Radionuclide diagnosis of diabetic foot osteomyelitis:

- bone scan
- labeled leucocyte scan

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Foot complications:
• pedal ulcers
• cellulitis / soft tissue infections
• osteomyelitis
• gangrene
• neuropathic osteoarthropathy

-most common causes of hospitalization in diabetic patients

-most common cause of nontraumatic lower extremity amputation

By 2030, 550 million people will have diabetes ≈ 10% of the world’s adult population

International Diabetes Federation (IWGDF), 2011
Up to 25% of the diabetic population is at risk for developing a pedal ulcer - the most common risk factor for subsequent amputation.

More than half of all foot ulcers will become infected requiring hospitalization.

3%-25% of them will require an amputation.

Pedal ulcers are portals of entry of infection and directly overlie more than 90% of cases of pedal OM.
FACTS ON DIABETES AND THE FOOT

- Throughout the world, up to 70% of leg amputations occur among people with DM.
- The rate of amputation for people with DM is 10 times higher than for people without DM.
- After an amputation, the chance of another amputation within 3–5 yrs is as high as 50%.

“It’s estimated that up to 85% of all amputations due to diabetes can be prevented.”

*The Lancet (cover), Nov 2005*
Osteomyelitis in the diabetic foot is associated with increased risk of amputation.

Early **diagnosis of osteomyelitis (OM) in the diabetic foot** reduces the need for amputation but detection is difficult:

**Coexisting disorders** may obscure the clinical signs of OM:

- ulcer/soft tissue infection
- Charcot arthropathy
- amputation

*Imaging is an essential part of the evaluation*
Radionuclide imaging modalities for the diagnosis of OM

- Bone scan with $^{99m}$Tc-diphosphonates
- Labeled leucocyte scan (*in vitro* labeled leucocytes with $^{111}$In-oxine or $^{99m}$Tc-HMPAO)
- *in vivo* methods of labeling leucocytes with antigranulocyte antibodies / antibody fragments
- PET - PET/CT: $^{18}$F- FDG / or in vitro labeled WBC with $^{18}$F- FDG
- $^{67}$Ga citrate scintigraphy
- $^{99m}$Tc- nanocolloid scintigraphy
- Immunoscintigraphy ($^{99m}$Tc ñ $^{111}$In HIG)
- Radiolabeled antibiotics

*Hybridic Imaging: PET/CT, SPECT/CT*
Advantages of radionuclide imaging

- Early lesion detection of functional changes earlier than structural changes

Indications:
- Infection/inflammation localization
  - Soft tissue vs bone involvement
  - OM vs Charcot
- Assessment of disease activity
  - Active vs treated OM
- Response to treatment evaluation

Absence of nephrotoxicity (vs contrast agents/gadolinium)
  Indicated in low GFR patients
Three phase Bone scan

- with $^{99m}\text{Tc}$ – diphosphonates (740 MBq $^{99m}\text{Tc}$-MDP or HDP)
- images: flow phase (1-5 sec frames for 1 min after injection), blood pool phase (static images within 5 min after the flow phase) & delayed phase (images 3 hrs p.i)

focal hyperperfusion + focal hyperemia + increased bone uptake on delayed images

compatible with OM

Positive within 24-48 h after the onset of symptoms
Sensitivity > 90% - specificity < 50%

False positive results in the diabetic foot
(stress fractures, uninfected Charcot joints, cured OM...)

Addition of 4th phase (24 h p.i) – not improve the specificity

Capriotti G, Chianelli M, Signore A. Nucl Med Commun 2006
meta analysis, 719 sites of diabetic foot OM
sensitivity 90,3% - specificity 46,4%

accuracy 65%
"It is time to reevaluate the role of the bone scan in diabetic foot infections. The value of the conventional bone scan, either as a screening test or as anatomical reference, is questionable, and its use in most cases probably is not warranted"
Bone scan alone is of limited value for diagnosing osteomyelitis in the diabetic foot

**Useful**
- **as a complementary study in patients with pedal ulcers** (for better anatomical localization of leucocyte scan findings)
- diagnosis of OM of bones not previously affected by other pathologic conditions (*unusual in the diabetic foot!*)

**Not useful**
- for diagnosis of OM superimposed on Charcot joints
- for monitoring response to treatment
Scintigrapy with in vitro labeled leucocytes

“Gold standard” nuclear medicine method for infection and inflammation imaging

- withdrawal of 30-50 ml blood
- separation of leucocytes
- labelling of leucocytes in vitro with $^{111}$In-oxine or $^{99m}$Tc-HMPAO (hexa methyl propylene amine oxime)
- reinjection of the radiolabeled leucocytes into the same patient
- imaging (4 - 24 h p.i)
Advantages of $^{99m}$Tc leucocyte labelling over $^{111}$In labelling

- improved spatial resolution - better anatomical localization
- lower radiation absorbed dose to the patient (EDE: 3.4 vs 11mSv)
- ability to complete the study in a single day (4h vs 24h imaging)
- availability, lower cost

After i.v. administration labelled leucocytes migrate actively (chemotaxis) into the inflammatory focus
Musculoskeletal infections

Labelled leucocytes do not accumulate at sites of increased osteoblastic activity in the absence of infection

Useful for **diagnosis** and **follow-up of osteomyelitis** in patients with pre-existing bone pathologies - fractures, prior surgery, joint prostheses, diabetic foot

Highly sensitive and specific (>85%) for diagnosing OM in the diabetic foot

*meta analysis*, **951 sites** with diabetic foot OM

<table>
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<th>Lesions</th>
<th>Sensitivity</th>
<th>Specificity</th>
<th>Lesions</th>
<th>Accuracy</th>
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<td>719</td>
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<td>$^{111}$In-WBC</td>
<td>463</td>
<td>86</td>
<td>428</td>
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<td>205</td>
<td>80.7</td>
<td>147</td>
<td>84.6</td>
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*Capriotti G. Nucl Med Commun 2006*
Diagnostic accuracy of commonly performed radionuclide methods for diabetic foot osteomyelitis: a retrospective study in 115 pedal sites

S. Georga, C. Manes et al. DFSG 2010, Uppsala, Sweden

<table>
<thead>
<tr>
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<th>LS</th>
<th>LS + BS</th>
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<tbody>
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<td>Sens</td>
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<td>90%</td>
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<tr>
<td>Spe</td>
<td>96.5%</td>
<td>97.8%</td>
</tr>
<tr>
<td>Acc</td>
<td>95.5%</td>
<td>94.7%</td>
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</table>

Diagnostic accuracy of LS is not affected by whether or not the patients have bone scan.
Interpretation criteria of labeled WBC-scan

**WBC-scan positive for OM**

- **focally increased leucocyte uptake at the site of suspected bone infection** (greater than surrounding soft tissue uptake or of the same intensity on both dorsal and plantar views)
- **spatially congruent bone/leucocyte scan findings** (when WBC scan is interpreted together with bone scan)

- amputation of the 5th R toe
- pedal ulcer 4th R toe

**OM of the 4th right toe**
WBC-scan negative for osteomyelitis

- no leucocyte accumulation at the site of suspected infection
- activity on leucocyte images without corresponding activity on bone images (soft tissue infection - incongruent images with bone scan)

- mild diffuse or no leucocyte accumulation at site of Charcot arthropathy
OM of the 4th right toe

- 55-yr-old woman with NIDDM
- plantar ulcer overlying the 4th right metatarsus

*Congruent BS / HMPAO-LS uptake at the base of 4th right toe, consistent with OM*

- Radiographic evidence of OM in repeated radiographs

**99mTc-MDP**
- Bone scan
  - Dynamic phase
  - Blood pool phase
  - Delayed images

**99mTc-HMPAO-LS**
Infected right foot plantar ulcer without OM

- 66-yr-old woman with NIDDM
- bilateral Charcot joints
- deep right midfoot plantar ulcer

Focal intense leucocyte uptake limited to the ulcer, incongruent with BS uptake
Diagnosis of OM superimposed on Charcot arthropathy

Detection of osteomyelitis (OM) superimposed on a neuropathic joint is a very difficult task.

Clinical presentation of acute Charcot arthropathy:
- warmth
- redness
- swelling
- pedal ulcer in 50%

In the presence of Charcot joint, radiographic identification of OM is also very difficult.
Diagnosis of OM superimposed on Charcot arthropathy

**MRI:** Principal MRI findings in OM are due to marrow edema

Bone marrow edema present in acute Charcot process limits the specificity of MRI for diagnosing superimposed OM

Bone scan

*Always abnormal regardless the presence or absence of infection*
WBC-scan: diagnosis of OM on Charcot joint or OM vs Acute Charcot arthropathy

The majority of cases of uninfected Charcot joints demonstrate no or mild diffuse uptake of labeled WBC distinguishable from the focal intense uptake observed in cases of OM.

In some cases of uninfected Charcot joints increased leucocyte accumulation (in the absence of infection) due to the presence of active bone marrow.
Complementary bone marrow scan
(with $^{99m}$Tc- sulfur or tin colloid)

**Indication:** differentiation between infection and normal leucocyte accumulation in active bone marrow (in sites of Charcot arthropathy or amputation)

- Incongruent HMPAO-LS/BMS images
  (activity on leucocyte images without corresponding activity on bone marrow images)

- Spatially congruent HMPAO-LS/BMS images

**Diagnostic accuracy of the combination of labeled leucocyte scan and bone marrow scan** > 90%
Bone scan (a): increased uptake in the left midfoot, LS (b): intense multifocal uptake in the left tarsal bones = congruent images suggestive of OM

Bone marrow scan (c) mild colloid uptake = OM

Osteomyelitis of the left tarsus superimposed on Charcot arthropathy

- 68-yr-old man, NIDDM
- established Charcot arthropathy of the left mid/hindfoot
- right forefoot amputation 1yr ago
- fever, pain & swelling of the left foot
Acute Charcot arthropathy without OM

- 50-yr-old woman, NIDDM
- 4-digit amputation & reconstructive surgery 1yr ago
- 3 wk history of pain, warmth & swelling of the right ankle and foot

**Bone scan**: increased uptake in the right tarsus, **LS**: diffusely increased uptake in the right tarsus, spatially congruent with colloid uptake on the **bone marrow scan**

**Outcome**: Improvement by 3-mo immobilization of the foot, without antibiotic treatment
Confirmation of cure of diabetic foot OM & determination of the correct time for medical treatment discontinuation is often difficult in clinical practice.

An imaging method reliable to prove the cure or the persistence of OM should be useful.

- Radiography
- MRI
- Bone scan

not helpful in assessing response to therapy.

remain positive for many months even after successful therapy.
Monitor response to treatment → WBC scan

abnormal leucocyte scan findings revert to normal 2-8 weeks after commencement of antibiotic treatment

Initial diagnosis of OM of the 3rd left toe

Bone scan

HMPAO-LS

No findings of OM in the follow-up LS after 4 months
Confirmation of cure of OM

Diagnosis of bilateral OM of the 5th toe

Follow-up WBC scan after 6 months antibiotic treatment

WBC scan
Diagnosis of OM of the 5th left toe

Follow-up WBC scan
After 4 months antibiotic treatment

Confirmation of cure of OM

WBC scan
Methods of in vivo labeling of WBC

Scintigraphy with $^{99m}$Tc-MoAbs-WBC

using $^{99m}$Tc-labeled monoclonal antibodies or antibody fragments against surface antigens expressed on granulocytes

$^{99m}$Tc anti-NCA-90 Fab’ fragment (Sulesomab-Leukoscan)
$^{99m}$Tc anti-SSEA-1 IgM (Fanolesomab-Leu Tech),
$^{99m}$Tc anti-NCA-95 IgG (Granuloscint),
$^{99m}$Tc besilesomab (Scimtimun)

Drawbacks of in vitro labeling of leucocytes

• time-consuming labeling procedure (2-3 h to complete)
• extracorporeal handling of potentially contaminating blood transmission of blood-borne pathogens
**Scintigraphy with $^{99m}$Tc- MoAbs-WBC**

**Mechanism of uptake in the infectious foci**

- (>90%) non-specific extravasation of free antibody at the infectious focus (due to locally increased capillary permeability) with subsequent binding to granulocytes already present there.

- (<10%) binding to circulating granulocytes that later migrate at the site of infection.

**Pros**

- Short preparation time
- No need to handle potentially contaminated blood
- High Sensitivity comparable to that of in vitro labelled WBC

**Cons**

- Lower specificity than the in vitro labelled WBC
- HAMA production
- ↑ cost
220 patients  
(orthopedic - 78 diabetics)

99mTc anti-NCA-90 Fab’ fragment  
(Sulesomab-Leukoscan)

sensitivity = 92%  
specificity = 75% (4h p.i) - 85% (24h p.i)  
accuracy = 88%


The role of antibody scintigraphy in evaluation of diabetic foot infections has yet to be defined

Could be alternatives to in vitro labeled WBC scan  
where there is no experience on in vitro labeling procedures
Hybridic imaging

- SPECT / CT
- PET / CT

Image fusion
- software
- integrated

Bone scan  X-ray  Fusion

Leucocyte scan  X-ray  Fusion

SPECT  CT  Fusion SPECT/CT
Better anatomical localization of scintigraphic findings
(of bone scan, labeled leucocyte scan or scan with $^{99m}$Tc-MoAbs-WBC)

$^{111}$In - WBC

Multiphase bone scan
(with $^{99m}$Tc- diphosphonates)

- useful for the diagnosis of OM in patients with no pre-existing regional pathology (unusual in the diabetic foot!)

- as a complementary study in patients with pedal ulcers (improve anatomical localization of WBC-scan findings)

Bone scan can be omitted in patients with established Charcot arthropathy
Conclusions

Radionuclide diagnosis of diabetic foot osteomyelitis

Tc99m-HMPAO-labeled leucocyte scan

the most accurate radionuclide method for the diagnosis of osteomyelitis in the diabetic foot

a negative study excludes infection

Tc99m-HMPAO-labeled leucocyte scan should be the first radionuclide imaging performed for the diagnosis of diabetic foot OM
In the forefoot

combination with bone scan could improve anatomical localization of leucocyte scan findings
differentiate osteomyelitis from soft tissue infection

In the mid/hindfoot

in cases of abnormal leucocyte accumulation on sites of Charcot arthropathy or amputation
additional bone marrow scan
differentiate pedal osteomyelitis from active bone marrow due to acute Charcot arthropathy or on sites of amputation
Evaluation response to treatment

Imaging modality of choice

Tc99m-HMPAO-labeled leucocyte scan

Pathological findings on leucocyte scan revert to normal quickly after successful treatment

A negative leucocyte scan could be useful as a guide to discontinue antibiotic treatment
Thank you very much