RESEARCH ARTICLE

The Value of Apparent Diffusion Coefficient from Diffusion-Weighted Imaging in Differentiating Osteomyelitis and Reactive Bone Marrow Edema in Diabetic Patients

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Abstract

Objectives: This study evaluated the diagnostic performance of the apparent diffusion coefficient (ADC) in distinguishing osteomyelitis from reactive bone marrow edema (RBME).

Methods: This cross-sectional study included three groups of consecutive patients with diabetic foot ulcers (DFU) presenting with osteomyelitis, RBME, or healthy bone. All patients had DFU and were referred for magnetic resonance imaging (MRI). Patients with a history of foot surgery or biopsy before MRI, those who received antibiotic therapy for three or more days before imaging, and those with contraindications to MRI were excluded from the study. Osteomyelitis was confirmed by tissue biopsy, whereas RBME was diagnosed by exclusion. All participants underwent diffusion-weighted imaging (DWI), and ADC values were measured independently by two radiologists who were blinded to the clinical diagnosis. The diagnostic performance of ADC was then assessed.

Results: A total of 45 patients with diabetic foot ulcers (DFU) were recruited, of whom 18 (40.0%) had osteomyelitis, 16 (35.6%) had reactive bone marrow edema (RBME), and 11 (24.4%) had healthy bone tissue. Osteomyelitis demonstrated significantly higher ADC values compared to normal bone ($P < 0.001$) and significantly lower ADC values compared to RBME ($P < 0.001$). Using a cut-off value of 1478.0×10^{-6} mm²/s, ADC differentiated osteomyelitis from RBME with an accuracy of 88.2%, sensitivity of 94.4%, specificity of 81.2%, and an area under the curve (AUC) of 0.958.

Conclusion: These findings support the applicability of diffusion-weighted imaging (DWI) as a non-invasive and accurate diagnostic tool for differentiating osteomyelitis from reactive bone marrow edema.

Level of evidence: IV

Keywords: Diabetes mellitus, Magnetic resonance imaging, Osteomyelitis, Reactive bone marrow edema

Introduction

Diabetic foot ulcers (DFUs) are among the major complications affecting patients with diabetes mellitus. The extent of tissue involvement in DFUs ranges from superficial ulcers to bone abnormalities, including reactive bone marrow edema (RBME), osteomyelitis, and intraosseous abscesses. Differentiating osteomyelitis from diabetic osteoarthropathy-related RBME is clinically significant and represents one of the most challenging diagnoses in patients with DFUs.[1] Delayed diagnosis of osteomyelitis increases the risk of permanent tissue damage and subsequent amputation.[2]

Various imaging modalities have been employed to diagnose diabetic foot osteomyelitis, including plain radiography, conventional magnetic resonance imaging (MRI), nuclear scintigraphy, fluorodeoxyglucose positron emission tomography (FDG PET), and labeled white blood cell PET. However, the utility of these modalities may be limited, as reactive bone marrow edema (RBME) can mimic osteomyelitis across different imaging techniques.[3,4] Recent reports also underscore diagnostic pitfalls in osteomyelitis presentations on musculoskeletal imaging Likewise,[5] highlights the ongoing burden of MSK infection (e.g., septic

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arthritis), reinforcing the need for precise imaging-based diagnosis. [6] Early signs of osteomyelitis typically appear on plain radiographs only after approximately two weeks, rendering this modality insensitive during the early stages of the disease.[7]

Although nuclear scintigraphy is sensitive, its specificity remains relatively low.[8] Currently, conventional MRI is considered the imaging modality of choice for diagnosing pedal osteomyelitis. However, the sensitivity and specificity of traditional MRI sequences are variable, and factors such as inflammatory changes and neuropathic disease can complicate accurate interpretation.[9]

Diffusion-weighted imaging (DWI) is an advanced MRI technique that has garnered increasing interest in the evaluation of various conditions, including bone tumors, soft tissue tumors, and infection,[10,11] which detects the random Brownian motion of water molecules.[12] Following image acquisition, the degree of diffusion is quantified as the apparent diffusion coefficient (ADC). The mean ADC value can be calculated by delineating a region of interest (ROI) on the ADC map. Interpretation of conventional MRI sequences depends on imaging parameters, which can vary between scanners and limit direct numerical comparison.[13] In contrast, ADC values are generally comparable across different systems when calculated for the same tissue, provided that the repeatability and reproducibility of the selected field strength and acquisition parameters are taken into account.[14,15]

Only a limited number of studies have evaluated the utility of diffusion-weighted imaging (DWI) for diagnosing osteomyelitis in patients with diabetic foot ulcers (DFU).[8,16] Eren et al. compared ADC values between DFU patients with (n = 9) and without (n = 21) osteomyelitis and reported a significant difference between the groups.[17] However, the authors did not assess the diagnostic performance of this quantitative parameter.[10] A more recent study evaluated the diagnostic performance of ADC, focusing solely on differentiating between DFU patients with and without osteomyelitis.[8] In this study, we aimed to assess the diagnostic accuracy of ADC derived from DWI in distinguishing, firstly, abnormal bone from healthy bone, and secondly, osteomyelitis from reactive bone marrow edema (RBME) in patients with DFU.

Materials and Methods

Study design and patient selection

This single-center cross-sectional study was conducted between 2020 and 2022 at an academic hospital. The institutional ethics committee approved the study (ethical code: IR.MUMS.MEDICAL.REC.1400.387), and informed consent was obtained from all participants. Consecutive patients with diabetic foot ulcers (DFU) who were referred for magnetic resonance imaging (MRI) were included. Exclusion criteria were as follows: 1) history of foot surgery or biopsy before diffusion-weighted imaging (DWI), 2) antibiotic therapy for 72 hours or more before DWI acquisition, and 3) any contraindications to MRI.

Study subjects were categorized into three groups: patients with osteomyelitis, patients with reactive bone marrow edema (RBME), and individuals with normal bone marrow. The diagnosis of osteomyelitis was confirmed by histopathological examination. RBME was diagnosed by exclusion, defined as the presence of degenerative or stress-related forefoot changes without clinical suspicion of infection during a follow-up period of at least three months. Subjects with normal bone marrow demonstrated normal bone signal intensity without any lesions on MRI. The average interval between symptom onset and imaging or tissue sampling was approximately two months.

Magnetic resonance image acquisition

All examinations were performed using a 1.5 Tesla MRI scanner (Avanto; Siemens Healthcare, Erlangen, Germany). Fat-suppressed diffusion-weighted imaging (DWI) was acquired in the sagittal and coronal planes employing a spin-echo, single-shot echo-planar imaging (EPI) sequence. The DWI acquisition parameters were as follows: repetition time (TR) = 4300 ms, echo time (TE) = 104 ms, field of view (FOV) = 280 × 280 mm^2, matrix size = 192 × 192 pixels, flip angle = 90°, section thickness = 4 mm, and interslice gap = 1 mm. Apparent diffusion coefficient (ADC) maps were generated using b-values of 0 and 1000 s/mm^2.

Image analysis

A radiologist with four years of experience in musculoskeletal imaging performed image analysis. For each patient with a bone lesion, three regions of interest (ROIs) were drawn at different sites within the lesion on the ADC map. These ROIs were subsequently reviewed and validated by a second radiologist with seven years of experience in musculoskeletal imaging. The mean ADC values from the three ROIs were averaged to obtain a single representative value for each lesion [Figure 1]. In patients without bone lesions (i.e., healthy bone), three ROIs were drawn in the calcaneus, and their mean ADC values were similarly averaged. The ROI size ranged from 20 to 50 mm^2. Both radiologists were blinded to the patients' clinical data and final diagnoses.

Statistical analysis

Qualitative data were presented as frequencies and percentages, while quantitative data were expressed as mean ± standard deviation. The Chi-square test was used to compare categorical variables, and one-way analysis of variance (ANOVA) was applied to compare quantitative variables across the study groups. Pairwise comparisons were conducted using post hoc analysis with Bonferroni correction to adjust for multiple testing. The diagnostic accuracy of diffusion-weighted imaging (DWI) for differentiating healthy bone from abnormal bone (osteomyelitis or reactive bone marrow edema [RBME]) and for distinguishing osteomyelitis from RBME was assessed using receiver operating characteristic (ROC) curve analysis, with the area under the curve (AUC) reported. Statistical analyses were performed using SPSS software (version 21), and a P value < 0.05 was considered statistically significant.

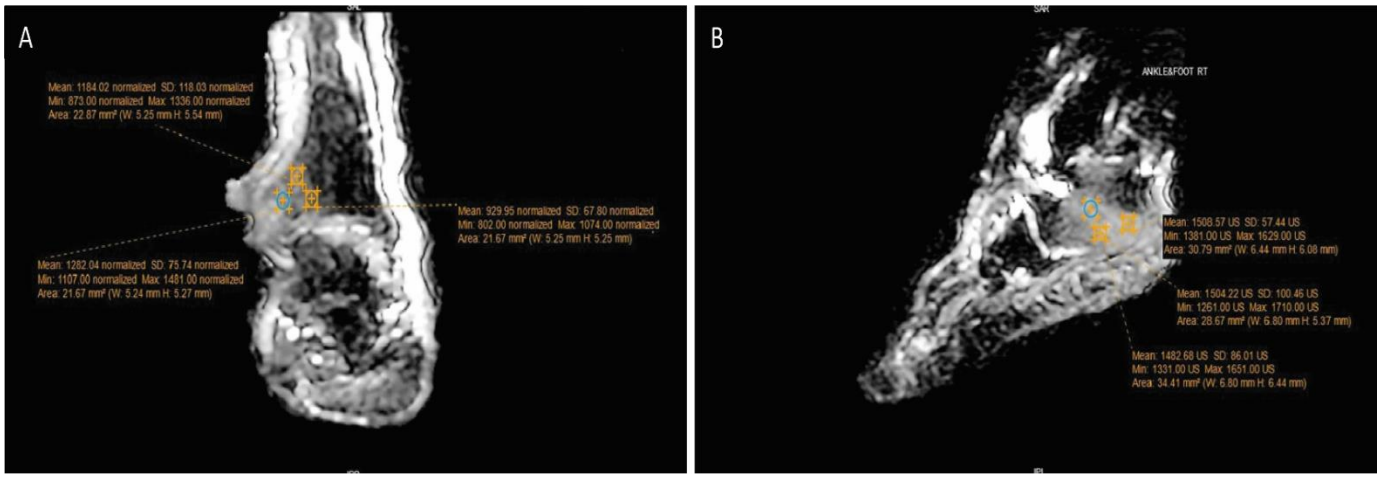

Figure 1. Measurement of bone ADC values (A) in a patient with osteomyelitis and (B) in a patient with reactive bone marrow edema

Results

Study subjects

A total of 45 patients with diabetic foot ulcers (DFU) were included in this study (25 males and 20 females; mean age, 54.22 ± 11.07 years). Among them, 18 patients (40.0%) were diagnosed with osteomyelitis, 16 (35.6%) with reactive bone marrow edema (RBME), and 11 (24.4%) with healthy bone tissue. Each patient presented with a single foot lesion, resulting in a total of 45 lesions. There were no significant differences in baseline characteristics among the study groups. Osteomyelitis was most commonly located in the calcaneus (50.0%) and metatarsal bones (44.4%). Detailed data are presented in [Table 1].

Table 1. Baseline Characteristics and location of ulcers based on the bone condition

Variables	Osteomyelitis (N=18)	Reactive bone marrow edema (N=16)	Healthy bone (N=11)	*P-value*
Age (years)	49.8 ± 12.2	53.9 ± 12.0	45.7 ± 11.2	0.93*
Sex (male)	10 (55.6%)	11 (68.8%)	4 (36.4%)	0.25**
ADC (× 10-6 mm2/s)	1196.7 ± 116.5	1562.9 ± 141.3	392.6 ± 58.3	< 0.001*
Location of ulcer				
Calcaneus	8 (44.4%)	4 (25.0%)	6 (54.6%)	0.33**
Metatarsal bones	9 (50%)	9 (56.2%)	5 (45.4%)	
Other locations	1 (5.6%)	3 (18.8%)	0 (0%)	

Data are presented based on mean ± SD or frequency (%). ADC: apparent diffusion coefficient
*ANOVA test was used.
**Chi-square test was used

ADC values in the study groups

The mean ADC value was 1196.7 ± 116.5 × 10^{-6} mm^2/s for osteomyelitis, 1562.9 ± 141.3 × 10^{-6} mm^2/s for RBME, and 392.6 ± 58.3 × 10^{-6} mm^2/s for healthy bone tissue [Figure 2]. These differences were statistically significant (P < 0.001). Intergroup comparisons demonstrated that ADC values were significantly higher in RBME compared to both osteomyelitis and healthy bone tissue (P < 0.001) [Table 2].

Diagnostic performance of ADC

Receiver operating characteristic (ROC) curve analysis demonstrated that ADC values perfectly differentiated abnormal bone tissue from healthy bone. Using an optimal ADC cut-off value of 783.5 × 10^{-6} mm^2/s, the sensitivity, specificity, and accuracy were all 100%, with an area under the curve (AUC) of 1.0 [Figure 3A].

ADC values also accurately distinguished osteomyelitis from reactive bone marrow edema (RBME), exhibiting a sensitivity of 94.4%, specificity of 81.2%, accuracy of 88.2%, and an AUC of 0.958 at a cut-off value of 1478.0 × 10^{-6} mm^2/s [Figure 3B].

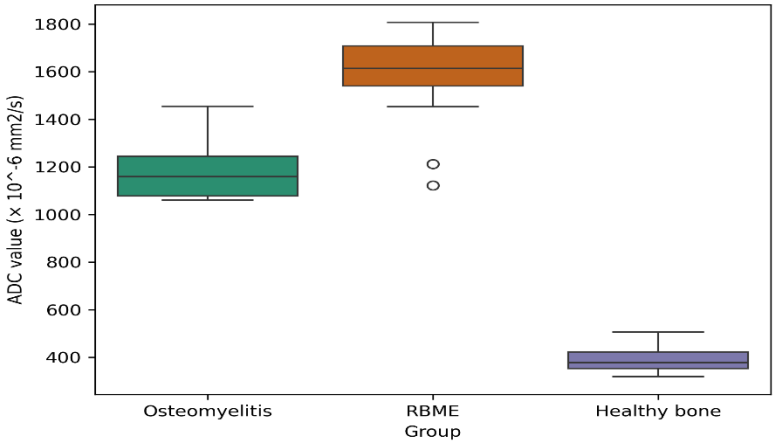

Figure 2. Boxplots showing the difference in ADC values among study groups. RBME: reactive bone marrow edema, ADA: apparent diffusion coefficient

Table 2. Intergroup comparison of ADC bone using post hoc analysis based on Bonferroni correction

	Osteomyelitis	Healthy bone	Reactive bone marrow edema
Osteomyelitis	-	< 0.001	< 0.001
Healthy bone	< 0.001	-	< 0.001
Reactive bone marrow edema	< 0.001	<0.001	-

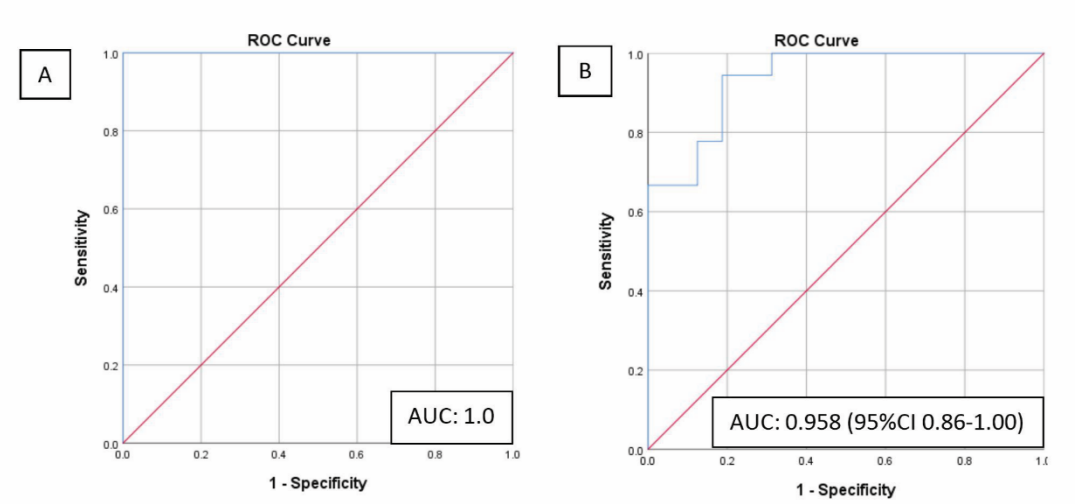

Figure 3. Receiver operating characteristic (ROC) curves for differentiation (A) between healthy bone vs. abnormal bone and (B) between reactive bone marrow edema vs. osteomyelitis. (A) ADC values were able to distinguish normal and abnormal bone marrow with a sensitivity and specificity of 100%. (B) ADC > 1478.0 × 10-6 mm2/s differentiated osteomyelitis from bone marrow edema with an accuracy of 95.8%, sensitivity of 94.4%, and specificity of 81.2%

Discussion

Differentiating osteomyelitis from reactive bone marrow edema (RBME) remains one of the most challenging diagnostic tasks in patients with diabetic foot ulcers (DFU). Conventional magnetic resonance imaging (MRI) is the primary imaging modality for assessing diabetic foot complications due to its ability to provide detailed visualization of soft tissue and bone. However, osteomyelitis and other causes of bone marrow edema, such as acute neuropathic arthropathy and post-procedural changes, often exhibit similar signal intensities on T1-weighted, T2-weighted, and short tau inversion recovery (STIR) sequences, thereby limiting specificity.[18-20] Additionally, fat-suppressed T2-weighted sequences, although highly

sensitive for detecting bone marrow abnormalities, lack the specificity necessary to reliably distinguish osteomyelitis from reactive bone marrow edema (RBME).[22] These limitations underscore the need for advanced imaging techniques, such as diffusion-weighted imaging (DWI), to enhance diagnostic accuracy. Unlike conventional sequences, the apparent diffusion coefficient (ADC) provides a quantitative parameter that facilitates standardized interpretation across different MRI systems when acquisition parameters are consistent. Our findings demonstrated that ADC values below 1478.0×10^{-6} mm^2/s are diagnostic for osteomyelitis, with a sensitivity of 94.4% and specificity of 81.2%. Furthermore, ADC values below 783.5×10^{-6} mm^2/s accurately ruled out bone abnormalities in patients with DFU, with 100% sensitivity.

Few studies have evaluated the utility of diffusion-weighted imaging (DWI) MRI as a diagnostic tool for osteomyelitis in patients with diabetic foot ulcers (DFU). Raj et al. reported that ADC values below 1570×10^{-6} mm^2/s demonstrated a sensitivity of 88.2% and specificity of 80% for diagnosing osteomyelitis.[8] However, the authors did not differentiate negative osteomyelitis cases into reactive bone marrow edema (RBME) or healthy bone tissue, and the study's relatively small sample size may have impacted its internal validity. Razek et al. identified a cut-off value of 1040×10^{-6} mm^2/s, yielding a sensitivity of 83% and specificity of 96% for distinguishing osteomyelitis.[14] Kruk et al. demonstrated that ADC values could distinguish normal from abnormal bone with 100% accuracy, sensitivity, and specificity at a cut-off value of 534.0×10^{-6} mm^2/s.[21] However, they did not establish a single cut-off value to differentiate osteomyelitis from RBME, instead proposing two thresholds for 95% sensitivity (ADC < 1155×10^{-6} mm^2/s) and 95% specificity (ADC > 1320×10^{-6} mm^2/s). It is noteworthy that their study evaluated lesions only in the forefoot.

A meta-analysis of 29 articles by Lauri et al. showed that WBC scan with 99mTc-HMPAO had 91% sensitivity and 92% specificity, while MRI had 93% sensitivity and 75% specificity.[24, 20] F-FDG-PET was found to have a sensitivity of 74% and a specificity of 91%.[25] Similarly, Dinh et al. conducted a systematic review of various imaging modalities for diagnosing osteomyelitis in patients with diabetic foot ulcers (DFU), concluding that MRI remains the most accurate imaging technique, with a sensitivity of 90% and specificity of 79%.[26] Although some of these imaging modalities demonstrate high diagnostic value, they are often expensive, not widely available, or limited in use for specific patient populations—for example, individuals unable to receive intravenous contrast. Diffusion-weighted imaging (DWI), which does not require contrast agents, may therefore represent a preferable option, especially for patients with DFU who frequently have comorbidities such as chronic renal failure.

The highest apparent diffusion coefficient (ADC) values were observed in reactive bone marrow edema (RBME), followed by osteomyelitis and healthy bone tissue. This pattern can be attributed to the biochemical properties of healthy and pathological bone marrow. Diffusion-weighted imaging (DWI) evaluates the movement of water molecules, and ADC quantifies changes in diffusion signal intensity using different b-values. The ratio of yellow to red bone marrow influences ADC values; increased yellow marrow (fat) reduces extracellular space, whereas a higher proportion of red marrow reflects microcirculation in well-vascularized tissue.[27] Moreover, alterations in vascular supply, particularly in vascular pathologies commonly observed in diabetic foot, may affect microcirculation. Additional factors, such as the presence of inflammatory cells, necrotic debris, or pus, also contribute to differences in diffusion characteristics between healthy and abnormal bone tissue.

In our study, the mean apparent diffusion coefficient (ADC) values were $392.6 \pm 58.3 \times 10^{-6}$ mm^2/s in healthy bone, $1196.7 \pm 116.5 \times 10^{-6}$ mm^2/s in osteomyelitis, and $1562.9 \pm 141.3 \times 10^{-6}$ mm^2/s in reactive bone marrow edema (RBME), consistent with previously reported values. This variation reflects the differing biochemical properties of these conditions. The bone marrow in diabetic RBME contains a higher proportion of water protons compared to osteomyelitis, resulting in increased tissue diffusivity.[28] Normal bone marrow ADC values typically range between 200 and 500×10^{-6} mm^2/s, as reported by Dietrich et al.[29] In contrast, bone marrow abnormalities generally exhibit elevated ADC values, with osteomyelitis reported in the range of 1100 to 1400×10^{-6} mm^2/s and RBME ranging from 1400 to 1900×10^{-6} mm^2/s.[30]

The findings of this study have significant clinical implications for the management of diabetic foot ulcers (DFUs), particularly in distinguishing between osteomyelitis and reactive bone marrow edema (RBME). This distinction is crucial for informing treatment decisions. Early and accurate differentiation between these conditions enables clinicians to implement targeted therapies, potentially reducing unnecessary surgical interventions and optimizing antibiotic regimens. Apparent diffusion coefficient (ADC) measurements derived from diffusion-weighted imaging (DWI) provide a non-invasive and quantitative tool that may complement, or in some cases replace, more invasive diagnostic methods such as biopsy. Furthermore, the ability to discriminate between normal and abnormal bone with high diagnostic accuracy may facilitate earlier intervention and reduce the risk of complications.

This study has several limitations. First, the sample size was relatively small. Although our cohort included more subjects than most previous similar studies,[8, 16,17,31] larger-scale investigations are needed to validate the diagnostic utility of diffusion-weighted imaging (DWI). Second, we did not assess potential confounding factors that may affect apparent diffusion coefficient (ADC) values, such as patient comorbidities and the stage of infection. Future research should incorporate these variables to better elucidate their impact on ADC measurements in patients with diabetic foot ulcers (DFU).

Furthermore, our study evaluated the diffusion characteristics of osteomyelitis, reactive bone marrow edema (RBME), and healthy bone, as well as the diagnostic accuracy of diffusion-weighted imaging (DWI) in

differentiating these conditions. However, we did not assess the potential incremental diagnostic value of DWI relative to conventional MRI sequences. Conventional MRI primarily relies on visual assessment, which can limit the identification of overlapping imaging features between osteomyelitis and RBME.[21] In contrast, apparent diffusion coefficient (ADC) measurements enable objective differentiation based on the microstructural properties of bone marrow. ADC quantifies the diffusivity of water molecules within tissues, reflecting the underlying microenvironment. In osteomyelitis, the destruction of trabecular bone, the presence of pus, necrotic debris, and hypercellularity restrict water diffusion, leading to lower ADC values.[28] This characteristic may enhance diagnostic accuracy when ADC is used in conjunction with conventional MRI sequences. Moreover, the reproducibility of ADC measurements across different MRI systems and protocols enhances the robustness of its clinical utility, providing a more consistent diagnostic approach compared to the subjective interpretation inherent in conventional imaging.

Conclusion

This study demonstrated that apparent diffusion coefficient (ADC) values obtained from diffusion-weighted imaging (DWI) serve as an accurate diagnostic tool for differentiating osteomyelitis from reactive bone marrow edema (RBME). Additionally, ADC measurements effectively distinguished healthy bone from abnormal bone in patients with diabetic foot ulcers (DFU). Thus, this technique may offer superior sensitivity and specificity compared to other imaging modalities; however, confirmation of this hypothesis requires further investigation.

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