Use of bone-SPECT/CT and Na[18F]F-PET/CT in hyperparathyroidism

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Hyperparathyroidism disrupts the balance of physiological bone formation and resorption by upregulating osteoclast activity. This leads to hypercalcemia, resulting in osteoporosis and eventually the formation of "brown tumors." Currently used radiological and nuclear medicine imaging for primary hyperparathyroidism face challenges in accurately diagnosing bone-related complications. Molecular bone imaging techniques routinely consist of bone scintigraphy, with possible addition of bone-SPECT/CT. Recently, renewed interest has emerged in the use of Na[18F]F-PET/CT. Both applications are highly sensitive to *in vivo* osteoblast activity. However, the latter technique offers improved spatial resolution and sensitivity, as well as shorter incubation and faster scanning. This article summarizes current limitations and potential improvements in bone-SPECT/CT and Na[18F]F-PET/CT imaging in selected patients with hyperparathyroidism, compared to other relevant techniques and clinical parameters.

KEYWORDS

hyperparathyroidism, bone-SPECT/CT, sodium fluoride PET/CT, brown tumor, benign bone disease, bone-related complications

Introduction

Currently used radiological and nuclear medicine imaging for primary hyperparathyroidism (PHPT) face challenges in accurately diagnosing bone-related complications. Limited sensitivity and specificity of radiological techniques and of planar nuclear imaging techniques hamper the early accurate staging of bone involvement in these patients. This article describes the potential role and limitations of advanced molecular and multimodality imaging techniques to identify bone involvement in PHPT, especially for bone-SPECT/CT and Na[18F]F-PET/CT.

Calcium homeostasis and bone abnormalities in hyperparathyroidism

Calcium homeostasis is a tightly regulated process aiming to maintain stable calcium blood levels (1). The parathyroid glands play a central role by secreting parathyroid hormone (PTH) in response to low serum calcium levels. PTH increases calcium release from bones and enhances renal calcium reabsorption. PHPT, which is characterized by excessive PTH production, increases osteoclast activity and therefore bone resorption, leading to hypercalcemia (1). This is reflected in biochemical marker measurements as well as dynamic histomorphometry (2). Hypercalcemia influences the

(neuro)muscular, skeletal, cardiovascular, renal, and gastrointestinal systems (3). Prolonged increased osteoclast activity will at first lead to a systemic decrease in the amount of normal bone tissue, i.e., osteoporosis (4), but may eventually result in lesional destruction of trabeculae and degeneration of the fibrovascular tissue, ultimately leading to cysts. These changes, known as osteitis fibrosa cystica, are a hallmark of persisting severe hyperparathyroidism (4–6). The newly originated cysts then become populated with macrophages, which may contain the iron-storage complex hemosiderin. Hemosiderin can be observed microscopically as a brown pigment (7). Deposition of hemosiderin, combined with the ingrowth of fibrovascular tissue into the dissecting osteitis cavities, may eventually form so-called brown tumors (5). Osteoporosis, osteitis fibrosa cystica, and brown tumors all weaken the bone, placing patients at risk for pathological fractures.

Though rare, as hypercalcemia is nowadays readily detected by routine calcium screening, brown tumors are an important clinical manifestation of uncontrolled hyperparathyroidism and their characteristics have been extensively documented in the literature (8–10). Brown tumors are more prevalent in primary hyperparathyroidism than in secondary forms and can affect various bones, including the ribs, pelvis, and facial bones (8, 9, 11). These lesions mimic malignancies radiographically and histologically, posing diagnostic challenges (1, 12). Recognizing the early signs of PHPT-related bone changes and understanding the pathophysiology of osteitis fibrosa cystica and brown tumors—along with their appearance across various imaging modalities—can facilitate timely intervention and help prevent irreversible skeletal complications.

Nuclear medicine techniques to image bone turnover

In healthy individuals, osteoblasts and osteoclasts work in a continuous feedback cycle of bone formation and resorption, called bone turnover (13). Several diseases, either originating from within or outside of the bone, may disrupt this balance. Bone diseases can be categorized as osteoclastic, osteoblastic, or a combination of both. In most benign bone and joint conditions, the osteoblastic component predominates (13). As described above, PHPT results in increased osteoclast activation and bone resorption (5). Bone remodeling in reaction to these lesions involves osteoblast activation (14).

Molecular bone imaging predominantly consists of bone scintigraphy, with the possible addition of cross-sectional single photon emission tomography with overlay of computed tomography (bone-SPECT/CT) (15). Recently, renewed interest in the use of sodium fluoride positron emission tomography (PET) with integrated CT (Na[^{18}F]F-PET/CT) has been expressed (13, 16, 17). Both techniques are highly sensitive to detect osteoblast activity through the injection of radiopharmaceuticals (18, 19). While the uptake mechanisms of these radiopharmaceuticals differ slightly, they are influenced by regional bone perfusion and ultimately bind to the surface of

hydroxyapatite crystals via chemisorption (20, 21). Na[^{18}F]F-PET/CT boasts rapid uptake in bone, faster scanning, and improved spatial resolution over bone-SPECT/CT, and the newest PET/CT scanners allow for minimal radiation exposure (13, 19). Both techniques have the capability to detect clinically relevant early changes in bone turnover, with proven additional value in the management of patients with benign and malignant bone disease (15–17). Where compared to conventional morphological bone imaging (i.e., x-ray, dual-energy x-ray absorptiometry, and standalone CT), these molecular imaging techniques identify bone changes several months before structural anatomical changes can be detected (15, 16, 21, 22).

Planar bone scintigraphy

Planar bone scintigraphy has been the cornerstone of nuclear medicine bone imaging for many decades. It is a known imaging modality to depict osteoblastic activity, dependent on vascularization, blood pool, and bone turnover, with the ability to detect generalized or focal metabolic changes in bone turnover (15, 23).

In several metabolic bone diseases, including PHPT, osteomalacia, and renal osteodystrophy, key findings on bone scintigraphy include increased tracer accumulation in the axial skeleton, long bones, periarticular zones, skull, mandibulae, and sternum (24). Still, in mild cases of metabolic changes and in asymptomatic patients, the sensitivity of these findings is poor, while the specificity in differentiating PHPT from other metabolic bone diseases, such as renal osteodystrophy, is also low (24). Therefore, bone scintigraphy is not routinely used to diagnose PHPT (15, 24).

Secondary hyperparathyroidism (SHPT), consisting of excessive secretion of PTH by the parathyroid glands in response to hypocalcemia, is the main cause of a metabolic superscan (23). When compared to malignant causes of a superscan, a metabolic superscan typically presents with homogeneous, symmetrical increased bone uptake, often featuring symmetrical uptake in the mandible and calvarium, as well as enhanced periarticular uptake and costochondral beading (23). However, differentiating between benign and malignant uptake with complete certainty cannot be achieved through planar scintigraphy alone.

Diagnosis becomes more challenging in severe or protracted cases of the disease due to the formation of brown tumors. Three-phase bone scintigraphy is highly sensitive in detecting these lesions by pinpointing accumulations of ^{99m}Tc-methyl diphosphonate (MDP). Bone scintigraphy outperforms ^{99m}Tc-sestamibi scan in detecting brown tumors (10).

The possibility of a brown tumor should be included in the differential diagnosis when focal accumulation of ^{99m}Tc-MDP is observed, especially in patients with diffuse abnormal uptake suggestive of metabolic bone disease (9, 25). However, a focal hotspot – with or without generalized abnormal uptake – is not specific to brown tumors, as fissures or fractures can also present in patients with metabolic bone disease (11, 24). In addition,

brown tumors are well known to mimic malignant bone lesions on planar bone scintigraphy and plain radiographs, making accurate differentiation essential (5, 9, 23, 26).

Correlation to other molecular or radiological findings and biochemical results (i.e., PTH) improves specificity (10).

Bone-SPECT/CT

Although planar bone scintigraphy is an impactful technique in case of clinically insufficiently explained hypercalcemia (23, 24), adding bone-SPECT/CT to the planar scan significantly improves the diagnostic value of the study (13, 15). SPECT improves spatial resolution, contrast, and localization, especially in complex three-dimensional (3D) structures, such as the skull, spine, pelvis, and hind- and midfoot (13). The main advantage, however, lies in characterizing focal lesions and in differentiating concurrent co-morbidity, such as bone metastases (27).

The addition of (low-dose) CT adds morphological characteristics to the uptake on SPECT and allows for attenuation correction, thus improving the quality of the SPECT images. Morphologically, brown tumors are depicted as well-defined, primarily lytic and often expansile lesions, predominantly occurring in the mandible, clavicle, ribs, and pelvis (28, 29). They can present with intra-focal calcifications, a sclerotic rim, and fluid-fluid levels (27). Attenuation values are in the range of blood and fibrous tissue, in the range of approximately +13 to +75 (28, 30). CT may also reveal additional pathology in or outside of the bones, such as hematoma or soft tissue swelling.

Although bone-SPECT/CT adds cost per patient, with exact expenses and reimbursement varying by region or country, its cost-effectiveness for metabolic bone disease remains unstudied (31). Furthermore, radiation exposure must be considered, as bone-SPECT/CT adds 0.2–2 mSv per bed position, depending on the region of interest (32). Despite these factors, integrating bone-SPECT/CT with planar scintigraphy is recommended for patients with suspected PHPT (15).

Sodium fluoride PET/CT (Na[^{18}F]F-PET/CT)

Sodium fluoride labeled with radioactive fluorine-18 (Na[^{18}F]F) precisely depicts *in vivo* blood flow into the bone and subsequent systemic and focal bone remodeling by imaging osteoblasts (21). It is a smaller compound compared to ^{99m}Tc-MDP and offers advantages in pharmacokinetics, including fast blood clearance, high first-pass extraction, low non-specific protein binding, and efficient bone uptake via chemisorption (20). This allows Na[^{18}F]F-PET to swiftly detect changes in osteoblast activity shortly after the onset of many (benign) bone diseases (13).

In comparison to the abovementioned bone scintigraphy protocols, including bone-SPECT/CT, Na[^{18}F]F-PET/CT offers 3D and cross-sectional imaging of the whole skeleton, with shorter incubation and acquisition times (19, 33). Na[^{18}F]F-PET/CT provides improved spatial resolution and more robust

quantification abilities (19, 34). Moreover, PET/CT hardware typically comprises new generation CT possibilities, leading to high-quality CT images, superior iterative metal artifact reduction (iMAR), and low radiation exposure. Typically, radiation exposure of whole-body Na[^{18}F]F-PET/CT is estimated at approximately 1.9 mSv for PET acquisitions and 2–3 mSv for low-dose CT (13, 19, 31, 34). These favorable characteristics, combined with recent shortages of ^{99m}Tc, have led to renewed interest in Na[^{18}F]F-PET/CT (19, 21). At the same time, Na[^{18}F]F-PET/CT increases costs per patient, has limited availability, and may not be reimbursed in certain countries or regions (16).

Na[^{18}F]F-PET/CT has already been proven to be safe and effective in different groups of patients with benign bone disease (35, 36). In patients with primary hyperparathyroidism, this imaging modality might be particularly useful, as it provides insights into both generalized and focal metabolic bone changes, while conveniently depicting the whole skeleton.

A metabolic superscan pattern on Na[^{18}F]F-PET/CT is characterized by diffusely increased homogenous Na[^{18}F]F-uptake in the axial and appendicular skeleton, including the calvarium and distal extremities, with decreased background activity in the soft tissues (37).

Given that PHPT is often diagnosed early, one might expect extensive literature describing this phenomenon on Na[^{18}F]F-PET/CT in detail. However, research remains relatively scarce, with more focus on the less frequently encountered osteitis fibrosis cystica and brown tumors (14, 21, 25, 37). In contrast, the metabolic superscan pattern is well documented in ^{99m}Tc-bone scintigraphy (15, 23, 24, 38, 39).

Other imaging techniques for characterizing lesions in PHPT

^{99m}Tc-MIBI SPECT/CT and ^{18}F-fluorocholine PET/CT and ultrasound are well-recognized imaging procedures for the detection of primary parathyroid adenoma (40, 41). Of these modalities, ^{18}F-fluorocholine PET/CT is considered the most sensitive technique, especially in small adenomas (25, 40). It is also capable of identifying brown tumors, with improved accuracy over ^{99m}Tc-MIBI or bone scintigraphy (40, 41). However, ^{18}F-fluorocholine PET/CT does not adequately reflect bone turnover changes and expresses a significantly lower target-to-background ratio for bone pathology in comparison with Na[^{18}F]F-PET/CT and bone-SPECT/CT. Furthermore, costs for ^{18}F-fluorocholine PET/CT are higher.

Since brown tumors share morphological characteristics with other lytic lesions (i.e., multiple myeloma or osteolytic metastases), conventional CT imaging alone cannot be used to confidently differentiate in all cases.

[^{18}F]FDG is a non-invasive imaging marker for increased macrophage activity and glucose transporters (GLUT1 and GLUT3). It likely also targets other cellular changes commonly associated with inflammation and infection (42). In the literature about patients with benign bone and bone marrow disease, [^{18}F]FDG-PET/CT is known to detect intra-articular changes, as

well as focal or systemic bone marrow changes (43–45). As described earlier, macrophages are involved in hemosiderin deposition in brown tumors, which may explain the increased [^{18}F]FDG-uptake (7). The sensitivity of [^{18}F]FDG-PET/CT for detecting brown tumors is reported to be higher than that of ^{99m}Tc-MIBI scintigraphy (46) and may detect brown tumors in unexpected localizations, such as in the mandible and maxillary bone (12, 47). In addition, its high sensitivity for these lesions, combined with routine whole-body imaging, often enables the detection of unanticipated brown tumors (48). However, a downside on the use of [^{18}F]FDG -PET/CT is its limited specificity, as [^{18}F]FDG-avid osteolytic lesions may also represent metastases of a solid tumor, such as pulmonary cancer (25).

Future perspectives

Similarities in the uptake mechanism of Na[^{18}F]F-PET/CT and bone scintigraphy, combined with the known superiority in imaging characteristics of the former, suggest that Na[^{18}F]F-PET/CT will perform well in revealing the metabolic superscan pattern. This capability, however, still has to be confirmed in a structured series of patients with PHPT. Ideally, a cost-effectiveness study should validate the use of Na[^{18}F]F-PET/CT over bone scintigraphy.

The activity of brown tumors on Na[^{18}F]F-PET/CT correlates with the renal glomerular filtration rate and serum calcium levels (14). In addition, the total metabolically active bone volume, as quantified by Na[^{18}F]F-PET/CT, is associated with serum PTH and alkaline phosphatase levels. This could even reflect clinical outcomes, such as the duration of postoperative intravenous calcium replacement and extended hospitalization after parathyroidectomy (14). According to Graf et al., the increased bone turnover in brown tumors can persist for an extended period after PHPT treatment (14). This means Na[^{18}F]F-PET/CT might be an appropriate imaging choice to evaluate not only patients with active PHPT, but also patients with a history of the disease. On the contrary, Jacquet-Francillon et al. report that after parathyroidectomy, the uptake of radiotracers in brown tumor lesions is reversible, emphasizing the dynamic nature of these lesions in response to treatment for hyperparathyroidism (25). Additional research is required to address this discrepancy.

In the near future, the addition of dynamic Na[^{18}F]F-PET/CT might deliver quantitative data on bone perfusion, blood pool, and bone turnover, possibly further improving the evaluation of hyperparathyroidism-related bone disease (21, 49). In addition, further evidence is needed to more conclusively state whether Na[^{18}F]F-PET/CT adds clinically relevant value over bone-SPECT/CT in patients suspect of PHPT. The limited current literature suggests that patients with previously indeterminate lesions in particular might benefit.

A multidisciplinary approach, incorporating clinical evaluation, biochemical testing, pathological examination, radiological imaging, and advanced molecular imaging including bone-SPECT/CT and Na[^{18}F]F-PET/CT, is pivotal to differentiate brown tumors from bone metastases and prevent misdiagnosis, especially in patients with osteolytic lesions and hyperparathyroidism (26, 50).

Conclusions

Planar bone scintigraphy is a valuable tool for investigating hypercalcemia in patients with suspected metabolic bone disorders. It reveals generalized increased bone turnover, while simultaneously (15, 23, 24) detecting focal bone disease (24). However, its limited specificity requires additional bone-SPECT/CT for adequate characterization of focal lesions (27, 29).

As Na[^{18}F]F-PET/CT offers superior image acquisition and quality, in theory, this seems to be a better imaging modality for the evaluation of these patients. However, the literature on this topic is still limited, and availability and reimbursement of the modality is not always guaranteed. Further research is needed to gather evidence on the use of Na[^{18}F]F-PET/CT for this indication and assess its cost-effectiveness.

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