CHAPTER **11**

# MRI EVALUATION OF OSTEOMYELITIS IN THE DIABETIC FOOT: Comparison with Surgical Pathology

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## BACKGROUND

Diabetes mellitus (DM) is at epidemic proportions, affecting about 17 million persons in the US. Numerous complications of DM affect multiple organ systems. The number one diabetes-related complication leading to hospitalization is foot infection, and almost two-thirds of these patients go on to a lower extremity amputation.[1-4] The pathogenesis and pathophysiology of diabetic foot infection has been well described. Risk factors for skin ulceration include peripheral neuropathy, insulin dependent diabetes, foot deformity, increased body mass, and decreased vision.[4]

Peripheral neuropathy is considered the number one factor in ulcer pathogenesis. Sensory neuropathy diminishes the body's ability to sense tissue damage. Motor neuropathy has been implicated in digital deformities, leading to abnormal pressure on weight-bearing areas and bony prominences. Autonomic neuropathy can cause vascular and dermatologic changes that decrease the body's natural defenses to invading organisms. Insensitive feet lead to neuropathic skin ulceration, which allows external pathogens to invade tissue. This can eventually lead to contiguous osteomyelitis (OM). Moreover, diabetics often have immunopathy, characterized by decreased leukocyte activity, which hastens deeper infection, and hinders its eradication.[4]

Diabetic foot infection presents as a wide spectrum of clinical entities, including cellullitis, abscess, and osteomyelitis. A diagnostic challenge arises when trying to differentiate between these various infectious syndromes. This is critical though, as the management of each of these infectious presentations can be drastically different. Laboratory examination has been shown to not correlate well with severity of diabetic foot infection. White blood cell (WBC) count, erythrocyte sedimentation rate (ESR), and C-reactive protein (CRP) level, often are either normal or nonspecific. Certain clinical tests, such as the "probe to bone" (PTB) test, have been touted in the past to be highly sensitive and highly predictive of OM in the diabetic foot.[5] However, more recent work[6] has shown that the test is more negatively predictive (i.e., a negative PTB test result virtually excludes the diagnosis of OM). These 2 studies demonstrate how the prevalence of a disease in a population will affect how accurate a particular test is to diagnose it.

Plain film radiography will lag, and not show obvious radiographic signs of OM anywhere from 2-4 weeks after the onset of acute osteomyelitis. Thus, it has low sensitivity. Changes depicted on plain radiography, however, are not specific and can be confused with neuropathic osteoarthopathy (another very common problem in the diabetic foot), post traumatic, and post surgical changes. Bone scintigraphy is a sensitive modality, but is not specific. Radionuclide-labeled leukocyte scans are more specific, but lack sensitivity.

Biopsy of suspected bone remains the gold standard for diagnosis, followed by microbiologic or histopathologic examination. Biopsy does have downsides though, as it is an invasive procedure, and it can carry the risk of spreading infection to adjacent healthy tissue. Magnetic resonance imaging (MRI) is said to have high sensitivity and specificity for the diagnosis of osteomyelitis in diabetics.[4,7,8] The MRI appearance of osteomyelitis is typically that of decreased signal intensity on T1-weighted images, and increased signal intensity on T2-weighted, or short tau inversion recovery (STIR) images. Marrow edema change is considered the primary sign of osteomyelitis by MRI.[1,9] Secondary signs include adjacent skin ulceration, adjacent inflamed soft tissue mass, sinus tracts, and cortical disruption.[8]

The purpose of this study was to examine the capability of MRI to diagnose suspected OM in diabetic patients. Most studies use the criteria of decreased signal intensity on T1-weighted images, and increased signal intensity on T2-weighted, or STIR images, plus adjacent ulceration or inflammatory soft tissue mass, to make the diagnosis of OM by MRI. We have noticed instances where marrow edema alone is the positive MR finding leading to the diagnosis of osteomyelitis. We felt that some of these conclusions are leading to "false positives," and are being diagnosed improperly. We sought to compare MRI findings of infected DM feet, with clinical concern for contiguous OM, and compare this to surgically-obtained bone, with subsequent histopathologic examination as our gold standard reference. We also

sought to determine the sensitity, specificitiy, positive predicitive value (PPV), and negative predictive value (NPV) of MRI in diagnosing OM in the feet of diabetics as a means of assessing test performance.

## MATERIALS AND METHODS

A retrospective review of a computer patient database of a single acute care hospital between the period October 2005 and September 2007 was performed. During this period, 50 consecutive patients presenting with diabetic foot infections were identified. Patients were identified by searching through multiple computerized databases with certain patient diagnoses (ICD-9 codes) and certain procedures (CPT codes) associated with them. The diagnoses that were searched were DM, pedal ulceration, infection, or osteomyelitis. Similarly, these patients were cross-referenced for having procedures performed such as biopsy, resection, or amputation involving the foot. Inclusion criteria was: 1) type 1 or type 2 DM, 2) diabetic foot infection, with clinical symptoms and signs concerning for OM, 3) MRI performed to evaluate for OM, and 4) biopsy, amputation, or surgical resection of tissue with subsequent pathologic examination to evaluate for OM.

**Sensitivity** = $\frac{TP}{TP + FN}$

the proportion of people with disease who have a positive test result

**Specificity** = $\frac{TN}{TN + FP}$

the proportion of people without disease who have a negative test result

**PPV** = $\frac{TP}{TP + FP}$

the proportion of patients with positive test results who are correctly diagnosed

**NPV** = $\frac{TN}{TN + FN}$

the proportion of patients with negative test results who are correctly diagnosed

Figure 1. Definitions and formulas for statistical analysis. TP = true positives; FP = false positives; TN = true negatives; FN = false negatives; PPV = predictive value; NPV = negative predictive value.

Exclusion criteria were 1) known tumor or malignancy in the foot, 2) recent surgery (<6 months) in the foot, and 3) recent severe trauma (<6 months) in the foot.

The rational for the exclusion criteria is that these are entities that could produce false positive results on MRI. Satisfaction of these criteria was accomplished by a careful review of each patient's medical record. Each MRI study obtained for an infected foot with concern for OM was carefully reviewed. The findings of each MRI were recorded, as well as the final diagnosis given by the interpreting radiologist. All MRI studies were performed in-house, at a single acute care hospital, and interpreted by the staff radiologists. All MRI studies were performed with and without intravenous (IV) gadolinium contrast, unless this was contraindicated by the patients' history. Most studies included IV gadolinium contrast.

Usually within 24 to 72 hours after obtaining the MRI, most of these patients went to surgery for definitive amputation, resection, or biopsy in order to eradicate, treat, or rule out OM. All of these surgeries were performed by experienced attending podiatric or orthopedic surgeons, usually with assistance from a podiatric surgery resident. Tissue obtained during surgery was then immediately sent to the pathology department in a sterile preservative-filled container. Specimens received gross and microscopic examination. Representative samples were decalcified, placed in cassettes, and sent for processing into permanent slides. All histopathologic examination was performed by staff pathologists. The pathologists' reports were reviewed. Gross and microscopic findings, as well as the final pathologic diagnosis, were recorded for each specimen.

Statistical analysis consisted of calculating sensitivity, specificity, PPV, and NPV. Sensitivity and specificity is calculated by determining true positives (TP), false positives (FP), true negatives (TN), and false negatives (FN) (Figure 1). TP was defined as a positive MRI and a positive biopsy. FP was defined as a positive MRI and negative biopsy. TN was defined as a negative MRI and a negative biopsy. Lastly, FN was defined as negative MRI and a positive biopsy (Figure 1).

## RESULTS

Fifty patients were identified who met the inclusion criteria. There were 39 men and 11 women whose mean age was 56.34 years. All of the patients were diabetic; they all presented with a pedal ulceration that was clinically infected, with a potential for underlying OM. The principle identifiers used to search through the computer database were 1) DM, 2) ulcer/foot infection, and 3) amputation or bone biopsy. Other associated diagnoses for

these patients were diabetic peripheral neuropathy (n = 18), peripheral vascular disease (n = 16), ulceration (n = 22), osteomyelitis (n = 12), and cellulitis (n = 2). These diagnoses were included in the computerized database that was used to identify the patient population. These diagnoses were either made on admission, or at discharge; the database did not distinguish between when the actual diagnosis was made. Patient characteristics are shown in Table 1.

Magnetic resonance imaging was performed on 19 left feet and 31 right feet. Fifty-seven individual bones were suspected of having OM; all of these bones were recovered, and examined pathologically for evidence of osteomyelitis. Some patients had more than 1 bone in their foot that potentially had osteomyelitis. The anatomic distribution of pedal bones studied is presented to Table 2. The forefoot was more often involved than the hindfoot, a finding that has previously been reported.[10]

Thirty-seven MRI studies were interpreted positive for OM. Seven studies were interpreted negative. Six studies were considered inconclusive, as the interpreting radiologist was not able to distinguish between reactive marrow edema or osteomyelitis. These were excluded from the analysis of determining the test performance. Thirty-seven bone biopsy specimens were positive for OM. Eleven studies were negative. Table 3 is a 2 x 2 contingency chart depicting the number of true positive, false positive, true negative, and false negative results.

Six patients were excluded from the statistical analysis. In each of these cases, the radiologist could not distinguish between marrow edema, representing inflammation caused by bone infection, versus "reactive" edema, that can occur when there is an adjacent focus of inflammatory soft tissue. Table 4 gives the specifics on these 6 patients.

Excluding the 6 patients who received inconclusive MRI examinations, statistical analysis was performed for the remaining cases. MRI of diabetic foot infections in this study had sensitivity of 86% and specificity of 29%, PPV of 86%, and NPV of 29% for the detection of osteomyelitis. The prevalence of OM in this group of patients was 74%.

**Table 1**

## PATIENT CHARACTERISTICS

| | |
|---|---|
| **Age** | 56.3 ± 14.2 years (range 28-86) |
| **Sex** | 39 men (78%)<br>11 women (12%) |
| **Foot distribution** | 19 Left<br>31 Right |
| **Prevalence of diabetes** | 100% |

**Table 2**

## ANATOMIC DISTRIBUTION OF BONES

| **BONE** | **NO. (%)** |
|---|---|
| hallux | 7 (12.3) |
| lesser toe | 20 (35) |
| 1st metatarsal | 5 (8.7) |
| lesser metatarsal | 15 (26.3) |
| sesamoid | 1 (1.8) |
| calcaneus | 7 (12.3) |
| other | 2 (3.5) |
| **Total** | **57** |

**Table 3**

## MRI RESULTS COMPARED WITH BIOPSY RESULTS FOR OM

| | | **PATHOLOGY** | |
|---|---|---|---|
| | | Positive | Negative |
| **MRI** | Positive | 32 | 5 |
| | Negative | 5 | 2 |

## DISCUSSION

The impact of diabetic foot infections, and the burden they represent to individual patients and the healthcare system, cannot be overemphasized. It is well known that foot problems are the number one reason for hospitalization of diabetic patients. When patients present with a diabetic foot infection, determining the extent or magnitude of the infection, including whether there is solely soft tissue involvement or bone involvement is one of the most important initial steps in management. This will determine if a surgical indication exists, which often calls for amputation, or otherwise debridement of large areas of tissue. Not only does it dictate surgery, but can also influence medical management, such as mode and duration of antibiotic therapy. Occasionally, the foot cannot be saved due to overwhelming infection; if the salvageable portion of the limb will not be functional, then the patient would be

**Table 4**

## EXCLUDED PATIENTS SECONDARY TO INCONCLUSIVE MRI

| PATIENT # AGE/SEX | BONE IN QUESTION | MRI FINDINGS | MRI DIAGNOSTIC IMPRESSION | PATHOLOGIC DIAGNOSIS | COMMENT |
|---|---|---|---|---|---|
| **1 46 male** | Right 4th proximal phalanx | Mild marrow edema in phalanx, diffuse subQ edema, fluid in flexor sheath | Reactive edema vs. OM | Positive OM | Initially, had a puncture wound, without clear evidence of OM. Had worsening symptoms 2 wks later. |
| **2 35 male** | Right calcaneus | Mild peripheral marrow edema, without assoc T1 hypointensity | Reactive edema, cannot rule out early OM | Negative OM | large posterolateral heel wound, clinically infected, neg PTB |
| **3 56 male** | Left calcaneus | Miniscule bone edema | Edema or OM of calcaneus | Negative OM | large infected posteroinferior heel wound, neg PTB |
| **4 56 male** | Right 1st distal phalanx | Mod diffuse edema, subtle T1 hypointensity | Reactive edema vs. OM | Negative OM | large ischemic wound on tip of hallux, (+) PTB, but no clinical signs of infxn |
| **5 50 male** | Right 3rd distal phalanx | Mild marrow edema on STIR, no T1 hypointensity | Reactive edema vs. OM | Positive OM (chronic) | chronic ulcer, clinically infected, (-) PTB |
| **6 56 male** | Right calcaneus | Minimal subcortical marrow edema & enhancement, mild cortical irregularity, overlying focal edema & ulceration | Possible minimal OM | Negative OM (acute inflammation of periosseous tissue) | Chronic heel ulcer |

better suited with more proximal amputation. Nevertheless, defining the presence and extent of OM in DM foot infections allows for limb preserving therapy.

This study attempted to evaluate the ability of MRI to diagnose pedal osteomyelitis in patients with diabetes and foot infection. Sensitivity and specificity was determined to be 86% and 29%, respectively. PPV and NPV was 86% and 29%, respectively. A recent meta-analysis by Kapoor et al[8] revealed that MRI performs well in the diagnosis of OM in the diabetic foot. In the group of studies they examined, they found rates of sensitivity to range from 77% to 100%, and rates of specificity from 40% to 100%. In their analysis, when MRI was compared with other modalities, it out performed all others for diagnosing OM. They concluded that MRI is the test of choice. However, they did note that few studies used histopathologic examination to confirm osteomyelitis.

The prevalence of OM in this group of diabetic patients presenting with a foot infection was 74%. In the meta-analysis by Kapoor et al,[8] the prevalence of osteomyelitis ranged from 31% to 88%, and averaged ~50%. Other studies that have compared MRI for diagnosing DM foot OM showed variable prevalence of disease. Craig et al[9] examined 13 diabetics with "high

clinical suspicion" for pedal OM. They found OM in 21 bones out of 57; the prevalence was 37%. Ertugrul et al[2] found histopathology-confirmed OM in 23 out of 31 patients (they did not give results of individual bones); the calculated prevalence is 74%. They only included patients who had greater than or equal to a Wagner grade 3 foot lesion.

Clearly, prevalence and the overall risk for OM affects the performance of MRI. A group of patients who are clearly at high risk for OM (i.e., presence of deep ulcer, positive "probe to bone" test result, etc.) will demonstrate higher test performance. Conversely, in a low risk population, where one expects low likelihood of finding OM, the test performance will not be as good. Our prevalence of OM in this group of DM foot infection may be explained by the patient population. Our hospital is known to care for a large group of underserved individuals, many of whom are diabetic with poor control, and with poor access to medical care. Most of our patients are actually admitted directly through the emergency room. Some of them present in frank sepsis or diabetic ketoacidosis. Therefore, the likelihood that they would have OM is high, and the ability of MRI to detect this is high as well. Clearly, prevalence greatly influences test performance.

Ertugrul et al[2] compared microbiologic culture, MRI, and labeled leukocyte scanning for diagnosing OM in 31 diabetic patients with significant (≥ Wagner grade 3) foot lesions. Histopathologic examination of surgically-recovered tissue served as their gold-standard. They determined MRI sensitivity and specificity rates of 78% and 60% respectively; PPV and NPV was 90% and 37.5%, respectively. They found comparable test performance results between microbiology, MRI, and radionuclide study.

Enderle et al[11] used high-resolution ultrasound to evaluate for chronic OM in 19 diabetic patients. Sensitivity and specificity of ultrasound for diagnosing OM was 79% and 80%, respectively. They determined ultrasound was superior to plain film radiography, comparable to bone scintigraphy, but inferior to MRI for detecting OM.

Craig et al[9] evaluated 57 bones in 13 patients with diabetes and clinical suspicion for foot OM with MRI, and correlated the findings with surgical pathology. They determined sensitivity and specificity rates of 90% and 72%, respectively. Their conclusion was that MRI was valuable for surgical planning in DM foot infection, but noted that marrow edema cannot be reliably distinguished from osteomyelitis. This often leads to false positive results. They did find that the more intense the marrow edema, the more likely this was osteomyelitis, and they suggested that in order to diagnose osteomyelitis, one must see increased signal changes, plus an adjacent soft tissue mass or ulcer.

The calculated sensitivity and PPV were both 86%. This is consistent with what has been reported in the literature. However, the specificity and NPV is lower than what has been reported. Specificity is the proportion of people without disease who have a negative test result. Mathematically, it is the number of true negatives divided by the sum of the number of true negatives plus false positives. This study had 5 false positives (Table 5). False positives are those with a positive MRI, but negative biopsy result. Given the formula for specificity, it is apparent that an increased number of false positives will decrease the specificity. Had all of these false positive cases been diagnosed correctly by MRI, the sensitivity would have been dramatically different, in fact, it would have been 100%. Examining each case in Table 5 demonstrates that each MRI had some, but perhaps not all diagnostic changes of OM.

Patient A essentially had all diagnostic criteria for OM, yet his biopsy showed focal, minimal nonspecific inflammation. On his T2-weighted images there was no evidence of cortical destruction (see Table 5). He was a poorly controlled diabetic with neuropathy, who presented with severe clinically infected foot.

Patient B, another poorly controlled diabetic, initially presented with infected, wet gangrene of his fourth toe, which was subsequently amputated, and left open to heal secondarily. A follow-up MRI demonstrated suggestive changes in the fifth toe. However, clinically the fifth toe did not track to the open wound, nor did it "probe to bone." After resection, no inflammatory changes or histologic abnormalities were noted.

Patient C was an older diabetic woman presenting with an infected heel ulceration. The MRI examination diagnosed "focal OM," also diffuse myositis and cellulitis. Specific findings of OM, such as increased signal on T2-weighted images or cortical destruction on T1-weighted images, were not given. The wound did probe to bone, however, despite all this, the pathology showed only fibrosis.

Patient D, a 51-year-old man, demonstrated findings for neuropathic osteoarthropathy across Lisfranc's joint, and on T2-weighted images demonstrated diffuse bone marrow enhancement involving bases of the metatarsals and corresponding tarsals. Histopathologic findings were consistent were Charcot arthropathy, but since some of these findings are also seen in chronic OM, the pathologist suggested giving consideration to that diagnosis as well. In reviewing available hospital records, it is unclear what the clinical evolution was for this patient.

Patient E actually presented with severe infection of her right foot and ankle, and had subcutaneous gas

**Table 5**

## CHARACTERISTICS OF THE FALSE POSITIVES (MRI POSITIVE FOR OM, PATHOLOGY NEGATIVE)

| PATIENT # AGE/SEX | BONE IN QUESTION | MRI FINDINGS | PATHOLOGIC FINDINGS | COMMENT |
|---|---|---|---|---|
| **A 50 M** | L 5th metatarsal head | T1: focal destruction distal end of L 5th met w/ assoc intraosseous edema and adjacent inflam ST changes. T2: Intraosseous edema w/o evidence of cortical destruction | bone fibrosis & mild chronic inflam. Marrow w/ serous material w/ scattered inlfam cells. No diagnostic changes of OM. | bone w/ focal minimal non specific inflammation |
| **B 48 M** | R 5th toe, proximal phalanx | TI: cortical indistinction & subjacent focal edema and enhancement of inferomedial aspect. T2: mild marrow edema w/in 3rd and 4th phalanges | No inflammatory changes. No histologic abnormality. | open wound @ 4th MTP joint did not connect or probe to 5th toe |
| **C 71 F** | R calcaneus | T1: focal OM affecting lateral calc Other: diffuse cellulites, myositis | Fibrosis of fibrous tissue | clinically infected heel ulcer, (+) PTB |
| **D 51 M** | Lesser tarsus (medial or intermediate cuneiform) | T1: fx-subluxation of TMT 2-5 jts T2: diffuse bone marrow enhancement involving bases of metatarsals and tarsals | medullary fibrosis and mild chronic inflammatory cell infiltrate incl lymphocytes and plasma cells | consistent with Charcot, but consider chronic OM |
| **E 61 F** | Left 1st metatarsal head | Evidence for OM affecting 1st metatarsal head, and base of proximal phalanx. Infected synovitis of joint space, and surrounding cellulitis. | chronic periosteal inflammation and chronic synovitis | none |

formation. She was taken emergently to surgery for below knee amputation. She also had a medial ulceration adjacent to the left first metatarsophalangeal joint, which warranted MRI of that location to rule out osteomyelitis. Pathologic examination of the resected first metatarsal head and corresponding proximal phalanx base showed chronic periosteal inflammation and chronic synovitis only, with normal bone. Again, no specific findings on the MRI report were given.

Craig et al[9] stressed the importance of using primary and secondary MRI signs of OM to make the correct diagnosis. They determined that marrow edema cannot be reliably distinguished from OM by MRI; 18 of 57 bones in their study demonstrated increased signal intensity by MRI, but only marrow edema at pathology. To diagnose correctly, an adjacent inflammatory soft tissue mass or ulceration needs to be present.

Examining the 6 cases that were excluded due to

inconclusive diagnosis reveals that in nearly all the instances, the interpreting radiologist could not distinguish between reactive edema versus osteomyelitis-associated marrow edema. Half the cases involved a phalanx, and half involved the calcaneus. To the authors' knowledge, it has never been established that these two anatomic areas are more difficult to interpret by MRI for osteomyelitis. The authors have noticed that particularly for clinically infected posterior heel ulcerations, even with a negative PTB test, MRI will still show increased signal within the calcaneus. On numerous occasions, the authors felt compelled to procede with diagnostic biopsy to rule out osteomylelitis. It should be noted that in the 3 excluded cases where the calcaneus was in question, the bone biopsy was negative. Further investigation focusing on calcaneal osteomyelitis in the setting of heel ulceration may be warranted.

Some of the weaknesses inherent to this study were that all of the surgeries were not peformed by the same individual. Also, clinical information, regarding ulcer size, depth or stage, results of probe to bone testing were not gathered. This could also provide valuable clinical information. Information regarding laboratory values could also have been valuable, such as white blood cell (WBC) count, erythrocyte sedimentation rate (ESR), and C-reactive protein (CRP).

This study was undertaken to compare the results of MRI in the diagnosis of OM in infected diabetic feet with surgical pathology as the gold standard. Specificity was good to excellent, comparable with previous work, however specificity was somewhat less than what has been reported. It is felt that an increased number of false positive results may have contributed to this. In these instances, not all the primary and secondary MRI signs of osteomyelitis were used to define OM. We feel this is important to arrive at the most accurate diagnosis as possible. This has important limb-sparing repercussions. In the end, MRI is simply a tool used by the surgeon to arrive at a final diagnosis. Even with an advanced imaging modality like MRI, clinical exam findings, like probe to bone test results, and laboratory results should be used to arrive at a final diagnostic impression. Occasionally, biopsy is still required for accurate diagnosis. At our institution, compared to the gold standard histopathology, MRI had good senstitivity and PPV, whereas the specificity and NPV may have been adversely affected by false positive MRI interpretations, where not all MRI diagnostic criteria were used.

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