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Infected Diabetic Foot Disease; Diagnostic Pathways and Current Imaging Recommendations.

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ABSTRACT:

The diabetic foot disease is a major public health problem and is expected to increase specifically in developing countries, Diabetic foot disease includes neuropathy, ulceration and infection. Infection is the most serious and is behind most amputations when involving bone. The diagnosis of diabetic foot osteomyelitis and differentiating it from soft tissue infection and neuro-arthropathy is difficult. After initial clinical, laboratory tests (ESR, CRP and CBC). basic standard X ray, possible CT and probe to bone test (when ulcer is present and appears deep), advanced imaging may be needed in many cases. when initial work up is not conclusive. and for better assessment of the location, and evaluation of the severity of infection. Advanced imaging includes MRI, labeled WBC with SPECT/CT with or without bone marrow scan and or F-18 FDG PET/CT and potentially integrated F-18 FDG-MR. MRI is the first modality of choice and scintigraphic studies follow if the MRI is not conclusive or contraindicated. FDG PET/CT has specificity comparable to, and in certain situations superior to MRI for diagnosing diabetic foot osteomyelitis, whereas WBC SPECT/CT retains the highest specificity and serves as the reference standard. Proper bone biopsy or deep tissue culture may be thought of as a definitive diagnosis in some cases.

Key words: Diabetic foot, Osteomyelitis, Imaging, Infection, Scintigraphy.

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INTRODUCION:

The diabetic foot disease is a major public health problem and is expected to increase specifically in developing countries, where prevalence of type 2 diabetes is projected to show the greatest rise. Diabetic foot disease includes neuropathy, ulceration and infection. Life time risk of foot disease is up to 25 % of 300 million diabetics worldwide [1,2,3].

Neuro-Arthropathy:

Diabetes is complicated by neuro-arthropathy, which involves progressive destruction of the bones, joints, and soft tissues, most commonly in the ankle and foot and has a reported prevalence in up to 13% of cases [4]. In neuro-arthropathy a combination of neuropathy, abnormal loading of foot, repeated micro trauma, and metabolic abnormalities of bone leads to inflammation, causing osteolysis, fractures, dislocation, and deformities [5]. Neuro-arthropathy is of two variants**;** hypertrophic neuro-arthropathy (Charcot Arthropathy), which involves mid and hind foot and is a consequence of neuropathy involving sensory fibers and atrophic neuro-arthropathy which involves the fore foot and is characterized by involvement of sensory and motor fibers.

Foot ulceration

Loss of sensation caused by peripheral neuropathy, ischemia due to peripheral arterial disease, or a combination of these may lead to foot ulcers. Additionally, abnormal pressure distribution due to deformities from arthropathy is also contributing. A systematic review (78 studies) reports a prevalence of 0.003-2.8% for diabetes related peripheral neuropathy and 0.01-0.4% for diabetes related peripheral arterial disease [6]. Diabetic foot ulceration occurs most frequent in plantar surface.

Infection

Foot infections are serious problem in patients with diabetes. Typically, diabetic foot infections start in a wound, most often a neuropathic ulceration. Foot infections occur in approximately 40% of diabetic foot ulcers [7] and more than 90% of cases of infections occur secondary to adjacent infected ulcers [8]. These infections are classified into mild (superficial with limited size and depth), moderate (deeper or more extensive), or severe (with systemic signs or metabolic changes). This classification helps determine which patients should be hospitalized, which may require special imaging procedures or surgical interventions including possible

amputation. Aerobic gram-positive cocci and especially staphylococci, are the most common causative organisms. Aerobic gram-negative bacilli may frequently co-exist in infections that are chronic or follow antibiotic treatment. Ulcers without evidence of soft tissue or bone infection do not require antibiotic therapy [9-10]. Diabetes related skeletal infection is a serious complication of diabetic foot as it increases the risk of treatment failure and lower extremity amputation. It contributes to 60% of amputations in diabetics [11]. Most patients who develop skeletal infections have long history of diabetes mellitus with a combination of changes predisposing to infection. These include angiopathy, ischemia, peripheral neuropathy, skin ulceration and immunopathy. Evidence of infection is present in more than 50% of diabetic foot ulcer cases. Furthermore, soft tissue infection may involve underlying osteo-articular structures in 20–60% of the cases according to the infection severity 20% in mild and moderate and in 50% to 60% of severe cases [12,13,14].

Diabetic Foot Osteomyelitis

Osteomyelitis of the foot, is the most serious complication in diabetic patients. It develops primarily by spread of contiguous soft-tissue infection to underlying bone. Certain clinical signs suggest osteomyelitis, but imaging is usually needed [12]. The condition is difficult to diagnose as the dilemma is to distinguish bone infection from noninfectious neuropathic osteo-articular lesions as well as soft tissue infection without bone involvement. Furthermore, it is difficult to treat and is associated with increased risk of relapsing infection, hospitalization episodes, and foot amputations [11].

Diagnostic strategy includes clinical examination with though history, laboratory tests specifically CBC, C-reactive protein (CRP), and erythrocyte sedimentation rate (ESR), or pro-calcitonin, X-ray (CT in some cases when target foot area is anatomically complex) and probe to bone test (if applicable). If osteomyelitis is suspected after this initial diagnostic assessment, bone biopsy and deep tissue culture (not superficial swab culture) and/ or special diagnostic imaging are required [15,16].

Clinical Diagnosis

Osteomyelitis is present in 44- 68% of patients with diabetic foot disease admitted to the hospital [17]. Clinical presentation varies and can be clinically silent in 35%-68% of cases [18-19] and is more difficult to diagnose in patients with no foot ulcers. Probe to bone test has an average sensitivity of 87-98 % and specificity 78-84% [16, 20, 21]. Although the size of foot ulcers is not reliable [21], osteomyelitis is suspected when are large (more than 2 cm) or deep (more than 3 mm), overlay a bony prominence, chronic and do not heal after appropriate care and when bone is visible or palpable on probing. The clinical dilemmas,

diagnose infection early to avoid amputation and ensure the most appropriate course of treatment.

Exposure of bone strongly correlates with presence of osteomyelitis in diabetics with infected ulcers and advanced specialized imaging may not be needed. In a study by Newman, 100 percent of infected ulcers exposing bone showed evidence of osteomyelitis while it was found in 68% when bone is not exposed [18]

Laboratory tests are generally not specific including WBC, C- reactive protein, and ESR. Although ESR of more than 70mm/h increases the likelihood of the condition and normal ESR lessens the likelihood of osteomyelitis but does not exclude it. More than one-half of the patients admitted with acute diabetic foot infection had a normal leukocyte count, and 83.7% had a normal neutrophil count Absence of leukocytosis, an absence of a left shift in a white blood cell differential, or lack of elevation of acute phase reactants does not exclude infection [22].

Diagnostic Imaging

Clinical diagnosis of osteomyelitis of diabetic foot is not possible in most patients and specialized imaging is needed is many cases. When diagnosis of osteomyelitis remains in doubt after initial assessment and tests including standard X ray and possibly CT, specialized imaging starts with MRI [15, 23]. Standard X ray has a poor sensitivity (28%-66%) but is useful as the initial screening examination, evaluates anatomic detail and previous surgeries as well as to evaluate other causes of pain such as fracture, arthropathy, or tumor [23]. Ultrasonography is a poor modality to visualize bone. CT has a limited role, difficult to differentiate soft tissue and bone infections and is limited by beam hardening artifact. MRI is the best morphologic modality as it is superior to differentiate soft tissue from bone infections and has the advantage of no ionizing radiation exposure. The reported sensitivity of MRI is 93 % and specificity of 84% [16,24,25]. It is the initial study of choice due to its high sensitivity [26. 27]. When MRI is not available, contraindicated or inconclusive, functional Modalities are very useful particularly in combined approach. Bone scan alone is not useful unless it is unequivocally negative excluding pathology. Gallium 67 has post specificity and is not a useful modality for detecting diabetic foot osteomyelitis. Labeled WBC whether In-111-WBC or Tc-99m HMPAO-WBC, is the most specific modality however it has poor spatial resolution making difficult for exact localization of infection. In addition, false positive results are seen due to reactivated bone marrow foci and also in some forms of neuro-arthropathy particularly in rapidly progressive variant. The sensitivity and specificity of this technique are 92% and 91 % respectively [24, 28]. Combined Bone/ Labeled WBC will show better location and adding bone marrow study when labeled WBC is positive helps differentiate infection from reactivated bone marrow and improves further the specificity [29]. Using SPECT/CT with the latter combined approach represent.

the best technique for detecting the condition [30]. Combined labeled WBC/bone marrow scan using SPECT/CT without bone scan is popular and provides accurate results although my experience adding the bone scan is preferred since it provides additional information given its extreme sensitivity in detecting any bone pathology with a sensitivity of 92% and specificity of 97%. WBC SPECT/CT shows evidence for evaluating remission or response (31,32). A recent meta-analysis study (26), shows accuracy of FDG PET comparable to MRI and Labeled leucocyte studies with a sensitivity of 89% and specificity of 92%. FDG PET/CT is particularity useful in case of suspicion of multifocal disease for rapid screening [26]. However, more studies and experience are needed since results including earlier meta-analysis study are variable and some recent studies underscored the technique in adequate detection of the condition [24,28, 33, 34]. Integrated FDG-PET/MRI offers enhanced anatomical resolution alongside metabolic characterization. Preliminary evidence indicates a strong diagnostic performance for recurrent or complex diabetic foot osteomyelitis with high accuracy, although this is based on small-scale studies (4). Table 1 summarizes the reported accuracy of the advanced imaging modalities for diagnosing diabetic foot osteomyelitis. **Table 1**. Accuracy of advanced imaging techniques for suspected infected diabetic foot (16, 24, 5, 30, 35).

Table 1: Modality of detection of infected diabetic foot disease.

Modality	Sensitivity (%)	Specificity (%)	Remark
MRI	93	84	First modality of choice
Combined Bone/ Labeled WBC SPECT/CT, BM	92	97	Current most accurate modality
FDG PET/CT	89	92	
Integrated FDG PET/MR	99	100	Based on small number of cases. Excellent potential

New experimental tracers include Ga-68-citrate, F-18 FDS, and others may have potential for clinical use (35,36). Small studies indicate that FDG-labeled autologous leukocytes may be more specific than non-cell-labeled FDG PET/CT; however, these findings remain experimental due to constraints in availability and validation [37,38]. **Figure 1** summarizes the imaging recommendation for adequate diagnosis of diabetic foot osteomyelitis.

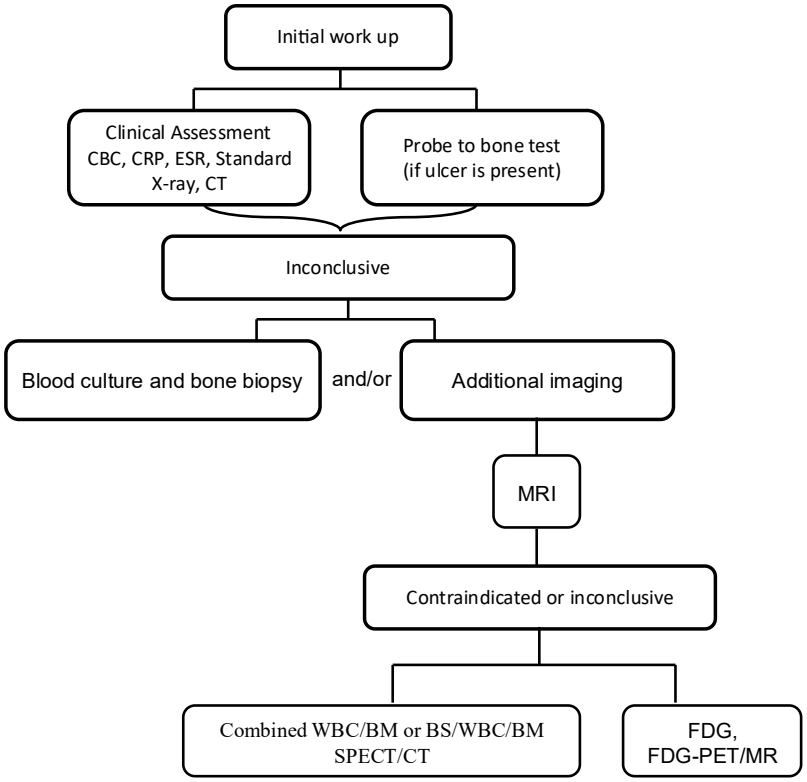

Figure 1: A diagram summarizing diagnostic pathways for infected diabetic foot disease

CONCLUSIONS:

The diagnosis of diabetic foot osteomyelitis is a dilemma, Proper clinical history and examination is a must along with relevant laboratory tests particularly ESR, CRP and CBC. Initial assessment with basic standard X ray and possibly CT scan can provide diagnosis. Probe to bone test when ulcer is present and appears deep if positive along with positive X-ray and elevated ESR prompt treatment given the high incidence of osteomyelitis when ulcer is exposing bone with no need for further imaging. When initial work up is not conclusive or confirmation, better assessment of the location, and evaluation of the severity for tailoring treatment, advanced imaging is needed. This includes MRI, labeled WBC with SPECT/CT with or without bone marrow scan and or F-18 FDG PET/CT. RI is the first modality of choice and scintigraphic studies follow if the MRI is not conclusive or contraindicated. WBC SPECT/CT is more reliable than FDG PET/CT particularly in differentiating Charcot neuro-arthropathy from superimposed osteomyelitis. Proper bone biopsy or deep tissue culture may be thought for definitive diagnosis in some cases.

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