Probe-to-bone testing for osteomyelitis in the diabetic foot: a literature review

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Article points

1. When making a clinical diagnosis of osteomyelitis in diabetes patients with foot ulcers and infection, the probe-to-bone test provides additional diagnostic information.
2. The probe-to-bone test should be performed with a blunt metal probe.
3. Interpreting the results requires the pre-test probability of osteomyelitis to be assessed.

Key words

- Diabetic foot infection
- Diagnostic tests
- Osteomyelitis

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The use of probe-to-bone testing in the diabetic foot is well recognised as a strongly predictive tool in the diagnosis of osteomyelitis when performed correctly. However, the benefit of the probe-to-bone is substantially influenced by the pre-test probability of the patient having, or not having, osteomyelitis. We reviewed the literature for papers describing the probe-to-bone test. From the six papers identified, we found the prevalence of osteomyelitis ranged from 22% in the outpatient setting to 55% for outpatient infected ulcers to 70% for hospitalised patients with more severe infections. The probe-to-bone test using a sterile metal probe provides valuable information where the likelihood of osteomyelitis is low after a negative test in the outpatient or low-risk setting. The likelihood is high after a positive test in a high-risk or inpatient setting.

During the management of diabetes-related foot ulcers, approximately 58–61% of patients will develop foot infection before the ulcers heal or reach remission (Lavery et al, 2007; Prompers et al, 2007; Armstrong and Mills, 2013). Clinical practice guidelines have been validated to support the staging and treatment of infection based on clinical criteria (Lavery et al, 2007a). When it comes to using clinical criteria to diagnose deeper infections such as osteomyelitis, however, clinician accuracy becomes no better than a coin flip. Several studies suggest that clinician accuracy for diagnosing osteomyelitis ranges from 0% to 54% (Newman and Fitton, 1983; Newman et al, 1991; Vesco et al, 1999). The probe-to-bone test is a clinical manoeuvre used to improve clinician accuracy in the diagnosis of osteomyelitis. The purpose of this paper is to review clinical studies describing the probe-to-bone test and clarify the information provided in outpatient and inpatient settings, where the prevalence of osteomyelitis and severity of infection vary.

Methods

PubMed was searched using the clinical trials filter for key words including: 'probe to bone'; 'probe'; 'diabetes foot ulcer'; and 'osteomyelitis'. The search for 'probe to bone' using the clinical trials and human studies filters yielded 173 papers that were available for review by both authors for potential inclusion. Other review papers were available to assist in searching for papers that may have been missed when using this search strategy. Inclusion criteria included human clinical studies that described the use of a metal probe for the probe-to-bone test and a standard method for diagnosing osteomyelitis in diabetic foot ulcers. Other inclusion criteria required test characteristics including prevalence, sensitivity, specificity, positive predictive value, negative predictive value, positive and negative likelihood ratios. The application of these criteria, including a recent review paper, yielded six papers for discussion: Grayson et al, 1995; Shone et al, 2006; Lavery et al, 2007b; Morales Lozano et al, 2010; Aragón-Sánchez et al, 2011; Mutluoglu et al, 2012; and Lipsky et al, 2016. For summary statistics, a weighted mean approach (Wrobel and Connolly, 1998) was used to determine prevalence, sensitivity, specificity, positive and negative predictive values and positive and negative likelihood ratios.

Results

Inpatient studies

In the first paper that described the probe-to-bone test, patients with infected foot ulcers were examined in the inpatient ward and their ulcers were probed

Table 1. Descriptive characteristics of studies describing the probe-to-bone test.

Study (year)	N	Sens (%)	Spec (%)	PPV (%)	NPV (%)	LR(+)	LR(–)	Prev (%)	Method of diagnosis
Outpatient									
Shone et al (2006)	81	38	91	53	85	4.22	0.68	23.5	Clinical
Lavery et al (2007)	247∫ / 217†	87	91	57	98	9.4∫ / 6.5†	6.81∫ / 6.5†	20	Microbiology
Infected outpatient									
Morales Lozano et al (2010)	132	98	78	95	91	4.5	0.02	79.5	Clinical and microbiology
Inpatient									
Grayson et al (1995)	75	66	85	89	56	4.4	0.15	66	Histology
Mutluoglu et al (2012)	65	66	84	87	62	4.13	0.24	60	Imaging and clinical
Aragón-Sánchez et al (2011)	338	95	93	97	83	14.34	0.06	72.4	Histology and microbiology

Key: N – number of participants/ulcers; Sens – sensitivity; Spec – specificity; PPV – positive predictive value; NPV – negative predictive value; LR(+) – positive likelihood ratio; LR(–) – negative likelihood value; Prev – prevalence; ∫ – total; † – infected

with a sterile, blunt stainless steel probe (Grayson et al, 1995). The diagnosis of osteomyelitis was made histologically and/or using clinical criteria. Grayson evaluated 75 hospitalised patients and determined that probe-to-bone had a sensitivity value of 66%, a specificity value of 85%, a positive predictive value 89%, and a negative predictive value of 56%. The stated prevalence of osteomyelitis in the 75 hospitalised patients was 66% using histology as confirmation or rejection of osteomyelitis.

Aragón-Sánchez and colleagues (2011) published the second study to exclusively describe the probe-to-bone test in an inpatient setting. This group studied 356 episodes of foot infection in 338 inpatients. The probe-to-bone test was performed in addition to plain X-rays. Patients with a positive test went on to surgery for histopathology and microbiology examination of specimens. Of the 91 patients with negative test results for both probing to bone and plain X-rays, 71 went on to have additional surgery and the other 20 were treated for cellulitis. Of these 91, six patients eventually demonstrated bone involvement or osteomyelitis ranging from 2 to 6 months later. Thus, of the 356 episodes included in the study, there was a false negative rate of 1.7%. The probe-to-bone test (*Table 1*) demonstrated a sensitivity of 95%, specificity of 93%, positive predictive value of 97%, negative predictive value of 83%, positive likelihood ratio of 14.34, and negative likelihood ratio of 0.06. The underlying prevalence of histologically-positive cases was 72.4% (Aragón-Sánchez et al, 2011).

Studies of actively infected ulcers

Two studies examined the diagnostic properties of the probe-to-bone test in actively infected ulcers: one in an outpatient setting (Morales Lozano et al, 2010) and the other in the combined outpatient and inpatient settings (Mutluoglu et al, 2012).

Morales Lozano and colleagues studied 210 foot ulcers, of which 132 were clinically suspicious for infection according to the International Working Group of the Diabetic Foot's definition of infection (Apelqvist et al, 2000). The 132 patients were further studied for the presumptive diagnosis of osteomyelitis using culture, plain X-ray, and probe-to-bone test. All of the patients underwent bone biopsy with histopathological examination for osteomyelitis. Of these, 79.5% of patients were confirmed as having osteomyelitis (Morales Lozano et al, 2010). The results of the probe-to-bone test are given in *Table 1*. A sensitivity of 98% and specificity of 78% was found in this study.

Mutluoglu et al (2012) studied 65 patients with infected foot ulcers and suspicion of osteomyelitis in both inpatient (n=49) and outpatient settings (n=16). Osteomyelitis was determined through a

Box 1. The criteria for clinical suspicion of osteomyelitis.

- An ulcer that has not shown a tendency towards healing for at least 4 weeks
- An exposed or visible bone at the base of the ulcer
- An ulcer in the forefoot overlying a bony prominence
- A swollen erythematous toe, namely the sausage deformity, associated with plantar ulceration.

clinical diagnosis of foot infection together with at least one criterion pointing towards clinical suspicion of osteomyelitis. The criteria for clinical suspicion of osteomyelitis are given in *Box 1*. The prevalence of osteomyelitis in this population was 60%. The probe-to-bone test demonstrated a sensitivity of 66%, specificity of 84%, positive predictive value of 87%, and negative predictive value of 62% (see *Table 1*).

Outpatient setting

The prevalence of osteomyelitis was studied in the outpatient setting by Shone and colleagues (2006), who followed 81 people with diabetes with 104 foot ulcers. The ulcers were probed by two podiatrists and the diagnosis of osteomyelitis was made based on clinical signs of infection along with destructive radiographic changes or characteristic changes on magnetic resonance imaging, or based on histopathology and microbiology analysis. Shone et al diagnosed 23.5% of patients (20.2% of ulcers) as being osteomyelitic during the follow-up period. The probe-to-bone test demonstrated a sensitivity of 38%, specificity of 91%, positive predictive value of 53%, and negative predictive value of 85% (see *Table 1*).

Lavery et al (2007b) also studied the prevalence of osteomyelitis in the outpatient setting using the probe-to-bone test. In a 2-year longitudinal cohort study of 1,666 diabetes patients, they identified 247 patients with a foot ulcer, with 151 patients developing 199 infections diagnosed using clinical criteria. Patients underwent bone biopsy, including histopathology and microbiology analysis, if there was clinical suspicion of osteomyelitis based on the probe-to-bone test and serial radiographs. Using this protocol, the underlying prevalence of osteomyelitis was 12% for foot ulcer patients and 20% for those with infection. The probe-to-bone test demonstrated a sensitivity of 87%, specificity of 91%, positive predictive value of 57%, and a negative predictive value of 98% (*Table 1*).

A weighted average of the above studies suggests an outpatient prevalence of osteomyelitis of 22%, with the probe-to-bone test giving a positive predictive value of 56%.

Discussion

Prevalence

As borne out in this review, the pre-test probability or prevalence of osteomyelitis is an important determinant of the information provided by a probe-to-bone test. *Table 1* gives the weighted average for the prevalence of the studies discussed across the continuum of care. As one moves along the clinical spectrum from outpatient foot ulcers with a low suspicion of osteomyelitis to hospitalised patients with severe infection, the prevalence increases from 22% in the outpatient setting (Lavery et al, 2007b) to 55% for outpatient infected ulcers (Morales Lozano et al, 2010) to 74% for hospitalised patients with more severe infections (Aragón-Sánchez et al, 2011).

Depth of infection versus the importance of diagnosis

Osteomyelitis represents a deeper and more severe diabetic foot-related infection associated with a higher risk of amputation (Schwegler et al, 2008), especially in the presence of peripheral arterial disease (Lavery et al, 2007a; Prompers et al, 2007). Making the diagnosis early can help preserve more of the foot if surgery is required, or result in a better outcome for the medical management of osteomyelitis.

Deeper foot infections involve more virulent organisms, as determined by culture (Sotto et al, 2007), and demonstrate improved outcomes with a longer duration of antibiotic treatment, regardless of bone involvement (Erdman et al, 2012). For example, Erdman and colleagues followed 77 patients with diabetic foot infections with suspected osteomyelitis for 3 months. They were evaluating the diagnostic characteristics of Tc-99m white blood cell (WBC)-labelled single photon emission computed tomography hybrid imaging for making the diagnosis of osteomyelitis. They created a composite scoring system based on the intensity of WBC uptake around blood vessels and the stage of bone destruction based on computed tomographic criteria based on the number of lesions and intensity of bone involvement. For intermediate composite scores, the prognosis was two-fold better with antibiotic therapy over 42 days regardless of bone involvement (Erdman et al, 2012). The prospective University of Texas San Antonio Foot Ulcer Classification System validation study found that deeper ulcerations were associated with higher rates of hospitalisation and amputation (Lavery et al, 2008). Taking the findings of Erdman and colleagues and Lavery et al together, it appears that in the absence of frank destruction of bone and joint, the duration of antibiotic therapy based on the depth of infection may be more important than making the diagnosis in

cases where diagnosis is not readily apparent using clinical criteria.

Clinical prediction rule

Several studies have examined clinical predictors of osteomyelitis other than the probe-to-bone test. Clinical signs associated with osteomyelitis include:

- Peri-wound inflammation and ulcer size >2 cm^2 (Newman and Fitton, 1983; Newman et al, 1991)
- A history of ulceration and the presence of multiple wounds (Lavery et al, 2009)
- Increased ulcer depth (Fleischer et al, 2009; Lavery et al, 2009).

Readily available laboratory tests can also assist in the diagnosis. In a case-control study of hospitalised patients with foot ulcers, an erythrocyte sedimentation rate (ESR) of >60 mm/h and C-reactive protein level of >3.2 mg/dl were associated with osteomyelitis in a multivariate model (Fleischer et al, 2009). Michail and colleagues studied serum markers in 61 patients with infected foot ulcers, 27 of which were osteomyelitic. All patients had ESR, C-reactive protein, WBC, and procalcitonin levels measured at baseline, 1 week, 3 weeks and 3 months after the start of treatment. The sensitivity and specificity levels for the osteomyelitis group are given in *Table 2*. All values had returned to almost normal by day 7, while the ESR remained elevated until the 3-month measurement in the osteomyelitis group (Michail et al, 2013).

Table 2. Serum marker levels of patients with osteomyelitis before treatment (Michail et al, 2013).

Marker	Level	Sens (%)	Spec (%)
C-reactive protein	>14 mg/L	85	83
Erythrocyte sedimentation rate	>67 mm/h	84	75
White blood cell count	>14 × 10^9/L	75	79
Procalcitonin	>0.3 ng/mL	81	71

Key: Sens – sensitivity; Spec – specificity

Study limitations

There are limitations to this review. Many of the studies rely on bone biopsy as the standard criterion for making a diagnosis of osteomyelitis. Some authors have called into question the validity of this criterion due to: diminished concordance with the pathological examination of slides (Meyr et al, 2011) or with histopathology and microbiology (Senneville et al, 2009); sampling errors in performing the procedure; and referral bias for performing the procedure, where not all patients with wounds have the procedure due to ethical considerations.

Conclusion

This literature review provides candidate variables for a prospective study testing the validity of a clinical prediction rule for osteomyelitis in diabetic foot-related infections. Rules for clinical prediction can help improve clinician accuracy and are useful in locations where advanced imaging is not readily available. The probe-to-bone test using a sterile metal probe provides valuable information where the likelihood of osteomyelitis is low after a negative test in the outpatient or in the low-risk setting. The likelihood is high after a positive test in a high-risk or inpatient setting. The authors propose that the depth of diabetic foot infection should be added to the Infectious Diseases Society of America clinical guidelines, as retrospective evidence suggests longer duration of antibiotic therapy for deeper infections is associated with better outcomes regardless of the presence of osteomyelitis. Future work should prospectively elucidate this working hypothesis for deeper wounds not requiring incision and drainage of abscesses or resection of necrotic bone. ■

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