Diabetic Foot: Beyond the Dogma

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Dogma

‘A belief or set of beliefs held by a group or organization, which others are expected to accept without argument’.
Diabetic Foot

- Diabetic Foot Ulceration (15%)
- Osteomyelitis (15% of DFU)
- Charcot Foot (0.1-7.5%)

Diagnosis

Management

SNDR: 62,681 patients: Diabetic foot- 3.3%
Diagnose sensory loss
Identify high risk patients
Educate and prevent Foot ulceration
5/12 RCTs: Effect of patient education on prevention of foot ulcers. Three studies demonstrated no benefit.

1989 RCT showed reduced incidence of foot ulceration (risk ratio (RR) 0.31, 95% confidence interval (CI) 0.14 to 0.66) and amputation (RR 0.33, 95% CI 0.15 to 0.76).

2008 RCT did not confirm this finding (RR amputation 0.98, 95% CI 0.41 to 2.34; RR ulceration 1.00, 95% CI 0.70 to 1.44).

Too late: 5 year mortality

The Health Improvement Network (UK)
414,523 people with diabetes
5 year mortality: 42.2%
Walsh et al Diab Med 2015

Case 1

- 64 yr old male
- T2D for 25yrs
- Retinopathy: PRP
- HTN 5yrs, eGFR 56
- Ulcer & Swelling foot 2 months
Investigations

• ESR 80
• CRP 142
• Pro-calcitomin 4.6 ng/mL
Diagnosis?

1. Cellulitis
2. Melanoma
3. Gout
4. Charcot
5. Osteomyelitis
Biomarkers

DFU vs osteomyelitis

• ESR >67 mm/hr (sensitivity 84%; specificity 75%)
• CRP >14 mg/L (sensitivity 85%; specificity 83%)
• **Procalcitonin >0.3 ng/mL: sensitivity 81%; specificity 71%**

- Osteomyelitis (n=24) v DFU (n=11).
- ESR, CRP, IL-6, IL-8, TNFα, MCP-1, MIP1α (no difference)
- **Procalcitonin increased** (P<0.04).

- 156 patients AKA/BKA v no amputation:
  - *(Procalcitonin 1.72 ng/mL v 0.105 ng/mL; p < 0.001).*

Van Asten et al. *Int Wound J* 2017; 14: 40-45
Reiner et al *J Foot Ankle Surg* 2017; S1067
Procalcitonin

• Procalcitonin is a 116 amino-acid peptide - precursor of the hormone calcitonin
Procalcitonin in sepsis

• Bacterial toxins (gram+/gram-) and cytokines stimulate production of Procalcitonin in all parenchymal tissues.

• Non endocrine tissues e.g. liver, lung, brain etc. do not have endocrine granules where calcitonin can be stored.

• Therefore PCT is immediately released into the bloodstream.
Which Test?

- Probe to Bone
- X-Ray
- Bone Scan
- MRI
- CT
Imaging
**Which test?**

**TABLE**

<table>
<thead>
<tr>
<th>Type of evidence</th>
<th>Number of patients</th>
<th>Diagnostic test</th>
<th>Gold standard comparison</th>
<th>Pooled results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Met-analysis of 9 cohort trials (8 prospective, 1 retrospective)</td>
<td>Total N=612</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>4 trials; N=177</td>
<td>Plain film</td>
<td>Histopathology or bone culture</td>
<td>Sensitivity 54% Specificity 68% LR+=1.7 LR-=0.68</td>
<td></td>
</tr>
<tr>
<td>4 trials; N=135</td>
<td>MRI</td>
<td>Histopathology or bone culture</td>
<td>Sensitivity 90% Specificity 79% LR+=4.3 LR-=0.13</td>
<td></td>
</tr>
<tr>
<td>6 trials; N=185</td>
<td>Bone scan</td>
<td>Histopathology or bone culture</td>
<td>Sensitivity 81% Specificity 28% LR+=1.1 LR-=0.68</td>
<td></td>
</tr>
<tr>
<td>2 trials; N=288</td>
<td>PTB</td>
<td>Histopathology or bone culture</td>
<td>Sensitivity 60% Specificity 91% LR+=6.7 LR-=0.44</td>
<td></td>
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<tr>
<td>Met-analysis of 21 cohort trials (8 prospective, 13 retrospective)</td>
<td>Total N=1027</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1 trial; N=35</td>
<td>Ulcer &gt;2 cm³</td>
<td>Bone biopsy</td>
<td>LR+=7.2 LR-=0.48</td>
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</tr>
<tr>
<td>3 trials; N=75</td>
<td>PTB</td>
<td>Bone biopsy</td>
<td>LR+=6.4 LR-=0.39</td>
<td></td>
</tr>
<tr>
<td>4 trials; N=108</td>
<td>ESR &gt;70 mm/hr</td>
<td>Bone biopsy</td>
<td>LR+=11 LR-=0.34</td>
<td></td>
</tr>
<tr>
<td>16 trials; N=567 (data pooled for 7 trials; N=217)</td>
<td>Plain film</td>
<td>Bone biopsy</td>
<td>LR+=2.3 LR-=0.63</td>
<td></td>
</tr>
</tbody>
</table>

ESR, erythrocyte sedimentation rate; LR+, positive likelihood ratio; LR-, negative likelihood ratio; MRI, magnetic resonance imaging; PTB, probe to bone test.

* Numbers of trials and patients don’t add up because multiple diagnostic tests were used in some trials.

† 10 trials were graded as a level II or III (included a blind comparison to the gold standard) and the rest were of low quality because they lacked blinding.
IWGDF guidance on the diagnosis and management of foot infections in persons with diabetes

- Antibiotic treatment empirical to cover g+ve/-ve/anaerobes, pseudomonas.
- Cephalosporins (cephalexin); Penicillin/β-lactamase inhibitor combinations (amoxicillin/ clavulanate); carbapenems (imipenem); fluoroquinolones (ciprofloxacin); Clindamycin, linezolid.
- Topical Antimicrobial peptides (Pexiganan, Gentamicin sponge).
- Gentamicin Impregnated beads.
- Antibiotic Duration: Mild DFI (1-2 weeks); Serious (3 weeks).

- Osteomyelitis: Resection + antibiotics (1 week).
- Osteomyelitis: No surgery- antibiotics 6-12 weeks.

- Ciprofloxacin 500mg bd + Clindamycin 150mg qds.

Lipsky et al Diabetes Metab Res Rev 2016; 32: 45-74
Case 2

- 45yrs old male.
- Type 1 diabetes 30 yrs.
- eGFR 38.
- Swelling right foot >1 month.

- CRP 2
- ESR 5
- Pro-calcitinin 0.1ng/ml
Often Misdiagnosed: Cellulitis, osteomyelitis, gout.
X-ray: Clinical & fracture/dislocation.
CT (fractures)
MR (bone marrow oedema)
‘How often have I seen persons, not yet familiar with this arthropathy, forget that behind the disease of the joint there was a disease far more important in character and which really dominated the situation’

J M Charcot 1868
Herbert William 1881

Causes are not fully understood.
No specific working definition or firm criteria for diagnosis.
Evidence base is currently too thin
Rely on professional opinion alone.

Jeffcoate W Diabetic Medicine 2015; 760-770
Pathogenesis

1. Pro-inflammatory cytokines (IL-1β, TNF-α) leads to activation of the receptor activator of nuclear factor κ-B ligand (RANKL-NFκB) pathway triggers the maturation of Osteoclasts and bone lysis.

2. Osteoblast-dependent osteogenic mechanism mediated via the Wnt/β-catenin pathway and its endogenous inhibitors, sclerostin and dickkopf-1.

3. Dislocation: Loss of CGRP nerve peptides and capsule weakness
What is elevated?

1. CRP
2. ESR
3. WCC
4. Pro-calcitonin
Is There a Systemic Inflammatory Response in the Acute Charcot Foot?

- 36 consecutive patients who presented to the Diabetic Foot Clinic with a red, hot swollen foot
- Skin foot temperature 3.1°C (2.4 – 4.2) > in the Charcot compared with the contralateral foot

**HOWEVER**

- Median CRP: 5.8 mg/l (5–11) and <5 mg/l in 47.2% of patients
- Median ESR: 21 mm/h (13–36)
- WCC: 7.0 (4 –11).
Charcot: Imaging

MRI: Sen-76.9%, Spec- 75%
T1 increased
T2 decreased

\( ^{18} \text{F} \)FDG PET:
Sen-100%, Spec-93%
1. Cellulitis
2. DVT
3. Gout
4. Charcot
5. Osteomyelitis
Management

Off-loading

Bisphosphonates

Calcitonin
5 yr malignancy: 4.1 v 2.9%

Surgery
Exostectomy, Arthrodesis

Denosumab
RANK-L inhibitor (Osteoclasts)

Teriparatide
Recombinant PTH (Osteoblasts)
Off Loading

1. Fibre glass cast, cast walkers, half shoes.
2. CDUK: 6-9 months.
3. Remission: Temp difference <2 °C.

Game et al. CDUK study: Diabetologia 2012; 55: 32–35
Case 3: Just another Ulcer!

- 80 yr old Bedouin male
- Type 2DM on Insulin
- 4 yr Hx of ulcer

- Initially coin sized with rapid growth in last 12 months.
- Fear of amputation

PET-CT confirmed widespread metastases
Histology: Nodular melanoma
Melanomas: 30% lower limb, 3-15% in foot

Malone et al. The Foot 2012; 235-239
Case 4: Just another Ulcer!

- 48 yr old male T2DM
- Hx of ulcer 18 months
- ‘Knot in his groin”
- Biopsy: S-100 & HMB-45 +ve (Amelanotic Melanoma)
- CT: Metastasis to inguinal lymph node and liver.
- Died 6 months later

Honey

Surat Al-Nahl: 68-69
‘There is a cure for people in it (honey)’

✦ Antibacterial,
✦ Anti-inflammatory,
✦ Removes odour,
✦ Reduces pain

Heals Wounds

Topical honey for the treatment of diabetic foot ulcer: A systematic review

Ramy Kateel a, Prabha Adhikari a,*, Alfred J. Augustine b, Sheetal Ullal c

Randomized clinical trials: (n=6) 546 patients
Case Series: (n=10) 317 patients

Kateel et al. Complementary Therapies in Clinical Practice 2016; 24: 130-133
A Randomized, Controlled Clinical Trial of Honey-Impregnated Dressing for Treating Diabetic Foot Ulcer

Muhammad Imran¹, Muhammad Barkaat Hussain² and Mukhtiar Baig³

Beri (Ziziphus jujuba) honey (Karak, Pakistan), gamma irradiated with confirmed Zone of inhibition >18 mm for Staph Aureus, impregnated on gauze dressing

<table>
<thead>
<tr>
<th>Total number of patients assessed for eligibility=610</th>
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</thead>
<tbody>
<tr>
<td>22 declined to participate</td>
</tr>
<tr>
<td>210 ineligible</td>
</tr>
<tr>
<td>49 had minor grade 3 or above</td>
</tr>
<tr>
<td>19 patients with &lt; 1 ml/l</td>
</tr>
<tr>
<td>54 Hb&lt;10gm/dl</td>
</tr>
<tr>
<td>15 ARR &lt; 0.7</td>
</tr>
<tr>
<td>44 uncontrolled DM (HbA1c&gt;7%)</td>
</tr>
<tr>
<td>47 local infection</td>
</tr>
<tr>
<td>975 randomly assigned</td>
</tr>
<tr>
<td>135 in experimental group (Beri impregnated dressing)</td>
</tr>
<tr>
<td>180 in control group (Normal saline dressing)</td>
</tr>
<tr>
<td>16 lost to follow-up</td>
</tr>
<tr>
<td>11 lost to follow-up</td>
</tr>
<tr>
<td>279 included in analysis</td>
</tr>
<tr>
<td>160 included in analysis</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Wound healing in honey treated patients (n=136)</th>
<th>Wound healing in saline treated patients (n=97)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td># Duration (days), median (IQR)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>18.00 (6-120)</td>
<td>29.00 (7-120)</td>
<td>&lt; 0.001*</td>
</tr>
</tbody>
</table>

Thank you