noninvasive measurement of bone turnover.[13] The investigators reported that ^{18}F-NaF PET/CT provides quantitative estimates of bone blood flow and metabolic activity that correlate with histomorphometric indices of bone formation in the normal bone tissue of the mini pigs (baby or small pigs). They concluded that ^{18}F-NaF PET/CT may facilitate follow-up of patients with metabolic bone diseases and reduce the number of invasive bone biopsies.[13]

In another study, researchers described a good correlation between ^{18}F-NaF metabolism and serum markers like alkaline phosphatase and parathormone levels in patients with renal osteodystrophy.[14] ^{18}F-NaF PET/CT study was useful to differentiate lesions with low versus high turnover in renal osteodystrophy and provided quantitative estimates of bone cell activity.

Furthermore, ^{18}F-NaF PET/CT was shown promising for quantitative assessment of the effects of bisphosphonate treatment on bone remodeling and metabolism in patients with glucocorticoid-induced osteoporosis.[15]

In a research study by the author's group, a significant correlation was found between semiquantitative ^{18}F-NaF PET analysis and T and Z scores on dual-energy x-ray bone-absorptiometry in lumbar spine of osteoporotic patients.[16] The potential of ^{18}F-NaF PET for prediction of bone mineral deficit, however, should be evaluated in future prospective studies.[16]

Inflammatory Bone and Joint Disease

Inflammatory and rheumatologic diseases involving bones and joints like rheumatoid arthritis and spondyloarthropathy are among the most common indications for conventional bone scintigraphy (BS). Tracer perfusion on early-phase images and distribution pattern of involved joints as well as intensity of tracer uptake on BS are useful for the detection and characterization of various inflammatory diseases and help guide treatment.

BS has important limitations, however, in assessment of inflammatory bone diseases despite its established indication. In a systematic literature review, BS was positive in only 52% of the patients with established ankylosing spondylitis (AS) and in 49.4% of the patients with probable sacroiliitis.[17] This low sensitivity might be one of the reasons that in many institutions MR imaging has replaced BS as the first-line imaging tool in patients with suspected AS or other spondyloarthropathies. MR imaging is more sensitive and has superior performance than BS in detecting sacroiliitis in the early stage.[18]

There are few publications assessing the impact of ^{18}F-NaF PET/CT in patients with rheumatologic disease. In a study, Strobel and colleagues[19] compared the value of ^{18}F-NaF PET/CT in