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RESEARCH

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The utility of chemical shift imaging and related Dixon images in evaluation of bone marrow edema-like changes in diabetic foot

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Abstract

Background Magnetic resonance imaging (MRI) is the best diagnostic tool for suspected diabetic foot osteomyelitis (DFO); adding T1-based Dixon to MR technique can identify the bone marrow edema-like signal observed in neuropathic joints and differentiate it from that observed in DFO. The aim of this study was to assess the diagnostic efficacy of chemical shift imaging (T1 in-phase and out-of-phase) and related Dixon sequence in differentiation between infectious edema-like signal found in osteomyelitis and bland edema signals observed in osteomyelitis mimickers (as neuropathic arthropathy). The study was conducted on 50 patients who were referred by surgical outpatient clinics between January 2020 and January 2022; they underwent MRI of the foot including T1-Dixon sequence.

Results There were variable bone and joint affection, and the most common location of bony affection in the study was the hind-foot. Forty-four out of fifty patients had bone marrow edema-like signals. Thirty-seven patients (74%) were diagnosed with osteomyelitis, whereas seven (14%) patients were diagnosed with non-infective/bland bone marrow edema signals which were related to Charcot arthropathy and/or nearby infection. Both visual and quantitative assessments of chemical shift imaging showed high sensitivity and specificity in diagnosis of DFO. The optimal cut-off point of signal intensity ratio for diagnosis of DFO was 1.005 with high sensitivity and specificity.

Conclusions Chemical shift imaging and related Dixon sequence were reliable methods in diabetic foot evaluation; they could help differentiate infectious edema-like changes of osteomyelitis from and bland edema of osteomyelitis mimickers with high sensitivity and specificity especially on using quantitative analysis of their signal abnormality.

Keywords Chemical shift imaging, T1-Dixon, In-phase, Out-of-phase, Bone marrow edema, Neuropathic arthropathy, Osteomyelitis, Osteomyelitis mimickers

Background

Diabetic foot syndrome is the most common musculoskeletal complication of diabetes mellitus; the most clinically important concerns are the neuropathic joints and osteomyelitis, both of which are considered as a major source of disability in diabetic patients [1–3].

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Many imaging tools have been used for diabetic foot evaluation, among which, magnetic resonance imaging (MRI) is considered the best diagnostic tool that could effectively evaluate the bone marrow affection as well as the soft tissue changes [4, 5]. However, MRI assessment of the diabetic foot is somewhat challenging, particularly when dealing with the frequently faced diagnostic dilemma, questionable diabetic foot osteomyelitis (DFO), in such cases, bone marrow signal abnormality of osteomyelitis can mimic that of neuropathic arthropathy [6, 7].

In order to improve MR detection of DFO, an additional image sequence that carries useful functional

aspects can make a change. T1-based Dixon sequence is an available technique found in almost all MR machines even in low field magnets. Although it is not widely used in foot MR protocols, T1-based Dixon has the ability to identify the bone marrow edema-like signal observed in neuropathic joints and differentiate it from that observed in diabetic foot osteomyelitis, this could be achieved by recognizing the changes in signal intensity of the suspected bone marrow abnormality on in-phase (IP) and out-of-phase (OP) images [8–10].

Aim of the work

The aim of this study was to assess the diagnostic efficacy of chemical shift imaging (T1 in-phase and out-of-phase) and related Dixon sequence as a part of non-enhanced MRI in differentiation between infectious edema-like signal found in osteomyelitis and bland edema signals observed in osteomyelitis mimickers (as in neuropathic arthropathy).

Methods

This observational analytic prospective study was conducted in MRI unit of our institution from January 2020 through January 2022, after being approved by the Faculty of Medicine Research Ethics Committee, approval number 300/2019.

Study participants

Fifty patients diagnosed with diabetic foot syndrome were referred from the surgical outpatient clinics to the MRI unit for MRI study of the foot. All patients underwent thorough medical history taking, complete clinical examination and arterial Doppler ultrasonography of the affected lower limb. An informed written consent was obtained from each patient prior to participating in the study.

Inclusion criteria

Inclusion criteria for patients were based on long standing diabetic foot ulcer/infection with or without signs of diabetes-related Charcot arthropathy and clinical suspicion of diabetic foot osteomyelitis.

Exclusion criteria

Contraindications to MRI examination such as claustrophobia, and patients underwent aneurysm clips or cardiac pacemaker, cochlear implant, etc., were the exclusion criteria.

MRI and CSI techniques

All MRI studies were performed on a 1.5-T Ingenia; Philips closed MR machine using flexible surface coil. The following sequences were performed for all cases:

1. Sagittal FSE T1WI (TR/TE 450/7), (matrix 192 × 175), (bandwidth 238.7), (slice thickness/gap 3.2/2 mm), (acquisition time 1.01 s), (FOV = 259).
2. Sagittal FSE T2-SPAIR (TR/TE 3163/60), (matrix 208 × 160), (bandwidth 438.4), (slice thickness/gap 4/3 mm), (acquisition time 2.06 s), (FOV = 264), frequency selective fat saturation.
3. 3D T1-Dixon sequence with four set images in long axis plane (TR/TEs, 6.5/4.4 and 2.2) (matrix 352 × 308), (bandwidth 634.1). (slice thickness 2 mm), (acquisition time 2.32 s) (FOV = 350).

Image analysis

Four radiologists with 22, 17, 14 and 12 years of experience read the images independently with consensus interpretation; the agreement was reached when more than two radiologists report the same imaging findings.

T1WI and T2-SPIAR sequences were carefully examined to detect and localize any bone marrow edema-like changes and/or soft tissue inflammatory changes (both appeared as hyperintense area on T2-SPAIR with corresponding areas of low signal intensity on T1WI). Once a bone marrow edema-like signal was observed, careful scrutiny of the extents and margins of marrow signal abnormality was carried out on the entire four set Dixon images, and then, the edema-like signal was analyzed visually and quantitatively by comparing its signals on both IP and OP images, one or more equal-sized region of interest (ROI) with equal number of pixels was placed over the area of investigation, and then, computation of signal intensity ratio (SIR) was obtained from OP/IP formula.

Treatment

Based on both clinical and radiologic findings, medical treatment was firstly tried in mild cases when the following criteria were fulfilled:

1. No persisting sepsis.
2. The patient can tolerate the prolonged therapy with appropriate antibiotics.
3. Good vascular status based on normal arterial Doppler ultrasonography that allows adequate drug availability within the tissues.

Surgical treatment was offered to more severe DFO cases when:

1. Surgical debridement is required for concurrent soft tissue necrosis/abscess.
2. Medical treatment was failed, or when its criteria were not fulfilled.

For neuropathic arthropathy, non-surgical management with casting was offered as long as it provides the foot the ability to rest flat on the floor and support ulcer-free foot. However, surgical fixation was performed in case of the unstable fractures/dislocations or foot deformities that could prevent normal walking or increase risk for foot ulcers.

Statistical analysis

Results of the MRI were recorded, tabulated and statistically analyzed using SPSS version 26.0. The qualitative data were described as number and percentage and were analyzed by using Chi-square test and Fisher's exact test. Quantitative data were described as mean, standard deviation and range, using Student's "t" test, if normally distributed or Mann–Whitney *U* test, and Kruskal–Wallis test, if not normally distributed. The accepted level of significance in this work was started at 0.05 ($P < 0.05$ was considered significant). Receiver Operating Characteristic (ROC) method was used to identify the optimal cut-off point of SIR for diagnosis of DFO. Inter-rater reliability was obtained for visual and quantitative assessment of bone marrow signal abnormality as well as for the presence of soft tissue necrosis.

Results

Thirty males (60%) and twenty females (40%) who complained of diabetes-related neuropathy with Charcot arthropathy and/or long standing diabetic foot ulcer were included in the study; their mean age was 51.8 ± 8.65 years (range 9–65 years). Forty-nine of them have type II diabetes, whereas only one patient has type I diabetes. All patients presented with unilateral foot disease, most of them were obese and had high body mass index, high blood sugar and high hemoglobin A1c level (Table 1).

Imaging findings

Variable bone and joint affections were observed in the study, the most common location of bony affection in the study was the hind-foot, and combined inter-tarsal (subtalar and mid-tarsal)/tarso-metatarsal joint affection was the most common joint disease in this study (Fig. 1). Six patients did not have any signal abnormality in the bone marrow (Table 2).

Table 1 Clinical and laboratory features of the cases ($n = 50$)

	Mean	SD
Body weight	95.22	14.84
Body mass index	31.520	3.903
Random blood sugar level	268.64	54.77
Hemoglobin A1c level	9.774	1.524

CSI findings

Forty-four out of fifty patients had bone marrow edema-like signals; Table 2 demonstrates visual and quantitative assessments of these signal changes on all sets of images of T1-Dixon sequence (Table 3).

Thirty-seven patients (74%) were diagnosed with osteomyelitis and underwent surgical debridement, whereas seven (14%) patients were diagnosed with non-infective/bland bone marrow edema signals, and the bland edema signals were related to either Charcot arthropathy or nearby arthritis (Table 4; Figs. 2 and 3). Using the operative management as a gold standard method, both visual and quantitative assessments of chemical shift imaging showed high sensitivity and specificity in diagnosis of DFO (Table 5). The optimal cut-off point of SIR was 1.005 that demonstrated maximum sensitivity and specificity for diagnosis of DFO (Table 6; Fig. 4).

Inter-rater reliability

The percent agreement in the study was high; it was 92.59% for quantitative assessments of bone marrow edema-like signals, 90.47% for visual assessments of bone marrow edema-like signals and 88.8% for the presence of soft tissue necrosis. The radiologic diagnosis was made in consensus; it was reached when more than two radiologists report the same imaging findings.

Discussion

MRI is the modality of choice for diagnosis of DFO and associated soft-tissue complications. Most MR protocols include T1-weighted sequence which has a great ability for anatomical detail depiction and is sensitive to marrow changes; also include fat suppressed T2-weighted sequence for detection of edema signal and any fluid collections in the bone marrow and soft tissue, post-contrast study can be performed, however; its routine use is debatable. Although post-contrast images could improve the specificity of MR in suspected DFO by detection of non-enhanced necrotic components and although the addition of a certain sequence as diffusion weighted images could add functional quantitative information that might help in detection of intra-osseous abscess, there are still many mimickers of DFO that may present a diagnostic challenge and show bone marrow edema-like changes such as mechanical stress-related changes, recent operative changes, and coexisting neuropathic arthropathy, all of these mimickers can complicate the MR ability to establish an accurate diagnosis. Moreover, not all diabetic patients are candidate for gadolinium administration as many patients have coexistent renal

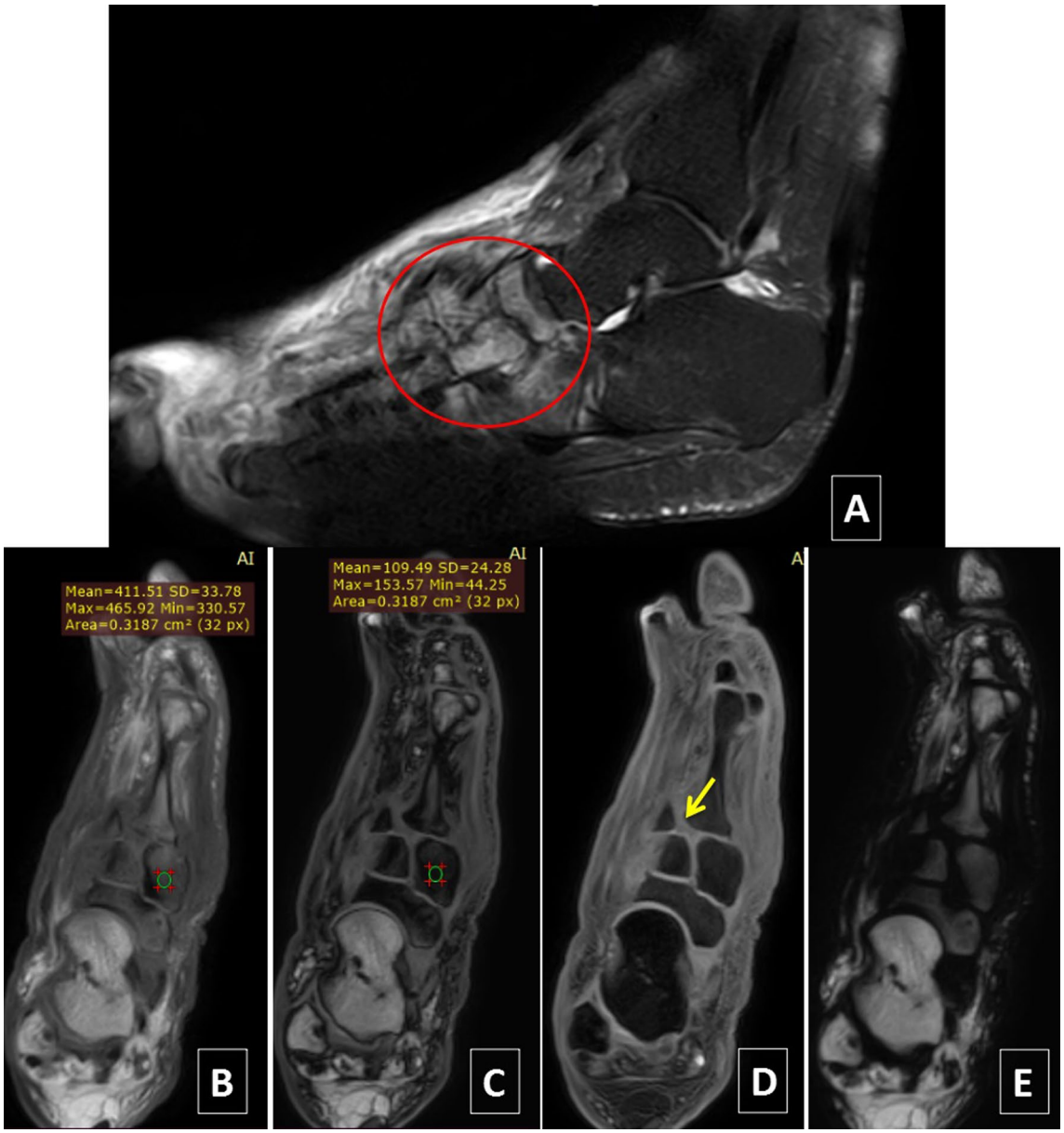

Fig. 1 Fifty-seven-year-old diabetic male patient presented with right dorsal foot swelling and redness with tarso-metatarsal instability and clinical suspicion of diabetic foot osteomyelitis. **A** Sagittal T2 SPAIR shows multi-focal bone marrow edema-like changes involving the mid-foot bones and the adjacent metatarsal bases (circle) with overlying dorsal subcutaneous edema signals. **B**–**E** Long axis T1-Dixon four-set images (IP, OP, fluid only and fat only images) demonstrate diffuse visual signal nulling of the affected bones in OP image (**C**) compared with IP image (**B**) and quantitative signal loss (signal intensity ratio = 0.26), note the Lisfranc dislocation (yellow arrow), features are consistent with neuropathic arthropathy without osteomyelitis

function impairment. In addition, diffusion weighted images suffer from low spatial resolution and could produce a low signal artifact at the metatarsal heads owing to their yellow marrow contents [4].

The application of T1-Dixon sequence in the current study is considered a novel issue that aimed to overcome the aforementioned challenges and improve the ability of non-enhanced MRI in identification of DFO, T1-Dixon sequence carried the main job in our study that could almost reach a standalone role in the absence of post-contrast study. In addition, the analysis of signal changes in in-phase and out-of-phase images in our study has provided a new quantitative measure through the use of SIR assessment. To the best of authors' knowledge, no

Table 2 Anatomic location of MR signal abnormalities ($n=50$)

		No.	%
Bone affection by region	Hind-foot	18	36
	Midfoot	14	28
	Forefoot	6	12
	Combined forefoot and midfoot	1	2
	Combined forefoot and hind-foot	1	2
	Combined midfoot and hind-foot	4	8
	No bone marrow signal abnormalities	6	12
Joint affection	No joint affection	24	48
	Inter-tarsal joints	10	20
	Combined inter-tarsal and tarso-metatarsal joints	12	24
	Combined tibio-talar and inter-tarsal joints	4	8

Table 3 Visual and quantitative assessments of bone marrow edema-like signals on all sets of images of T1-Dixon sequence (n = 44)

		No.	%
Visual assessment			
IP	Low bone marrow signal	44	100
OP	No signal nulling	35	80
	Signal nulling compared with IP	9	20
Water only	Faint hyperintense signal	44	100
Fat only	Very low signal	44	100
Quantitative assessment (SIR)	No signal nulling (OP/IP > 1)	36	82
	Quantitative signal nulling (OP/IP < 1)	8	18

Table 4 Different diagnoses in the study participants based on their management and operative results ($n=50$)

Diagnosis	No	%
Osteomyelitis with no significant soft tissue affection	20	40
Osteomyelitis with soft tissue abscess and/or necrosis	9	18
Osteomyelitis with concurrent Charcot arthropathy	8	16
Charcot arthropathy, no osteomyelitis	6	12
Non-septic arthritis with effusion/synovitis, no osteomyelitis	1	2
Parietal abscess, no bone affection	6	12

available published data concerned with the use of chemical shift or T1-Dixon imaging in diabetic foot evaluation [11].

The current study showed forty-four out of fifty cases demonstrated bone marrow edema-like signals with a clinical suspicion for DFO; thirty-seven of them (74%) were surgically diagnosed with osteomyelitis. This high rate of DFO is expected and would be considered as a normal consequence to the study's inclusion criteria (long standing diabetic foot ulcer/infection with or without signs of diabetes-related Charcot arthropathy and clinical suspicion of diabetic foot osteomyelitis). In a meta-analysis, Kapoor et al. [12] reviewed sixteen studies utilized MRI for diagnosing foot osteomyelitis and found that the prevalence of DFO was averaged approximately 50% and ranged from 32 to 89%. The high prevalence of DFO in our study and in other studies is generally attributed to the excellent soft tissue characterization offered by MRI and the opportunity to detect the deep collection of necrosis/pus more specifically than other imaging methods do [12].

In the current study, the visual analysis of marrow signal abnormality on primary image sets of Dixon sequence (in-phase and out-of-phase images or CSI) demonstrated high sensitivity and specificity in detecting DFO that equal to 91.9% and 84.6%, respectively, and visual assessment was able to differentiate DFO cases from their mimics as neuropathic arthropathy by the presence of signal nulling in out-of-phase images compared with the in-phase images, visual assessment detected thirty-five cases of DFO. On the other hand, the quantitative evaluation of signal abnormality using SIR and a cut-off-value of 1.005 increased such sensitivity to 94.6% and increased

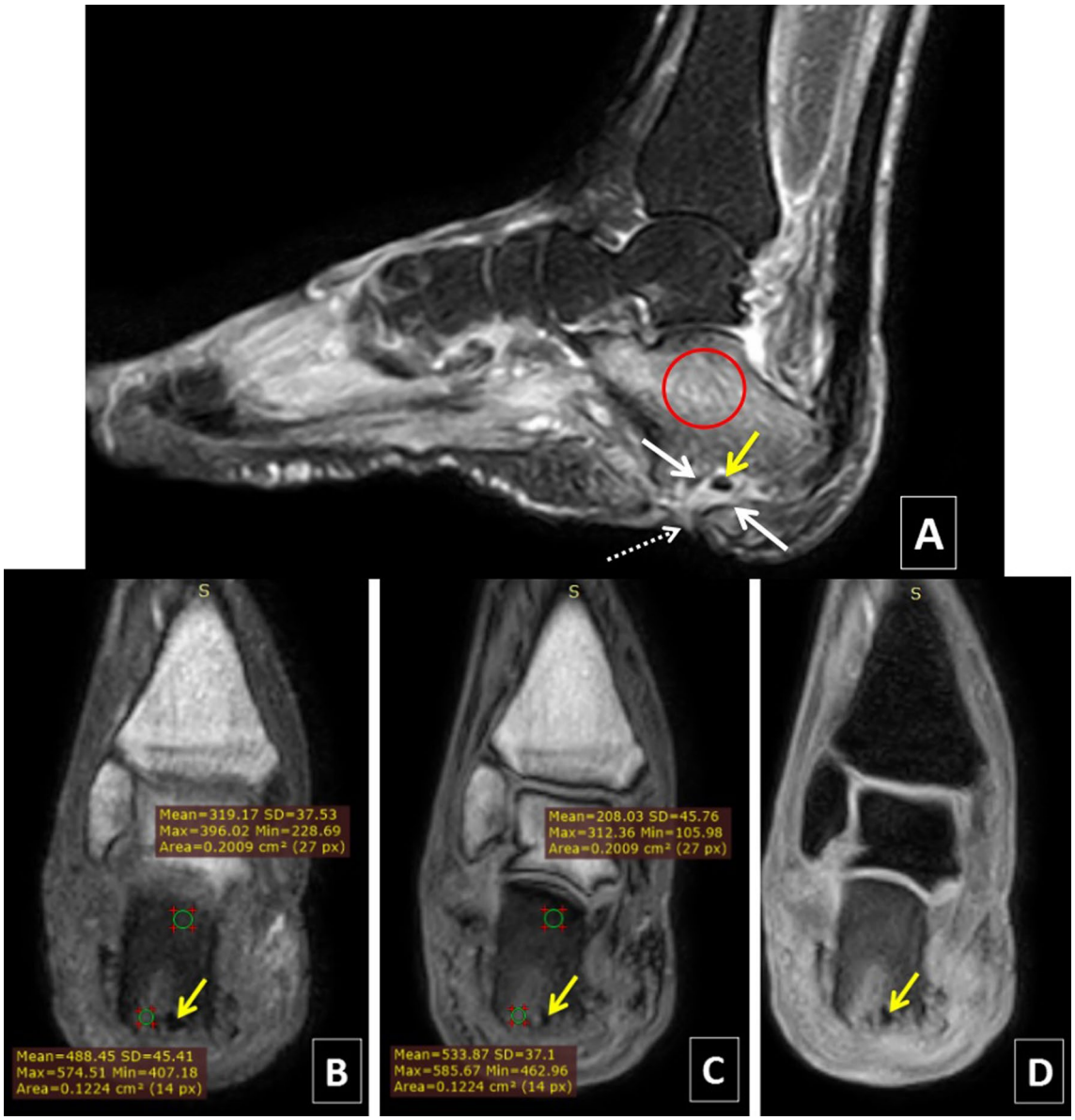

Fig. 2 Fifty eight year-old diabetic male patient presented with chronic right heel ulcer with suspected diabetic foot osteomyelitis. **A** Sagittal T2 SPAIR shows diffuse bone marrow edema-like changes involving the calcaneus (circle) with inferior calcaneal fluid signal abscess (white arrows) which contains a small low signal focus likely air bubble (yellow arrow), note the skin ulcer (dashed arrow). **B**–**D** Short axis IP, OP and fluid only images show persistent signal of the inferior calcaneal abscess demonstrate by visual and quantitative assessments of OP and IP with high signal intensity ratio = 1.09. The remaining upper portion of the calcaneus demonstrates diffuse visual and quantitative signal nulling on OP image (**C**) compared to IP image (**B**) (signal intensity ratio = 0.65). Note that the marrow edema signals show faint hyperintensity on fluid only image (**D**) compared with that on T2 SPAIR (**A**) due the T1 weighting of Dixon sequence. Features are consistent with calcaneal osteomyelitis with adjacent reactive edema signals

the NPV and accuracy as well, quantitative evaluation was able to detect an additional case of DFO, and the specificity remained unchanged among both visual and quantitative evaluations. The difference in edema pattern between DFO and its mimics on CSI could be basically explained by the difference in chemical composition of the extra-cellular fluid in both categories, in case of DFO, the extra-cellular fluid is consisted of exudate which is highly cellular and contains thick infected materials and pus. In the absence of osteomyelitis, the bone marrow edema pattern of DFO mimics would be simple and bland; it consisted of transudate which is an abnormal

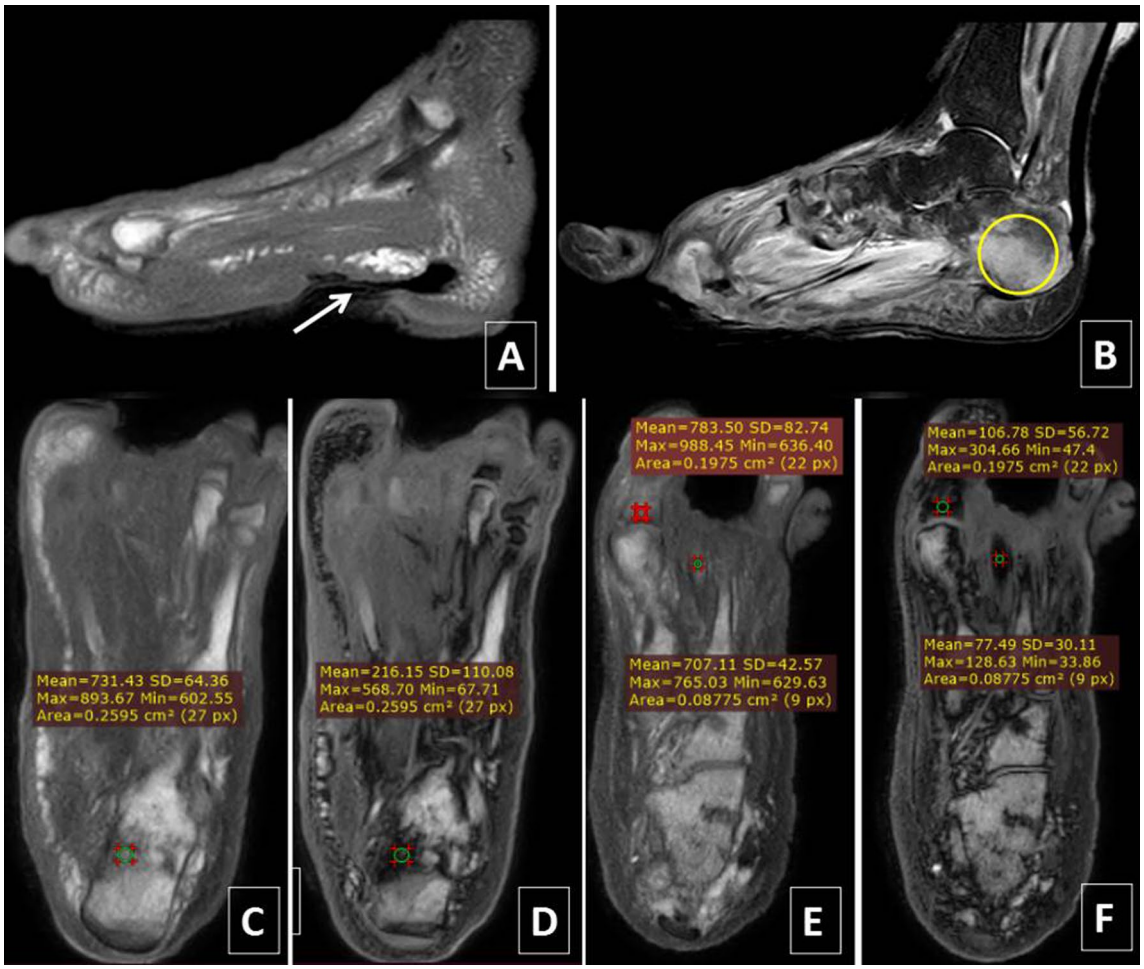

Fig. 3 Forty-nine-year-old diabetic male patient, with past history of left 2nd and 3rd toe amputation due to previous DFO, presented with chronic left heel ulcer and suspected diabetic foot osteomyelitis. **A** Sagittal T1WI shows deeply seated ulcer of the heel (arrow). **B** Sagittal T2 SPAIR shows diffuse bone marrow edema-like changes involving the calcaneus (circle). **C** and **D** Long axis IP and OP images show visual and quantitative signal nulling of the affected area on OP image (**D**) compared with IP image (**C**) (signal intensity ratio = 0.29). **E** and **F** Long axis IP and OP images at different level show visual and quantitative signal nulling of the 1st proximal phalanx and the 2nd metatarsal shaft on OP image (**F**) compared with IP image (**E**) (signal intensity ratio = 0.13 and 0.1, respectively). Features are consistent with multi-focal bland edema signals without osteomyelitis

Table 5 Sensitivity, specificity, positive predictive and negative predictive values of T1-Dixon study in diagnosis of DFO

	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)	Accuracy (%)
Visual assessment of T1-DIXON	91.9	84.6	94.4	78.6	81.9
Quantitative assessment using signal intensity ratio	94.6	84.6	94.7	91.7	89.9

increase in the amount of extra-cellular fluid not its composition, and it does not demonstrate high cellularity in contrast to the exudate, or contain infected materials [13].

Many studies have utilized MRI examination in diabetic foot complications, they have yielded a generally high sensitivity (> 80%) and varying specificities; however, these data are clearly shown in a meta-analysis of twenty-one studies reviewed by Llewellyn et al. [14] who found that the specificity of MRI for DFO among all studies employing MRI had a wide range of values and was often poor; in other word, the potential problem of MRI is over-diagnosis of DFO. The recent studies within this meta-analysis include La

Table 6 Area under curve (AUC) and optimal cut-off point of the SIR identifying DFO using receiver operating characteristic (ROC) method

AUC	0.819
Cut-off point	1.005
P-value	0.001
95% CI	0.660–0.978
Sensitivity	94.6%
Specificity	84.6%
PPV	94.7%
NPV	91.7%
Accuracy	89.9%

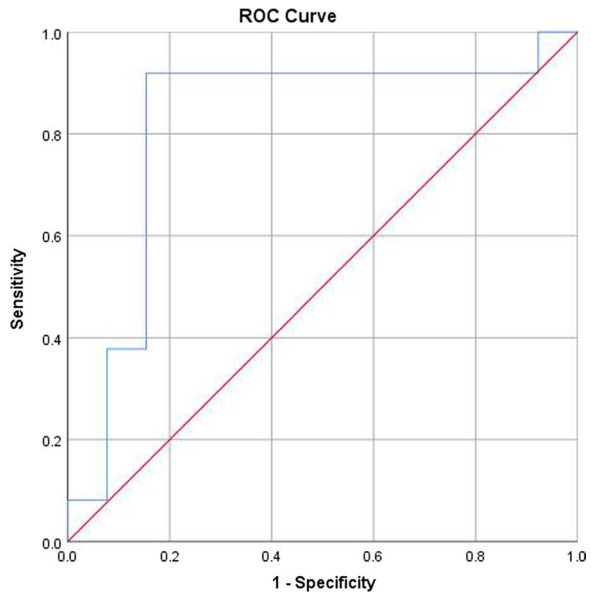

Fig. 4 Receiver operating characteristic (ROC) graph showing sensitivity, specificity and area under the curve for SIR of the bone marrow edema-like changes

Fontaine et al. [15] who studied the utility of Tc-99m WBC SPECT/CT and MRI in diagnosing of DFO and found that the sensitivity of MRI was high (87%), but the specificity was very low (37%), the positive predictive and negative predictive values were 74% and 58%, respectively. Furthermore, Nawaz et al. [16] evaluated the diagnostic performance of different imaging modalities for the diagnosis of osteomyelitis in the diabetic foot and found that MRI correctly diagnosed DFO in 20 out of 22 with sensitivity, specificity, PPV and NPV of 91%, 78%, 56%, and 97%, respectively. On the other hand, Mahendra et al. [17] studied the diagnostic accuracy of MRI and its impact on surgical decision in 34 patients with complicated diabetic foot who underwent MRI prior to surgical intervention; they showed that both sensitivity and specificity of MRI for osteomyelitis were high that equal to 100% and 90%, respectively. In another study employing MRI for suspected DFO in 102 diabetic patients, Zaiton et al. [7] found high sensitivity, specificity, PPV and NPV equal to 97.5%, 88.5%, 96.3% and 92%, respectively [7, 14–17].

The high sensitivity of chemical shift imaging in the current study could be in agreement with most sensitivities in most studies particularly the recent ones, although none of which employed the chemical shift MR imaging or Dixon sequence in their protocols. In addition, the increasing sensitivity from 91.9 to 94.6% with the use of quantitative analysis and SIR in our study renders the chemical shift imaging in the foreground among other studies.

Regarding the specificity of chemical shift imaging in our study, it would be comparable to Mahendra et al. [17] and Zaiton et al. [7] whose studies yielded high specificities of MRI in DFO diagnosis, although their MR protocols are different. The authors believe that this comparison could gain acceptance particularly if we take into account that the main role in our study fell upon the chemical shift imaging. The heterogeneity of specificity results among other studies, that could be somewhat disturbing, would be explained partly by variable presence of DFO mimickers among different studies, and partly by the potential difference in participants' inclusion criteria; for example, some studies have selected their participants from complicated cases who were prepared for surgical intervention and underwent MRI study as a routine pre-operative assessment, and this could in turn weaken the study design and could be a source of bias due to unusual patient selection [18].

Study limitations

The study included a small number of Charcot arthropathy cases compared with those diagnosed with DFO; in addition, it depended on clinical improvement as a follow up measure for them instead of utilizing a post-treatment CSI due to some logistic difficulties. The small number of Charcot arthropathy cases could be attributed to the study's inclusion criteria which were restricted to long standing diabetic foot ulcer/infection with clinical suspicion of DFO. Another limitation was the lack of contrast enhanced study which would aid in confident determination of bone necrosis. Larger study with recruitment of much milder cases and utilization of post-treatment CSI may be recommended. Furthermore, comparative multiparametric study might be recommended with addition of post-contrast MRI and/or diffusion weighted images.

Conclusions

Chemical shift imaging and related Dixon sequence were reliable methods in diabetic foot evaluation; they could help differentiate infectious edema-like changes of osteomyelitis from and bland edema of osteomyelitis mimickers with high sensitivity and specificity especially on using quantitative analysis of their signal abnormality.

Abbreviations

DFO	Diabetic foot osteomyelitis
IP	In-phase
OP	Out-of-phase
ROC	Receiver operating characteristic
ROI	Region of interest
SIR	Signal intensity ratio

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Not applicable.

Author contributions

MFA carried out the study design, image reading, statistical analysis, in addition to editing of publications. AMH carried out editing of publications, AHH carried out editing of publications, EAA carried out of image reading and statistical analysis, SSMM carried out data collection and imaging analysis, and AMA carried out editing of publications/presentation as well as imaging analysis and editing of publications. All authors read and approved the final manuscript.

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Availability of data and materials

The datasets used and analyzed during the study are available from the corresponding author on reasonable request.

Declarations

Ethics approval and consent to participate

The study was approved by the Research Ethics Committee of the Faculty of Medicine, Minia University, on August 2019; reference number of approval: N/A. All cases gave written informed consent to participate in the research.

Consent for publication

All patients included in this study gave written informed consent for data publishing contained within this study.

Competing interests

The authors declare that they have no competing interests.

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