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Abstract

Purpose of review: This review article attempts to summarize the current state and applications of the hybrid imaging modality of PET-MRI to metabolic bone diseases. The advances of PET and MRI are also discussed for metabolic bone diseases as potentially applied via PET-MRI.

b) Recent findings: Etiologies and mechanisms of metabolic bone disease can be complex where molecular changes precede structural changes. Although PET-MRI has yet to be applied directly to metabolic bone disease, possible applications exist since PET, specifically ¹⁸F-NaF PET, can quantitatively track changes in bone metabolism and is useful for assessing treatment, while MRI can give detailed information on bone water concentration, porosity, and architecture through novel techniques such as UTE and ZTE MRI.

c) Summary: Earlier detection and further understanding of metabolic bone disease via PET and MRI could lead to better treatment and prevention. More research using this modality is needed to further understand how it can be implemented in this realm.

Keywords

Positron emission tomography-magnetic resonance imaging (PET-MRI); musculoskeletal diseases; metabolic bone disease; imaging

Introduction

The development of various imaging modalities has improved our understanding of the musculoskeletal system and its disorders. Imaging methods such as radiography, ultrasound, computed tomography (CT), magnetic resonance (MR), and positron emission tomography (PET) have different strengths and weaknesses depending on the anatomy and

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Compliance with Ethical Guidelines

Conflict of Interest

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Disclosure statement

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pathophysiology being examined. MR imaging provides soft-tissue contrast for visualization of bone marrow, muscles, tendons, ligaments, cartilage and fat.

However, conventional MRI is limited in sensitivity to cortical bone due to the tissue's low proton density and short T_2 relaxation times. Conversely, PET uses positron-emitting radiotracers to provide unique functional and metabolic information but must rely on additional imaging systems for localization due to its limited spatial resolution (1). Given the complicated presentation and pathogenesis in many musculoskeletal disorders a single imaging method may not be ideal. Further, there is a need for earlier detection of disease to optimize treatment planning and evaluate its effectiveness.

The recent introduction of hybrid imaging systems such as PET-MRI fuses the advantages of each single imaging modality such that complex diseases and disorders of the musculoskeletal system can be better understood. Still evolving, PET-MRI may be promising for the study of musculoskeletal diseases and more specifically, metabolic bone disease (2). In this review we explain how PET imaging can be applied to metabolic bone disease and how MRI can generate improvements.

2. PET-MR Imaging: A New Approach For Studying Metabolic Disease

Clinical assessment of metabolic bone diseases relies on evaluating the bone and the associated fracture risk. Typically, dual-energy x-ray absorptiometry (DXA) estimation of areal bone mineral density (BMD) is used to diagnose osteoporosis and other metabolic bone diseases. This test has limited capabilities to detect early osteoporosis, assess fracture risk or monitor therapy response (3). PET imaging offers the ability to provide clinicians with quantitative images and metabolic and molecular information that other imaging modalities cannot comparably provide. Since these metabolic and molecular changes often precede structural changes PET imaging could potentially detect diseases earlier. However, PET imaging requires the high resolution and anatomical information via an imaging modality like MRI to localize where these metabolic and molecular changes are occurring. PET combined with MRI has the potential to combine the advantages of each.

While PET-CT scanners have been used in clinical medicine since the early 2000s (4), PET-MRI systems were introduced more recently. PET-MRI exposes patients to lower radiation doses when compared to PET-CT since the CT exposure component is eliminated. This is important when considering how these modalities can be applied to patient populations (5). A study that used whole body FDG PET-CT scanning aimed to estimate the radiation dose from PET, CT, and PET-CT (6). It was found that the effective dose from PET scanning was 6.23 mSv, and three diagnostic CT protocols were estimated to be 13.45, 24.79, and 31.91 mSv for female patients and 13.65, 24.80, and 32.18 mSv for male patients, respectively. The CT component contributed between 54% and 81% of the total combined dose ; higher in radiation dose than PET scanning alone. MRI is also a favorable modality compared to CT for numerous musculoskeletal disorders because of it's superior soft tissue contrast. In the case of cortical bone however, CT is considered superior to MRI. PET-MRI attempts to combine the advantages that each single imaging modality presents for musculoskeletal imaging, much like PET-CT scanners (7,8). The PET radiotracer provides functional

information on glucose uptake or bone metabolism, while MRI provides the necessary soft tissue contrast to differentiate between different anatomical structures.

3. Tracers

Three radiotracers have shown potential for nuclear imaging of metabolic bone diseases: ^{18}F -fluorodeoxyglucose (^{18}F -FDG), $^{99\text{m}}\text{Tc}$ -labeled phosphates, ^{18}F -sodium fluoride ($^{18}\text{FNaF}$). Molecular imaging with $^{99\text{m}}\text{Tc}$ -labeled phosphates and ^{18}F -NaF have emerged as attractive methods for evaluating metabolic bone disease due to their affinity for newly mineralizing bone. They are also less invasive than bone and bone marrow biopsies and have increased specificity compared to serum markers (9,10).

3.1 ^{18}F -FDG

An analog of glucose, ^{18}F -FDG, is the most extensively used PET radiotracer in general clinical practice (11,12). ^{18}F -FDG is appealing for evaluating musculoskeletal disease because activated inflammatory cells and sites of infection exhibit increased glucose consumption; the tracer would be competitively taken up by cells with high metabolic needs. These sites of inflammation or infection could potentially be marked with high intensity signals on PET images (13).

3.2 ^{18}F -NaF

While both SPECT imaging with $^{99\text{m}}\text{Tc}$ -labeled phosphates and PET imaging with $^{18}\text{FNaF}$ are able to quantify bone turnover throughout the body and at specific sites of interest, ^{18}F -NaF is thought to be preferable because of the higher spatial resolution and three-dimensional acquisition of PET imaging compared to gamma camera studies. Further, ^{18}F -NaF is better able to localize bone due to its high uptake and its rapid clearance from soft tissues (14). Lastly, $^{99\text{m}}\text{Tc}$ -MDP can bind to plasma proteins complicating measurements of plasma clearance (15).

Bone formation and resorption are compelling targets for imaging in the study of bony disorders. ^{18}F ions can exchange with hydroxyl ions ($-\text{OH}$) on the surface of hydroxyapatite to form fluorapatite (16,17) which is then incorporated into bone. ^{18}F -NaF uptake on PET images can help to elucidate osteolytic and osteoblastic activity as well as bone blood flow (18,19) for studying bone remodeling. The two primary methods for quantifying bone turnover with ^{18}F -NaF are measuring standard uptake values (SUV) and kinetic modeling of rate parameters of tracer kinetics between tissue compartments. SUV is more commonly used and is measured by normalizing the mean ^{18}F -NaF concentration in the bone for injected activity and body weight (20).

Image analysis by pharmacokinetic modeling of dynamic PET uptake offers a more quantitative approach (21). Hawkins et al. were first to implement a dynamic scan method (Hawkins method) for quantitative ^{18}F -NaF PET studies (22) and quantitative ^{18}F -NaF PET was the first radiotracer to measure bone plasma clearance rather than bone uptake (17, 23–26). Therefore, dynamic ^{18}F -NaF PET imaging can be used to measure effective bone to blood plasma flow, and bone blood flow can be estimated from the tracer input and bone to blood plasma flow (27). A disadvantage of the Hawkins method is that only one region can

be imaged (restricted to the field of view of the PET scanner) (Figure 1) with a 45+ minute dynamic scan and single injection of ^{18}F -NaF (27). In contrast, SUV measurements require only a short static scan (~5 minutes) for the region to be imaged (27), allowing multiple regions to be scanned after a single injection within a reasonable scan time. A limitation of SUVs is that the injected tracer is shared throughout the body (28) and a change in plasma clearance in one site of the body can alter the amount of tracer available for other sites. Thus, SUVs are influenced by the amount of tracer available at the measurement site and provide only a semi-quantitative measure of activity (27). In contrast, plasma clearance measurements are able to provide an absolute measurement of tracer activity and kinetics at the local level (27).

3.2a Studies using ^{18}F -NaF to measure bone metabolism— ^{18}F -NaF PET-MRI has been utilized to measure bone metabolism in several musculoskeletal disorders. In knee osteoarthritis (OA), ^{18}F -NaF PET-MR imaging was able to detect and characterize metabolic bone activity in bone abnormalities on MRI in patients with knee pain or prior knee injuries (Figure 2) (29). ^{18}F -NaF has been applied to posttraumatic osteoarthritis (PTOA) after anterior cruciate ligament transection (ACLT) to study the role of bone metabolism in early OA. In a canine model using ^{18}F -NaF PETCT co-registered to MRI, uptake of ^{18}F -NaF in the bone of the post-transection ACLT knees increased over time (30). More recently it was shown that in human subjects with ACL-reconstructed (ACLR) tears ^{18}F -NaF uptake was significantly elevated in the ACLR knee compared to the contralateral, unaffected knee (31). Further, subchondral bone ^{18}F -NaF SUVmax was associated with early signs of collagen matrix damage in the adjacent cartilage as measured by increased T_2 relaxation time. This suggests that ^{18}F -NaF of bone uptake may be a marker of early disease in OA and reflect bone turnover. Additionally, ^{18}F -NaF has been shown to detect increased bone turnover at areas of new bone formation around stress fractures. It was demonstrated that PET-MRI may be able to diagnose stress fractures and stress reactions in cases where no pathological findings are present on X-ray (32). These studies collectively demonstrate that ^{18}F -NaF can be a useful marker for the assessment of bone turnover to study metabolic bone diseases.

4. PET Applications to Metabolic Bone Disease

Metabolic bone disorders are often associated with changes in bone turnover and metabolism that can lead to bone fractures, bone deformities and disability if left untreated. ^{18}F -NaF is a logical PET tracer to use when tracking these diseases and MRI provides the anatomical detail needed. Due to a lack of PET-MRI studies on metabolic bone diseases a review of PET applications is offered along with inferences on how PETMRI could be applied.

Studies have shown that maximum standardized uptake values (SUV) for ^{18}F -NaF PET correlate well with net uptake of fluoride to bone mineral and osteoblastic activity due to disease (26). Treatments that lead to a decrease in osteoblastic activity correlate with a decrease in SUV, so SUV can be used not only to assess metabolic bone disorders but also to quantify responses to treatment. Bisphosphonates are commonly used to prevent and treat many metabolic bone diseases by inducing apoptosis in osteoclasts. They work by reducing bone turnover and suppressing bone metabolism which allows for BMD to increase with

continuous use (20). Therefore, patients' responses to bisphosphonate therapy could be tracked using SUV measurements.

4.1 Osteoporosis in Postmenopausal Women & Glucocorticoid-induced Osteoporosis

Postmenopausal women are the largest population affected by osteoporosis. ^{18}F -NaF PET has been used to study osteoporosis specifically in postmenopausal women. Compared to premenopausal women, postmenopausal women have been found to experience increased bone turnover (33,34). Glucocorticoid-induced osteoporosis is the most common secondary form of osteoporosis (35). Glucocorticoid use, and more generally exogenous steroid use, leads to osteoporosis through multiple pathways consisting of decreased absorption of calcium, increased excretion of calcium, inhibition of osteoblasts and increased osteoclast proliferation and activity leading to bone resorption (36,37).

A study on postmenopausal women using ^{18}F -NaF found a significant difference in bone turnover between patients treated with hormone replacement therapy (HRT) and untreated women (38). The skeletal plasma clearance to bone, K_{bone} (in mL/min) was evaluated using the area under the plasma clearance curve (AUC). AUC estimates of skeletal clearance for ^{18}F -NaF were significantly lower in women receiving HRT compared to the untreated group (61.8 vs. 67.2 mL/min, $P = 0.045$), which would be expected since HRT decreases bone turnover and less ^{18}F -NaF would be incorporated into the bone. This study demonstrates the utility of using ^{18}F -NaF to monitor changes in bone turnover in patients undergoing treatment for osteoporosis.

A study by Frost et al. assessed postmenopausal women starting treatment with the bisphosphonate risedronate, using dynamic ^{18}F -NaF PET scans of the lumbar spine (22). The authors found that plasma clearance decreased by 18% ($P = .04$) after six months of risedronate treatment. Plasma clearance measurements via dynamic PET are feasible for quantifying response to therapy in osteoporosis.

Treatment with alendronate, another bisphosphonate, was monitored in a study that included 24 postmenopausal women treated with oral glucocorticoids and alendronate over a period of 12 months (20). Static ^{18}F -NaF PET scans taken at baseline, three months, and 12 months (Figure 3) revealed a 14% decrease in SUV in the lumbar spine that accompanied a 8.2% increase in lumbar spine BMD at 12 months, as expected from bisphosphonate therapy in patients with glucocorticoid-induced osteoporosis. Thus, SUV measurements via ^{18}F -NaF PET may be useful in the monitoring of response to therapy in glucocorticoid-induced osteoporosis.

4.2 Differentiating Between Osteoporotic Fractures and Other Fracture Types

^{18}F -FDG PET has the potential to differentiate between traumatic fractures and fractures due to malignancies. Studies have found that acute osteoporotic or traumatic fractures do not show increases in ^{18}F -FDG uptake on PET scans (39,40). On the contrary, fractures due to malignant or infectious processes do show increases in ^{18}F -FDG uptake because macrophages and other inflammatory cells have increased glucose needs. In combination with MRI, ^{18}F -FDG PET-MRI can be used to distinguish between pathologic and osteoporotic fractures relative to MRI alone, improving diagnostic specificity.

4.3 Diabetes

Combined QCT (quantitative computed tomography) and MRS studies have shown that the frequency of fragility fractures is correlated with lower levels of unsaturated fat and higher levels of saturated fat in bone marrow (41). Subjects with diabetes and fractures had the lowest marrow unsaturation and highest saturation of bone marrow fat levels (41). A study using ^{18}F -FDG PET and MRI compared the vertebral bone marrow of diabetic and healthy pigs and found a significant inverse correlation between the bone marrow fat content and glucose uptake (42). Since vertebral bone marrow fat is significantly increased in osteoporosis when compared to osteopenia or normal bone density (43) and higher bone marrow fat is correlated with a decrease in BMD (44), it would be expected that vertebral bone marrow glucose uptake would be low in diabetic pigs and more generally, in patients with diabetes induced osteoporosis.

4.4 Renal Osteodystrophy

Renal osteodystrophy is a complex bone disorder resulting from kidney disease with many different features. There may be increased or decreased turnover depending on the disease type. As the kidneys help to regulate calcium and phosphate levels, improperly functioning kidneys can affect bone turnover and formation.

A study using ^{18}F -NaF PET to examine patients with renal osteodystrophy found that uptake of ^{18}F -NaF into bone strongly correlated with serum alkaline phosphatase, a marker of bone turnover and serum parathyroid hormone levels, which regulates the concentration of calcium in the blood (45). Additionally, the incorporation of ^{18}F -NaF into bone correlated well with bone turnover via histomorphometric indices in iliac crest biopsies. The indices were higher in patients with high-turnover renal osteodystrophy and lower in patients with low bone turnover and in healthy subjects. These results illustrate the potential utility of using ^{18}F -NaF PET to assess patients with renal osteodystrophy and to track their response to therapy.

Another recent study scanned patients with end-stage renal disease (ESRD) and control subjects using ^{18}F -NaF PET-CT (46). It was concluded that a qualitative comparison (by two nuclear medicine specialists) of ^{18}F -NaF images of the control and ESRD patients showed no difference in image quality between the two groups such that the images produced were sufficient for assessing disease. A bone to soft tissue (B/S) index was then calculated by dividing the bone SUV average and the SUV average over soft tissue. The extraction of ^{18}F -NaF in bone was higher in ESRD with a B/S index of 4.03 compared with 2.48 in controls ($P=0.01$). As an extension, ^{18}F -NaF PET-MRI could be used in future studies to assess patients with renal osteodystrophy since bone and soft tissue could be analyzed structurally and functionally while also comparing the utility of ^{18}F -NaF PET-MRI to ^{18}F -NaF PET-CT.

4.5 Paget's Disease

Paget's disease involves increases in bone resorption and formation leading to fragile and misshapen bones (47). One study aimed to quantify indices of regional bone metabolism in Paget's disease and compare the indices to normal bone via dynamic ^{18}F -NaF PET scans

(48). It was found that compared with normal bone pagetic bone demonstrated higher values of plasma clearance to bone mineral (1.03×10^{-1} vs. 0.36×10^{-1} ml/min per milliliter; $p = 0.018$) and clearance to total bone tissue (2.38×10^{-1} vs. 1.25×10^{-1} ml/min per milliliter; $p = 0.018$) reflecting increased mineralization and blood flow, respectively. Release of ^{18}F -NaF from bone mineral was significantly lower in pagetic bone ($p = 0.022$) suggesting ^{18}F -NaF binds tighter to bone mineral in pagetic bone. The authors concluded that dynamic ^{18}F -NaF PET may be useful when measuring regional bone metabolism in Paget's and other bone diseases (48).

Treatment for Paget's disease relies on reducing the breakdown of bone typically through the administration of bisphosphonates (49). ^{18}F -NaF PET could be used to assess patients' responses to medication (50) similar to the aforementioned studies on bisphosphonate treatment for osteoporosis (20,22,38). MRI could provide additional information on the amount of bone water through UTE and ZTE MRI methods while also allowing visualization of soft tissues in this disorder.

5. Improvements via MRI

Along with the information on bone metabolism provided by PET, additional information on bone is offered by improvements in MRI. Specifically, ultrashort echo time (UTE) MRI and pore water measurements can be used to quantify bone quality and fracture risk. Ultimately, the fusion of PET and MRI via hybrid PET-MRI has the potential to further our understanding of metabolic bone diseases and to detect changes at an earlier stage.

5.1 UTE MRI and Pore Water Measurements

Cortical bone and its porosity are important contributors to bone strength (51). Cortical or compact bone refers to the denser outer shell of bone tissue which is approximately 90% bone and 10% pore space by volume. Measurements of cortical porosity may help discriminate subjects with fragility fractures from those without fractures, independent of bone mineral density (52,53). Studies have demonstrated that pore water increases in postmenopausal women and patients undergoing dialysis, two groups with increased fracture risk (54,55).

Recent technical improvements in MRI have made it possible to assess and visualize cortical bone (Figure 4) which has a very short T_2 relaxation time (<1 msec) by using an ultrashort echo time (UTE). Rajapaske et al. described the clinical application of a method to map volumetric cortical bone porosity (the porosity index) (56). The *in vivo* reproducibility study demonstrated mean coefficients of variation for cortical and total bone porosity of 2.2% and 2.0%, respectively. Further, the authors showed that they could capture pore size information (as validated by microcomputed tomography) and detect a range of porosity indices *in vivo* (15–31% and 24–38% for cortical and total bone regions).

A study using nuclear magnetic resonance (NMR) suggested that measuring the “free” pore water concentration could be a surrogate measure for cortical porosity (57). UTE MRI has demonstrated that cortical bone water concentration is increased (65%) in postmenopausal women as compared to premenopausal women (58). Further, patients with renal

osteodystrophy had higher bone water concentration than premenopausal women (135%) and postmenopausal women (43%) (58). Another study examined the effect of alendronate treatment on water concentration in the femoral shafts of rats through UTE MRI (59). The authors found that alendronate treatment decreased water concentration in a dose-dependent manner. These studies support the notion that increased porosity correlates with increased fragility risk and that measuring bone water in metabolic bone diseases can be useful. UTE MRI is a promising method that provides quantitative information about cortical bone, its porosity and its water concentration, which affect bone fragility.

Another recently introduced MRI method is ZTE (zero echo time) MRI, which can produce comparable images of bone to CT (Figures 5,6,7). ZTE MRI produces signal for bone and allows for segmentation of bone features for MR-based attenuation correction of PET data. One study used proton density (PD)-weighted zero TE (ZT) imaging for morphological depiction and segmentation of cranial bones. The authors concluded that the imaging method provided robust and efficient depiction of bone structures in the head with exceptional contrast between air, soft tissue and bone (60). Furthermore, PDweighted ZTE imaging is expected to be relevant for attenuation correction in PET-MRI. Both ZTE and UTE MRI show promise for the imaging of bone tissue as it relates to PET-MRI and metabolic bone diseases.

6. Conclusion

Metabolic bone diseases lead to changes in bone turnover and metabolism and treatments typically rely on regulating osteoclast and/or osteoblast activity. PET-MRI, and more specifically, ^{18}F -NaF PET-MRI, is suited for diagnosing metabolic bone disease, assessing fracture risk, and monitoring patients' response to therapy. The metabolic information from ^{18}F -NaF PET about bone remodeling and strength could supplement anatomical information clinicians receive from MRI for metabolic bone disorders such as osteoporosis, renal osteodystrophy, Paget's disease, fibrous dysplasia, osteomalacia and parathyroid disorders. One of the advantages of hybrid PET-MRI systems for imaging metabolic disorders is that the molecular changes (i.e. changes in bone metabolism) often precede structural changes (i.e. fractures, bone deformities) and hybrid imaging could highlight the presence of both.

PET-MRI is a recently available advanced tool for diagnosis of metabolic bone diseases. Further research is warranted given the limited number of prevalent studies PET-MRI reported so far for assessing metabolic bone disease. There is great potential in combining novel MRI methods such as UTE or ZTE MRI with novel PET radiotracers to study specific diseases. In the short term, ^{18}F -NaF PET-MRI promises even more specificity for diagnosis, earlier detection and improved characterization of metabolic bone disease.

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This study demonstrates how zTE MRI can be used to distinguish bone and could be useful in MR-based attenuation correction of PET data, as it pertains to PET-MRI and metabolic bone diseases.

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Figure 1.

18F-NaF PET images showing (A) a sagittal image of the lumbar spine (L1– L4) and (B) a coronal image of the proximal femur. Both images are 2-dimensional projection views of the complete 3-dimensional PET scan data, and both are limited by the 15-cm field of view of the PET scanner. In the femur image, 18F-NaF activity collecting in the urinary bladder during the 1 hour dynamic scan has been removed to give a clearer view of the uptake in bone. [Blake GM, Frost ML, Moore AE, et al. The assessment of regional skeletal metabolism: studies of osteoporosis treatments using quantitative radionuclide imaging. *J Clin Densitom* 2011;14:263–71. with permission].

Figure 2.

¹⁸F-Fluoride PET (SUV) and MRI images of a male patient with posttraumatic osteoarthritis showing concordance between a BML (blue arrowhead) and osteophytes (red diamond arrows) on MRI with high ¹⁸F-fluoride uptake on PET. Additionally, a focal region of high uptake on PET (magenta line arrow) did not exhibit bone abnormalities on MRI but was adjacent to a grade 2 cartilage defect (light blue solid arrow). [Kogan F, Fan AP, McWalter EJ, et al. PET/MRI of metabolic activity in osteoarthritis: A feasibility study. *J Magn Reson Imaging* 2017;45(6):1736–45. (24) with permission]. Used with permission from John Wiley and Sons.

Figure 3.

(A) Midsagittal 18F-fluoride PET image through lumbar vertebrae showing region of interest within vertebral bodies (at right is magnification of L1–L5 vertebral bodies, with squares indicating regions of interest). (B) Coronal image of pelvis and both proximal femurs (at bottom is magnification of left femoral neck, with square indicating region of interest). [Uchida K, Nakajima H, Miyazaki T, et al. Effects of alendronate on bone metabolism in glucocorticoid-induced osteoporosis measured by 18F-fluoride PET: a prospective study. *J Nucl Med* 2009;50:1808–14. (16)]

Figure 4.

MRI of a cadaveric forearm. While cortical bone produces a signal void on a conventional fast-spin echo (FSE) sequence (A), signal is detected from cortical bone with the use of an inversion recovery ultrashort echo time (IR UTE, TR/TI 300/120 ms) pulse sequence (B).

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Figure 5:
Comparable images from (A) isotropic 3D PD-ZTE and (B) nearisotropic CT for grading of CNF stenosis. Images courtesy of Hospital for Special Surgery MRI Laboratory.

Figure 6:

Comparable 3D reconstructed surface models of gleno-humeral joint from ZTE and CT, following manually-supplemented region-growing segmentation. (A) Posterior aspect of joint where Hill-Sachs defect is clearly visible. Cortical thinness and spatial resolution of ZTE result in surface porosity (superior aspect of glenoid in ZTE). (B) Anterior aspect of joint. 'Furrowing' artifact due to coarser spatial resolution is visible in ZTE. (C) En face glenoid surface. Note 3 holes (anchors, labrum repair). There is a discrepancy in the segmentation of the superior hole in ZTE, owing to coarser spatial resolution/partial volume effects. Images courtesy of Hospital for Special Surgery MRI Laboratory.

Figure 7:

ZTE vs CT imaging of the hip. Axial images were acquired and multiplanar reformatting was performed for coronal and sagittal image reconstruction. Clinically relevant measurements for groin pain were taken from the images. Images courtesy of Hospital for Special Surgery MRI Laboratory.