Novel Musculoskeletal and Orthopedic Applications of ^{18}F -Sodium Fluoride PET

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KEYWORDS

• Fracture • Osteoarthritis • Ankylosing spondylitis • Temporomandibular disorder • Arthroplasty
• Infection • Osteoporosis • Osteosarcoma

KEY POINTS

- ^{18}F -sodium fluoride (NaF) PET can detect causes of bone pain and traumatic injuries that cannot be successfully visualized by other modalities such as radiography, bone scintigraphy, computed tomography, and magnetic resonance. Thus, NaF-PET may contribute to the assessment of occult fractures, child abuse, and stress-related injuries.
- NaF-PET is an excellent modality to assess osteoarthritis, ankylosing spondylitis, and temporomandibular joint dysfunction. More studies are needed to determine its potential role in inflammatory arthropathies such as rheumatoid arthritis and psoriatic arthritis.
- Complications of orthopedic surgery such as hardware loosening and infection are readily visualized by NaF-PET. Heterotopic ossification after surgery is another possible imaging target that requires further exploration.
- Metabolic bone diseases such as osteoporosis and Paget disease can be evaluated over time with NaF-PET to determine effects of pharmacologic interventions such as bisphosphonates and teriparatide.
- NaF-PET may have a role in assessing primary bone tumors such as osteosarcoma, helping to determine response to treatment and guiding patient management decisions.

INTRODUCTION

The bone-seeking properties of ^{18}F -sodium fluoride (NaF) were first described in 1962 by Blau and colleagues,¹ who used this positron-emitting radiotracer in skeletal scintigraphy. Both high uptake by bone and rapid plasma clearance of NaF

were determined to be advantages in imaging skeletal metabolism.² The mechanism of NaF uptake relies on the exchange of OH^- for $^{18}\text{F}^-$, converting hydroxyapatite on the surface of the bone matrix to fluorapatite.^{2,3} One hour after NaF is administered intravenously, only 10% remains in the plasma compartment because of a first-pass

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extraction rate of 100%, allowing excellent contrast resolution.⁴

However, the use of NaF was largely abandoned after the introduction of phosphate-based tracers labeled with ^{99m}Tc.⁴ The first of these was ^{99m}Tc-polyphosphate, which was described in 1971,⁵ followed by ^{99m}Tc-methylene diphosphonate in 1975.⁶ Compared with NaF, bone scintigraphy (BS) with ^{99m}Tc-labeled agents had the advantage of a longer half-life (6.0 hours vs 110 minutes) and photons with lower energy (140-keV vs 511-keV), allowing easier detection by conventional gamma cameras.^{4,7-9} Over the next 4 decades, developments in PET scanners allowed the detection of high-energy photons, resulting in the widespread adoption of many ¹⁸F-based tracers.^{3,4} As PET imaging with 2-deoxy-2-[¹⁸F]fluoro-D-glucose (FDG) continues to expand, increased efficiency in the production and delivery of ¹⁸F-labeled tracers has resulted in greater NaF availability.⁹ Several properties of NaF, such as lower protein binding and higher plasma clearance, justify its superiority to ^{99m}Tc-labeled tracers.¹⁰ In addition, the increased spatial resolution of PET compared with gamma cameras presents a significant advantage.⁷ Consequently, the promise of high-resolution skeletal imaging has sparked a growing interest in assessing musculoskeletal disorders by NaF-PET.

Quantitative PET parameters used to measure new bone formation include bone plasma clearance expressed as K_i and bone uptake expressed as a standardized uptake value (SUV).¹¹ Calculation of plasma clearance is based on rate constants that describe the movement of NaF between plasma, bone extracellular fluid, and bone mineral compartments. To obtain these data, the Hawkins method represents the standard protocol, requiring 60-minute dynamic imaging and arterial or venous sampling and only allowing the assessment of a single skeletal site at a time.¹² More recently, simplified methods of estimating K_i have been developed, such as that proposed by Siddique and colleagues,¹³ which nonetheless requires 4 venous blood samples taken at 10-minute intervals starting 30 minutes after tracer administration. Alternatively, NaF uptake can be measured throughout the skeleton with a single static scan and no need for blood sampling. SUV represents the detected activity concentration in an area, normalized to the administered activity and the patient's body weight or lean body mass.¹¹

A major focus of NaF-PET imaging has been the assessment of skeletal metastases from prostate and breast cancer.¹⁰ Although NaF-PET represents a sensitive method of detecting osteoblastic

changes, other PET tracers are available that are more appropriate in this domain. Because bone metastases start with seeding of the red marrow by malignant cells, PET imaging with FDG, ¹⁸F-fluciclovine (FACBC), radiolabeled choline, or prostate-specific membrane antigen ligands constitutes a more direct approach and has the advantage of detecting intramedullary lesions that have not resulted in reactive bone remodeling.^{14,15} By contrast, indirect evidence of metastasis provided by bone imaging modalities is not appropriate for detecting cancer cell activity, unless malignant cells themselves express osteoblastic activity, as in osteosarcoma.¹⁶ Rather, NaF-PET, combined with computed tomography (CT) or magnetic resonance (MR) for anatomic correlation, has a promising role in the imaging of benign musculoskeletal disorders that cause direct changes in osteoblastic activity. This article discusses the novel applications and utility of NaF in the assessment of musculoskeletal trauma, arthropathies, back pain, orthopedic complications, metabolic bone disease, and other osseous and soft tissue disorders.

MUSCULOSKELETAL TRAUMA

The first-line imaging modality to assess for traumatic fracture is conventional radiography, and CT can be used to detect and characterize occult and complex fractures with high sensitivity.¹⁷ Recent investigations have suggested the superiority of NaF-PET/CT to conventional modalities in the detection of pathologic fractures, fatigue fractures, and occult fractures.¹⁸⁻²² Jeon and colleagues²³ retrospectively analyzed NaF-PET/CT images obtained a median of 290 days after ankle injury in a study that included 95 patients with fracture, 12 with Achilles tendon rupture, 12 with ligament injury, and 2 with complex regional pain syndrome. All patients with fractures were found to have NaF-avid lesions, and only 8 in the non-fracture group had negative NaF-PET/CT findings. Further, various PET parameters, including maximum SUV (SUVmax), mean SUV (SUVmean), metabolic target volume (MTV), and total lesion activity (TLA = SUVmean × MTV) were all inversely correlated with ankle range of motion. The feasibility of imaging stress fractures with NaF-PET/MR was investigated in 20 patients with foot pain by Crönlein and colleagues.²⁴ Despite negative findings on radiography, 4 stress fractures and 7 stress reactions involving the foot and ankle were identified by PET/MR. A comparative study between PET/CT and PET/MR by the same group found that both hybrid modalities identified the same 42 lesions across 22 subjects with foot

pain of unclear cause.²⁵ They reported that NaF uptake expressed as SUVmax and SUVmean was highly correlated between PET/CT and PET/MR. Although PET/CT was noted as being superior for the diagnosis of osteoarthritis, the ability to assess bone marrow resulted in PET/MR being favored in the diagnosis of stress fractures and bone marrow edema. Spriet and colleagues²⁶ reported a study of 9 racehorses, in which NaF-PET/CT imaging was performed on 16 forelimbs and 4 hindlimbs. The investigators found that NaF-PET/CT detected lesions that were not present on BS, CT, or MR, and they concluded that early detection of stress injuries by PET could play a role in preventing catastrophic fractures in horseracing.

Indications for NaF-PET/CT in children and young adults have primarily been for benign disorders.²⁷ The bones of the thorax and extremities have been observed to have increased NaF avidity in cases of fracture and stress injury.²¹ As with BS, NaF uptake may be present at the pubic synchondrosis as part of normal development.^{28,29} One application of NaF-PET/CT that has been proposed is in the evaluation of child abuse. In a study of 22 pediatric patients with suspicion of having been abused, Drubach and colleagues²¹ found that although high-detail skeletal survey detected 156 fractures, imaging with NaF-PET detected 200 fractures (**Fig. 1**). The investigators calculated the sensitivities of NaF-PET and skeletal survey by comparing baseline imaging studies with follow-up skeletal survey imaging performed 10 to 24 days later. The results suggested that NaF-PET was superior to baseline skeletal survey in detecting fractures involving bones of the thorax, such as the ribs, sternum, scapulae, and clavicles, with a sensitivity of 92%. The sensitivity of NaF-PET in detecting posterior rib fractures was determined to be 93%. At the same time, NaF-PET was found to be inferior in the detection of classic metaphyseal fractures, with a sensitivity of 67%, whereas skeletal survey had a sensitivity of 80%. Overall for all lesions, NaF-PET was found to have a sensitivity of 85%, whereas skeletal survey had a sensitivity of 72%, and the investigators concluded that, in addition to initial radiographic evaluation to assess for metaphyseal fractures, further imaging with NaF-PET may warrant consideration in order to uncover injuries that would otherwise not be evident until follow-up imaging.

In general, the preliminary investigations into the assessment of traumatic injury by NaF-PET/CT and NaF-PET/MR show great promise. To gain a better understanding of how this technology can best be used in a variety of clinical scenarios, larger prospective trials are urgently needed.

Fig. 1. Maximum intensity projection NaF-PET in a 2-month-old boy. Multiple posterior rib fractures (arrows) and left lateral anterior rib fractures (arrowheads) are visualized bilaterally. (From Drubach LA, Johnston PR, Newton AW, Perez-Rossello JM, Grant FD, Kleinman PK. Skeletal trauma in child abuse: detection with 18F-NaF PET. *Radiology*. 2010;255(1):173-181; with permission.)

ARTHROPATHIES

NaF has shown success in visualizing changes associated with joint degeneration such as in osteoarthritis (OA) and temporomandibular disorder (TMD).³⁰⁻³⁹ Both FDG and NaF activities at the knee were assessed in 97 subjects in a study by Al-Zaghal and colleagues,⁴⁰ who found uptake of both tracers was correlated with body mass index. Studies from the same group have similarly found associations between body mass index and NaF uptake at the sacroiliac and hip joints, which are often involved in OA.^{41,42} A retrospective study in 34 subjects by Khaw and colleagues³⁰ showed increased NaF uptake measured at the joints of the elbows, hands, knees, and feet with higher subject body weight, which is a major factor in degenerative joint disease. The interaction between cartilage and bone at the knee in patients with early signs of OA has been successfully imaged by NaF-PET/MR, and an association between NaF activity and pain was described in cases without morphologic abnormalities.³⁵ This finding suggests that NaF activity can explain underlying pathophysiology before changes are evident on conventional modalities, a notion that is supported by a study that found, in 172 NaF-avid lesions associated with knee pain or injury,

that 63 appeared normal on MR.³⁴ In addition to the potential for early diagnosis, the predictive power of NaF-PET was shown in a study of 57 hip joints by Kobayashi and colleagues,³⁶ who showed that SUVmax predicted pain worsening and minimum joint space narrowing. Regarding the assessment of TMD, NaF-PET/CT seems feasible in diagnosis and determining the response to treatment.^{32,38}

Conventional BS is commonly used in joint diseases such as rheumatoid arthritis (RA), ankylosing spondylitis (AS), and psoriatic arthritis (PsA). In a meta-analysis of 25 studies, the sensitivity of BS in detecting AS in 361 patients was 51.8%, with a sensitivity of 49.4% for detecting sacroiliitis in 255 patients.⁴³ In contrast, the higher sensitivity of MR has resulted in its replacement of BS as the first-line modality for spondyloarthropathies at some institutions.⁴ A major limitation of MR is the limited field of view obtained by whole-body MR, which often does not include distal extremities. As investigators continue to assess its validity, NaF-PET/CT may represent a useful modality in assessing various inflammatory joint diseases.

Although visualization of inflammation with FDG is suitable for imaging RA and PsA,^{44–50} several studies have reported the utility of NaF in imaging AS.^{51–60} Son and colleagues⁵⁴ examined 49 patients with AS and 19 patients without AS, all of whom had inflammatory low back pain for at least 3 months. Enthesopathy, syndesmophytes, and sacroiliitis were identified on NaF-PET/CT. Overall, NaF-PET/CT was found to have a sensitivity of 79.6% and a specificity of 84.2% in the diagnosis of AS. A study by Strobel and colleagues⁶¹ used NaF-PET/CT to evaluate sacroiliitis in 15 patients with AS and 13 patients with mechanical back pain. By calculating the ratio of NaF uptake in the sacroiliac joint to the uptake in the sacrum, the investigators used a cutoff of 1.3 as indicating sacroiliitis. Using this method, the sensitivity of NaF-PET/CT in sacroiliitis was found to be 80% with a specificity of 77%. To compare modalities in AS, whole-body MR and NaF-PET/CT were used to image 10 patients with AS.⁶² At the sacroiliac joint, NaF uptake was found to correlate with bone marrow edema on MR, and there was a modest correlation at the spine. The investigators explained that the correlation was weaker than expected, possibly because of NaF-PET/CT portraying bone remodeling that occurs independently from inflammation. In a study of 12 patients with AS imaged by NaF-PET/MR, Park and colleagues⁵⁶ found that baseline NaF uptake was independently associated with syndesmophyte formation on radiography at 2-year follow-up. These findings may indicate utility for NaF-PET

combined with both CT and MR in the evaluation of AS and a need for further investigation into this field of study.

Using NaF-PET/CT to assess the effects of treatment regimens, Bruijnen and colleagues⁶³ studied 12 patients with active AS receiving anti-tumor necrosis factor therapy (Fig. 2). Imaging was performed at baseline and 12 weeks after initiation of treatment. In patients who responded to treatment after 24 weeks, NaF uptake was found to decrease at the costovertebral and sacroiliac joints after 12 weeks, whereas no significant changes were observed in nonresponders. Although NaF uptake at 12 weeks correlated with clinical evaluation at 24 weeks, clinical evaluation at 12 weeks did not correlate with later clinical evaluation. This finding suggests that NaF-PET/CT can predict eventual treatment efficacy, even when PET findings contradict early clinical evidence. Other studies examining patients with AS treated with anti-tumor necrosis factor therapy have found success in predicting treatment response from NaF uptake measured from baseline NaF-PET/CT images.^{52,53}

A limited number of studies have examined NaF activity at the joints in RA and PsA. In a preclinical trial using mice with glucose-6-phosphate isomerase-induced arthritis, NaF-PET/CT was found to correlate with the degree of bone destruction.⁶⁴ Another trial using a murine model found that anti-tumor necrosis factor therapy resulted in increased NaF activity at growth plates and was associated with increased osteoblasts, osteoid formation, and trabecular bone mass.⁶⁵ Watanabe and colleagues⁶⁶ assessed the hands of 12 patients with RA by FDG-PET/CT and NaF-PET/CT to compare the utility of the 2 tracers. SUVmax of both tracers as measured in the joints were found to correlate with one another. The NaF-PET parameter calculated by summing SUVmax from the metacarpophalangeal joints, proximal interphalangeal joints, and regions of the wrists was associated with the disease activity score in 28 joints, the modified health assessment questionnaire (mHAQ), radiographic progression, and the presence of erosions. Jonnakuti and colleagues⁶⁷ reported that NaF uptake in the knees of patients with RA was associated with Kellgren-Lawrence grading, suggesting that NaF-PET/CT can track bone changes associated with RA over time. Tan and colleagues⁶⁸ imaged 234 distal interphalangeal joints from 10 patients with PsA, 10 patients with OA, and 10 healthy controls. Compared with that of OA, NaF uptake in PsA involved the distal phalanges more diffusely, with increased uptake at the tufts, periosteum, and entheses. As imaging with NaF-PET is applied to

Fig. 2. Baseline (A) and 12-week follow-up (B) NaF-PET images of an patient with AS starting anti-tumor necrosis factor therapy. Although NaF activity in some AS lesions decreased (*solid arrows*), activity in other lesions increased (*dashed arrows*). Uptake at the facet joints was considered to be a result of osteoarthritis (*arrowheads*). (From Bruijnen STG, Verweij NJF, van Duivenvoorde LM, et al. Bone formation in ankylosing spondylitis during anti-tumour necrosis factor therapy imaged by 18F-fluoride positron emission tomography. *Rheumatology* (Oxford). 2018;57(4):631-638; with permission.)

new areas, it is imperative that, in addition to OA and AS, its potential role to portray bone involvement in other arthropathies is considered and investigated on a large scale.

BACK PAIN

Analogous to previous studies that used BS and single-photon emission CT (SPECT),^{69–74} NaF-PET/CT has been used to assess benign causes of back pain.^{75–77} Athletes are particularly at risk of injuries resulting from repetitive hyperextension (Fig. 3).⁷⁸ A common cause of low back pain in young athletes is spondylolysis, defined as a defect or stress fracture involving the pars interarticularis that commonly affects the lumbar spine. Pars fractures show increased bone turnover until the bone is finished healing.^{77,79} Grant and colleagues⁹ report that, in their experience, correlation with CT confirms pars fracture in about half of cases with abnormal NaF uptake, with the other half likely representing patients with pars stress without spondylolysis. The investigators also reported that, generally, normal NaF uptake corresponds to normal anatomy of the pars

interarticularis on CT, except in cases of long-standing spondylolysis where bone turnover is at baseline.

Not only does NaF-PET/CT facilitate the diagnosis of pars stress but it can also help diagnose other potential causes of back pain, such as facet arthropathy.^{80–82} The observation that NaF uptake at the cervical, thoracic, and lumbar spine is associated with increased body weight in healthy individuals suggests that NaF-PET/CT can detect early changes in the spine related to degeneration.⁸³ In 42 adult patients with back pain and no history of spine surgery, NaF-PET/CT scans identified the cause of pain in 37 (88%) of the patients.⁸² Furthermore, NaF activity at lumbar facet joints has been found to correlate with both MR findings and clinical disability.⁸⁰ Mabray and colleagues⁸¹ observed that, in 30 adult patients who underwent imaging by NaF-PET/CT, uptake of NaF was only weakly correlated with CT Pathria grade of facet osteoarthropathy. Thereby, the investigators reasoned that the assessment of bone turnover with NaF provided new information that can be used to supplement structural data provided by CT.

Fig. 3. NaF-PET maximum intensity projection (A), transaxial (B), and fused PET/CT (D) images in an 18-year-old female dancer with extension-based low back pain show significant activity at the sacroiliac joints, whereas minimal abnormality is apparent on CT (C). (From Grant FD. 18F-fluoride PET and PET/CT in children and young adults. *PET Clin.* 2014;9(3):287-297; with permission.)

Although many causes of back pain are related to muscular injuries or abnormalities associated with intervertebral discs, osseous involvement is common. Therefore, NaF-PET should be considered as the imaging modality of choice in these cases even when malignancy is not suspected. In a study of 15 adolescent patients with back pain, Ovadia and colleagues⁷⁷ found that NaF-PET/CT revealed positive findings in 10 patients, which included spondylolysis, frank fracture, osteoid osteoma, osteitis pubis, sacroiliitis, and disc herniation. Pseudoarthrosis associated with lumbosacral transitional vertebrae is another cause of back pain that can be evaluated by NaF-PET/CT.²⁷ Lim and colleagues⁷⁶ identified back pain caused by vertebral body ring apophyseal injury and stress or injury at the spinous process, pars interarticularis, pedicle, sacroiliac joint, and transitional vertebra-sacral articulation. Usmani and colleagues⁸⁴ reported the case of a 34-year-old woman with severe low back pain, whose L5 vertebra contained a hemisacralized left transverse process. The transverse-sacral articulation showed NaF avidity, consistent with Bertolotti syndrome. A study in 55 patients with lumbosacral transitional vertebrae by the same investigators showed a strong correlation between NaF uptake and the presence of symptoms.⁸⁵ These early studies and case reports show the significant utility of NaF-PET in the evaluation of musculoskeletal back pain, warranting further investigation into the potential role PET may play in the diagnosis, management, and follow-up of this serious cause of disability.

ORTHOPEDIC COMPLICATIONS

Faced with an aging population, the prevalence of OA is increasing, and joint replacement surgery is becoming more common.^{86,87} Postsurgical complications include instability, infection, fracture, and loosening, and the ability to discriminate between infection and aseptic loosening has important implications for patient management.⁸⁸⁻⁹¹ The first-line modality after hip or knee arthroplasty is radiography, which can show subsequent fractures and dislocations. Although the high sensitivity of 3-phase BS can be used to rule out postsurgical loosening and infection,⁹² the addition of anatomic information in SPECT/CT can improve the otherwise low specificity.⁹³ Scintigraphy with gallium-67 (Ga67) and indium-111 (¹¹¹In)-labeled white blood cells represent other methods of increasing the specificity of 3-phase BS.⁹⁴⁻⁹⁶

Several studies have indicated that NaF-PET has utility in assessing complications related to hip arthroplasty.⁹⁷⁻¹¹⁹ Increased NaF activity can indicate stem loosening in patients experiencing pain but with equivocal radiograph findings.⁹⁹ To determine the efficacy of denosumab in preventing periprosthetic bone loss, which contributes to loosening, Nyström and colleagues¹⁰⁰ quantified bone turnover with NaF-PET. They noted that, in patients treated with denosumab, the increase in uptake after surgery was not as great as the increase in the patients receiving placebo. Even higher uptake in septic loosening is observed compared with aseptic loosening. By visually

assessing the proportion of the bone-implant interface that showed NaF avidity, Kobayashi and colleagues¹⁰⁹ diagnosed infection in 65 hip prostheses by NaF-PET/CT with a sensitivity of 95% and a specificity of 98%. In a comparative study between NaF-PET/CT and FDG-PET/CT, 42 patients with painful hip prostheses suspected of loosening underwent imaging before revision arthroplasty to determine whether or not infection was present.¹⁰² The sensitivity and specificity of NaF-PET/CT were 75% and 96%, respectively, whereas the sensitivity and specificity of FDG-PET/CT were 94% and 92%, respectively. Although imaging with NaF resulted in higher specificity, the investigators argued that the overall diagnostic performance with FDG was more suitable for routine clinical practice. As an analog to 3-phase BS, multiphase NaF-PET has been proposed to assess for infection. In a demonstration of early-phase imaging in a patient with cellulitis, Li and colleagues¹²⁰ suggested that NaF-PET images acquired 2 minutes after tracer administration can be used to visualize increased regional blood flow at infected areas. Although future investigations may assess the feasibility of this method in a larger number of patients, there is currently limited evidence regarding early-phase NaF-PET in infection. Choe and colleagues¹⁰⁸ found that, by using NaF-PET to identify active lesions in total hip arthroplasty patients, they achieved a higher accuracy of tissue sampling in the diagnosis of periprosthetic infection. Besides hip arthroplasty, NaF-PET has been used to image knee, ankle, and shoulder arthroplasties.^{121–125} A study that included 24 hip and 13 knee prostheses found that NaF-PET/CT had a sensitivity of 95% and a specificity of 87% in diagnosing periprosthetic loosening (**Fig. 4**).¹²³ The viability and fusion of femoral allografts in 7 patients who underwent reverse total shoulder arthroplasty was assessed by NaF-PET/CT, which showed a similar amount of uptake in the allografts as in reference vertebrae.¹²¹

Spinal orthopedics is another area that may benefit from NaF-PET, which may have a role in predicting healing and identifying complications such as nonunion, pseudarthrosis, infection, and hardware loosening.^{126–131} In pediatrics, Grant²⁷ reported utility in determining the cause of pain in children who underwent spinal fusion surgery for scoliosis. Fischer and colleagues¹³² studied 20 patients who underwent cervical or lumbar intercorporeal fusion and found that increased NaF activity could be visualized in cervical cages for up to 8 years after intervention and up to 10 years in lumbar cages (**Fig. 5**). The investigators suggested that this may represent unsuccessful

fusion, which could be a result of stress or micro-instability. In a comparison between NaF-PET/CT, plain radiography, and CT, fusion was assessed in 8 patients after en bloc spondylectomy.¹³³ Although radiographs and CT showed successful fusion in all patients, NaF-PET/CT findings indicated nonunion in each case, showing a large discrepancy in findings between these modalities.

Although more studies are needed, other orthopedic applications of NaF-PET include assessing the effects of Taylor Spatial Frame treatment,¹³⁴ as well as determining the progression of graft incorporation after anterior cruciate ligament reconstruction.¹³⁵ NaF activity can also be informative for surgical planning. In patients with hip fractures, decreased NaF activity was predictive of future need for joint replacement surgery.¹³⁶ In a study of patients with osteonecrosis, 9 out of 17 hips had NaF avidity in the absence of findings on BS, SPECT, and MR, which shows the importance of this modality.¹³⁷ Patients with posttraumatic and postsurgical chronic osteomyelitis after unsuccessful surgical intervention were imaged by both FDG-PET/CT and NaF-PET/CT in a study by Christersson and colleagues.¹³⁸ In all 8 patients assessed, PET determined the culprit sequestrum, and, in 4 patients, an additional sequestrum with no clinical signs was identified. Follow-up revealed no clinical indications of recurrence and negative PET findings in all patients. Because both the disorder and the treatment often directly affect bone activity in orthopedics, it is logical that imaging with NaF-PET has a large role to play in managing patients before and after surgical procedures. Preliminary studies in this area are very promising, and future studies should focus on surgical planning as well as using NaF-PET to investigate the healing process or associated complications after treatment, which could be overlooked by conventional modalities.

METABOLIC BONE DISEASES

Osteoporosis is a systemic disease of bone, in which reduced bone mass results in greater fragility and risk of fracture. Because osteoporosis mostly occurs in elderly men and postmenopausal women, its prevalence is expected to increase with current demographic trends.¹³⁹ Osteoporotic fractures often involve the vertebrae, hip, distal forearm, or shoulder.¹⁴⁰ To assess for osteoporosis, bone mineral density (BMD) determined by dual x-ray absorptiometry (DXA) and expressed as a T score is the current standard of care. Representing the number of standard deviations from average BMD in a young healthy population, a T score between -1.0 and -2.5 is diagnostic for

Fig. 4. NaF-PET and PET/CT images of a 72-year-old woman who underwent total hip arthroplasty 12 years earlier. High NaF uptake involving the right acetabular component suggests loosening. No loosening is suspected in the right femoral component or in either components of the left arthroplasty. (From Koob S, Gaertner FC, Jansen TR, et al. Diagnosis of peri-prosthetic loosening of total hip and knee arthroplasty using (18)F-Fluoride PET/CT. *OncoTarget*. 2019;10(22):2203-2211; with permission.)

osteopenia, whereas a T score less than -2.5 is considered osteoporosis.¹³⁹ However, some investigators have questioned the accuracy of DXA-derived BMD,^{141–143} and 1 study found that most women with hip fracture had T scores more than -2.5 , showing the low sensitivity of this technique.¹⁴⁴ Rather than BMD, bone turnover can be used to evaluate patients for osteoporosis. However, established methods face certain limitations.¹⁴⁵ Bone turnover markers can be used to evaluate overall metabolic activity but suffer from low sensitivity and cannot assess individual skeletal sites. Alternatively, transiliac biopsy after double labeling with tetracycline is invasive and limited to 1 area of the skeleton.

Bone imaging with functional modalities such as PET is a sensitive method that can overcome the limitations associated with other bone turnover assessments.^{146,147} A study by Piert and

colleagues¹⁴⁸ used NaF-PET to assess bone turnover at the vertebrae of healthy pigs and compared their findings with histomorphometric data derived from iliac crest biopsies. The influx rate and volume flux of NaF were found to correlate with the mineral apposition rate, and the investigators concluded that NaF-PET may represent a noninvasive method of following metabolic bone diseases over time, decreasing the need for invasive bone biopsies. NaF-PET has had success in detecting both postmenopausal and glucocorticoid-induced osteoporosis.^{149–153} A study of 71 male and 68 female subjects observed a decrease in NaF uptake at the femoral neck with age, correlating with BMD from CT.¹⁵⁴ In patients diagnosed with osteoporosis by DXA, NaF activity at the lumbar spine is significantly lower than in healthy persons and in patients with osteopenia.^{151–153} Bone formation at other skeletal sites

Fig. 5. Low-dose CT (left), fused NaF-PET/CT (middle), and NaF-PET (right) images of a 52-year-old male patient who underwent 2 adjacent intercorporeal fusions (C3/4, C4/5). At 79 months postoperatively, both cervical cages still show increased NaF activity. (From Fischer DR, Zweifel K, Treyer V, et al. Assessment of successful incorporation of cages after cervical or lumbar intercorporeal fusion with [(18)F]fluoride positron-emission tomography/computed tomography. *Eur Spine J*. 2011;20(4):640-648; with permission.)

as determined by NaF-PET include the pelvis, tibia, parietal bone, humerus, and sternum.^{155,156}

The effects of antiresorptive therapy with bisphosphonates result in a rapid decrease in osteoclast activity, followed by a gradual decrease in osteoblast metabolism. Several studies have observed this expected decrease in bone formation after treatment with risedronate and alendronate.^{151,157–159} Uchida and colleagues¹⁵¹ observed a significant decrease in SUV at the lumbar spine after 3 months of treatment with alendronate, whereas no significant changes in serum bone-specific alkaline phosphate were observed until 6 months, and DXA did not show a significant change until 12 months. In 11 postmenopausal women treated with alendronate and 9 treated with risedronate, Frost and colleagues¹⁶⁰ found that NaF activity remained suppressed in the spine in both groups 12 months after discontinuation of therapy. However, after 12 months of discontinuation in the alendronate group, an increase in NaF uptake at the hip and femoral shaft was seen.

In contrast, teriparatide therapy causes increased activity in both osteoblasts and osteoclasts. As expected, increased bone turnover at the spine, femoral shaft, and pelvis portrayed by NaF-PET was described in a study of 18 postmenopausal women after 6 months of teriparatide therapy.¹⁶¹ A study by the same group saw significantly greater NaF clearance at the hip, femoral neck, lumbar spine, and pelvis in patients after 12 weeks of taking teriparatide, whereas no changes were observed in a control group taking calcium and vitamin D only.¹⁵⁶

Paget disease, characterized by increased osteoclast activity followed by increased osteoblast activity, and renal osteodystrophy, in which chronic kidney disease results in abnormally low or high bone turnover, are other disorders that may benefit from NaF-PET assessment.^{162–167} NaF activity is higher in pagetic bones and has been found to decrease after 1 month of treatment with bisphosphonates, followed by a further decrease after 6 months.¹⁶⁶ Despite normal biomarkers, increased NaF activity was observed in most patients. In 11 patients with renal osteodystrophy, Messa and colleagues¹⁶⁷ determined that clearance of NaF could differentiate between high bone turnover in secondary hyperparathyroidism and low-turnover bone disease. Further, NaF clearance correlated with serum alkaline phosphatase and parathyroid hormone levels as well as with histomorphometric data. After parathyroidectomy and medical therapy in 2 patients, NaF clearance was found to decrease by approximately 30% to 40%. These studies imply that NaF-PET is much more sensitive than the existing

approaches for assessing the involvement of bones throughout the body in a variety of metabolic disorders. Although the implementation of routine PET imaging may present challenges in terms of cost and radiation exposure, NaF-PET could play a key role in therapy development, in which sensitive tests are needed to evaluate early biological effects in vivo.

OTHER OSSEOUS AND SOFT TISSUE DISORDERS

Aside from the aforementioned major applications of NaF-PET in bone and joint disorders, an array of other potential areas of investigation have been suggested by preliminary observations. Osteonecrosis, including medication-related osteonecrosis of the jaw, seems to be a promising area in need of further study,^{168–172} in addition to assessment of fibrous dysplasia.^{173,174} Increased NaF uptake in the otic capsule in patients with otosclerosis compared with healthy controls suggests a potential role in diagnosis.¹⁷⁵ With regard to benign primary bone tumors, both osteoid osteoma and osteoblastoma are known to show NaF avidity.^{77,176–178} Similarly, malignancies such as osteosarcoma and Ewing sarcoma can be identified with this modality.^{179–182} Case reports show the successful identification of osteosarcoma metastases by NaF-PET in the lungs, in the right ventricle of the heart, and in the abdominal and paraspinal muscles.^{183–185} Further, by detecting greater osteosarcoma disease extent than was apparent on structural imaging, NaF-PET contributed to the decision in 1 case of changing from curative intent to palliative intent.¹⁸⁶

Regarding disorders arising from nonosseous structures, NaF activity has been observed in Langerhans cell histiocytosis, in which focal uptake was observed throughout the skeleton.¹⁸⁷ Significant uptake has also been shown in a case of vertebral body hemangioma.¹⁰ Other neoplasms reported to show NaF activity include neurofibroma,¹⁸⁸ meningioma,¹⁸⁹ uterine leiomyoma,^{190,191} ovarian cancer,¹⁹² bladder cancer,¹⁹³ glioblastoma,¹⁹⁴ and medullary thyroid carcinoma.¹⁹⁵ Certain normal tissues, such as breast tissue, have moderate NaF activity at baseline,¹⁹⁶ which can even be appreciated in drug-induced gynecomastia in men.¹⁹⁷ NaF-PET can also show physiologic calcification of intracranial structures,^{198,199} as well as heterotopic ossification after surgery.²⁰⁰ In addition, NaF uptake has been reported in the gastrointestinal wall caused by hypercalcemia²⁰¹ and as a sequela of Japanese schistosomiasis.²⁰² Although the significance of these findings is still unclear, an important

extraosseous indication for NaF-PET is in the evaluation of vascular microcalcification, with the possibility of NaF surpassing FDG as the PET tracer of choice in assessing atherosclerotic activity.^{203,204}

SUMMARY

The rise of NaF-PET and its combination with CT and MR present new opportunities to assess benign musculoskeletal disorders with a greater sensitivity compared with conventional approaches. In particular, conditions affecting the skeleton and joints stand to benefit greatly from PET findings that would otherwise be missed on conventional radiographs, BS, CT, or MR. As a result, previously undetermined causes of bone pain may be elucidated, and sites of occult traumatic injury could be discovered, findings that have important implications for patient care. In addition to its diagnostic role, NaF-PET can be used to evaluate pharmacologic and surgical interventions designed to treat osseous structures. Orthopedic surgeons in particular are faced with managing complications that can be better characterized by NaF-PET than with other modalities. Moreover, drugs such as teriparatide and bisphosphonates cause direct changes in NaF activity before the effects are evident by any other means. As clinicians continue to gain a better understanding of this modality, its future role in other bone and soft tissue disorders is still undetermined, and large-scale prospective studies are warranted to investigate its utility.

CLINICS CARE POINTS

- Although NaF-PET/CT can be used to detect bone metastases, PET tracers that portray tumor activity such as FDG or radiolabeled PSMA ligands are more appropriate in this setting.
- Many benign musculoskeletal conditions can be detected by NaF-PET, which can play a role in diagnosis and monitoring.
- NaF-PET and its hybrid modalities can assist in orthopedic planning as well as in evaluation for postsurgical complications such as infection.
- PET quantification allows precise evaluation of metabolic bone diseases. NaF uptake reflects bone turnover, pathologic changes in which are present years before changes in bone mineral density.

DISCLOSURE

The authors have nothing to disclose.

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