Weill Cornell Medicine-Qatar
Continuing Professional Development

Diabetic Foot Challenge

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DISCLOSURE STATEMENT

Speaker:

Rayaz A. Malik, MD

- Has disclosed that he serves on the Speaker's Bureau for Pfizer and Lilly

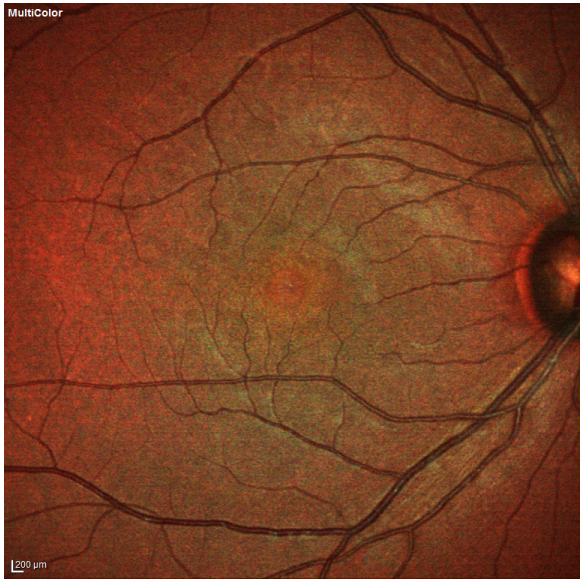
- Will not be discussing the off-label or investigational use of products

Weill Cornell Medicine-Qatar

Referral

- 50 year old Qatari male with Type 1 DM 32 years.
- HbA1c 6.8%
- BP: 118/64
- ACR: 1.2, eGFR-86
- Lipids normal (Statin)

What Next?



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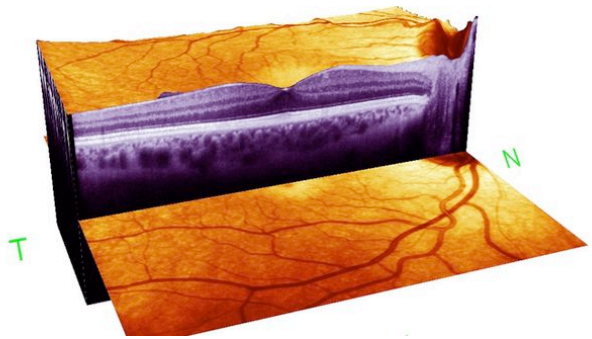
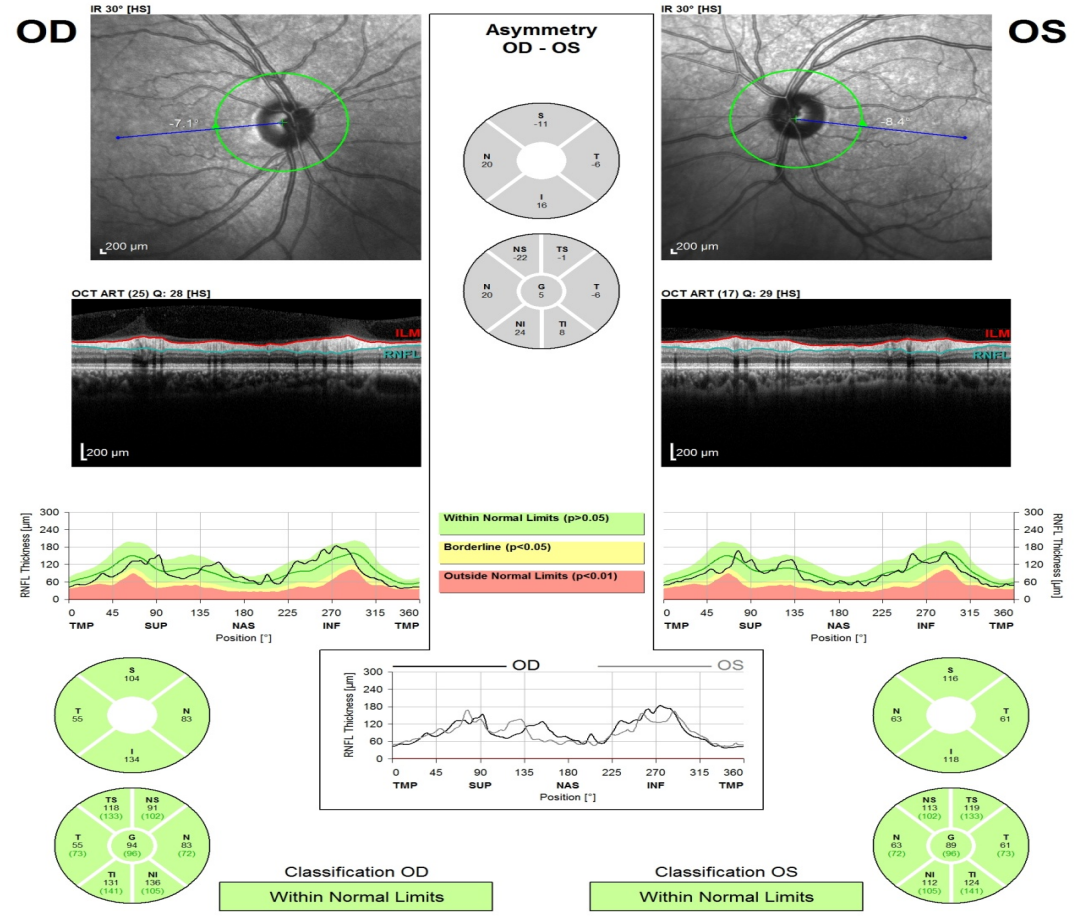


RNFL Single Exam Report OU
SPECTRALIS® Tracking Laser Tomography

HEIDELBERG ENGINEERING

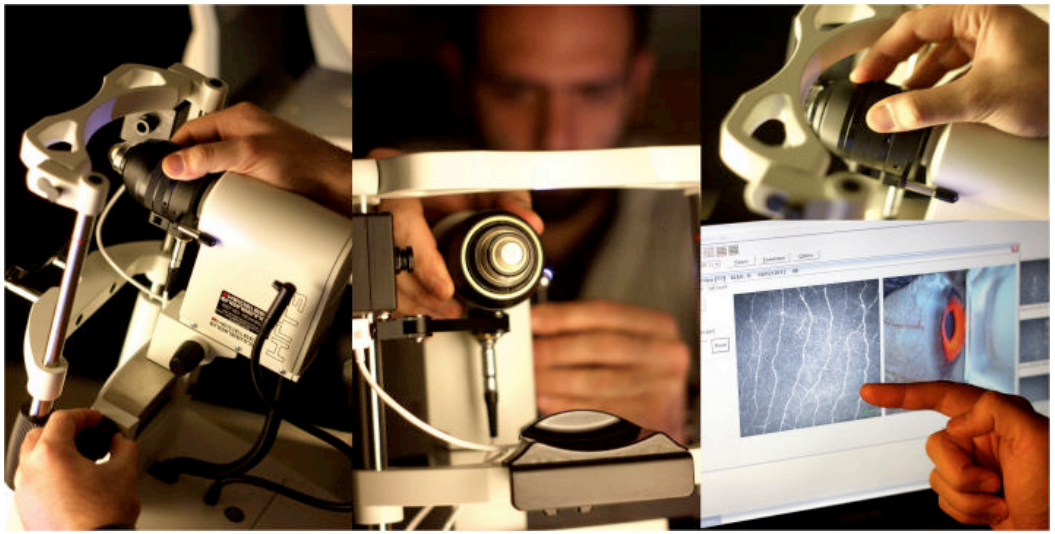
Diagnosis: --- **Comment:** ---

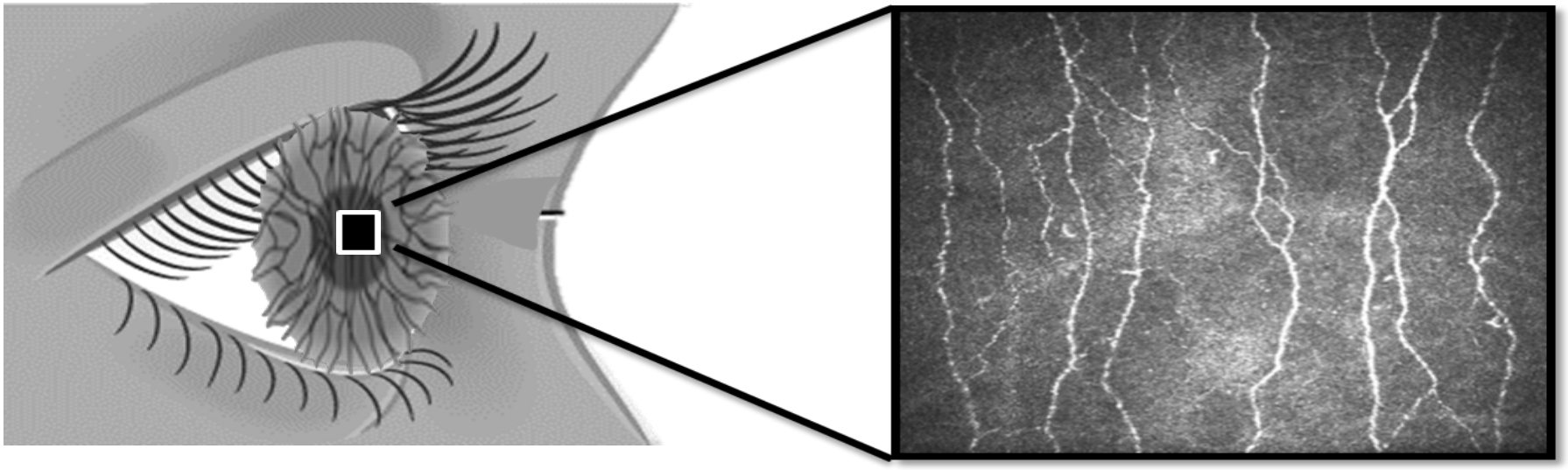


Notes:

Date: 12/9/2015 Signature:

Corneal Confocal Microscopy





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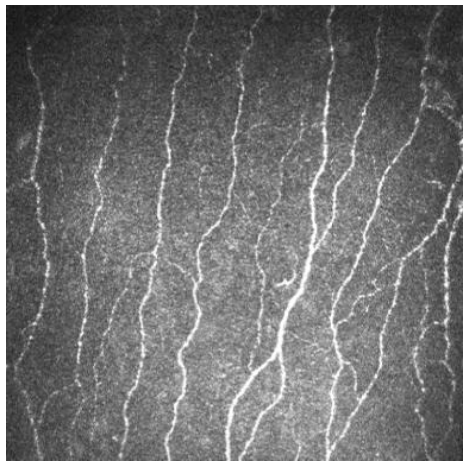
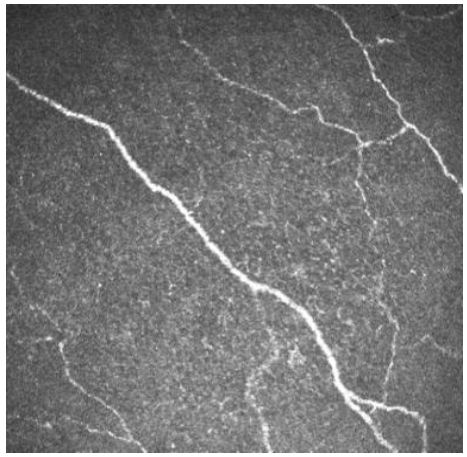
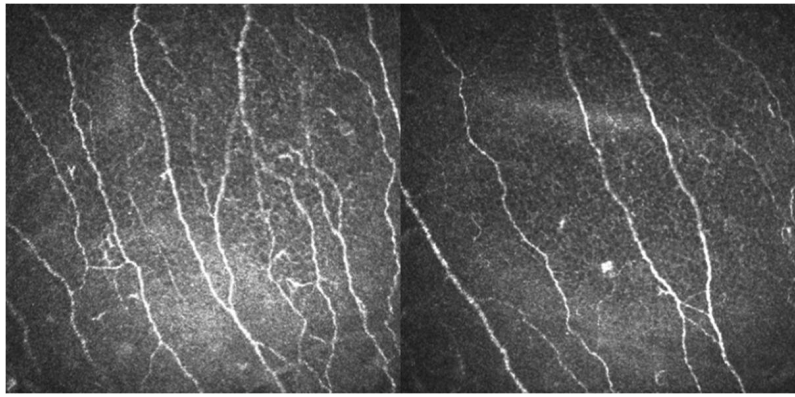
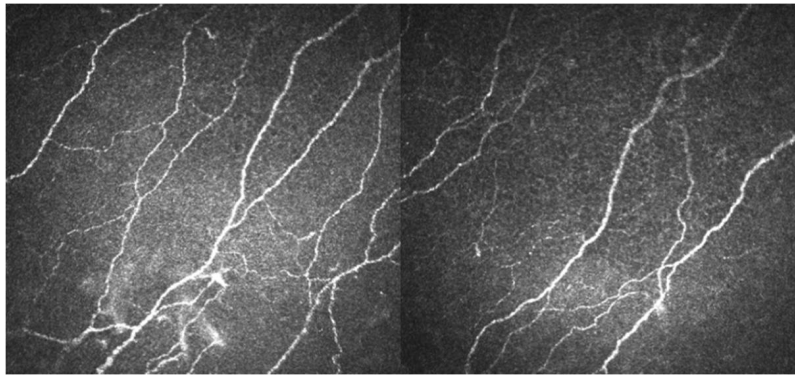


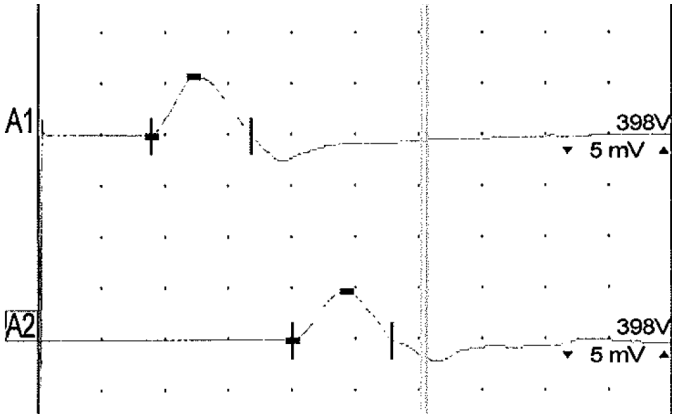


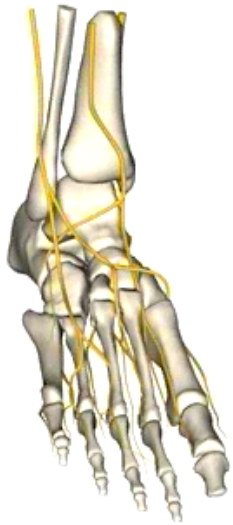


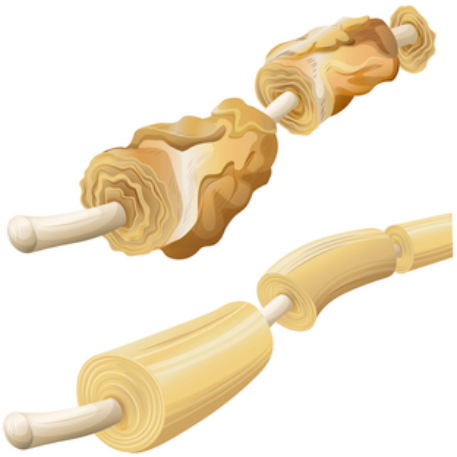


Corneal nerve fibre density (CNFD): 26.0 ± 10.0 no./mm² (control: 36.5 /mm²)
Corneal nerve branch density (CNBD): 83.3 ± 40.3 no./mm² (control: 76.0 /mm²)
Corneal nerve fibre length (CNFL): 21.9 ± 6.6 mm/mm² (control: 25.8 mm/mm²)

Electrophysiology







Nerve	Amplitude (mV)	NCV (m/s)
Median	5.8	20 (45-70)
Ulnar	0.5	19 (48-74)
Radial	0.6	10 (48-70)
Peroneal	1.6	14 (44+)
Sural	2.5	13 (46-64)

Genetics

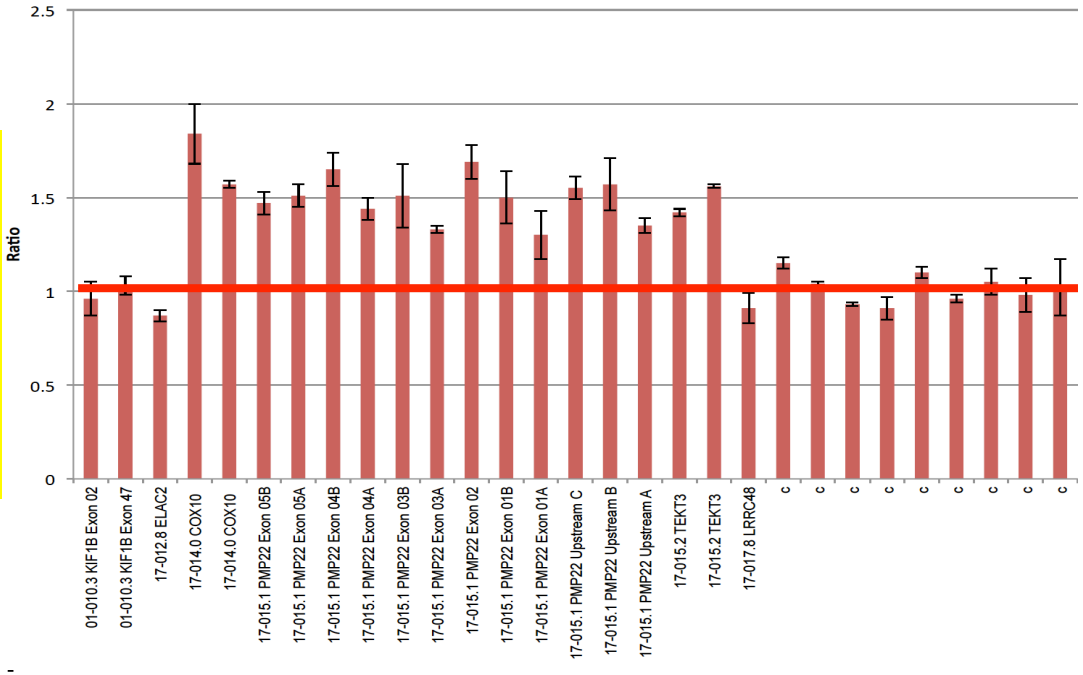
But
No Family Hx.
Age 50

NORMAL

Genetics

MLPA* (Multiplex Ligation-dependent Probe Amplification) (deletion or duplication) of PMP22 gene

De Novo Mutation 10%



Son 14 Clumsy

Probes for each of the five PMP22 exons are present in this probemix.

CMT: Incidence 1:2500 (AD)
(1) PMP22 duplications (CMT1A) (60%) encodes a 22 KD protein in Schwann Cells
(2) PMP22 deletions (HNPP)
(3) PMP22 point mutations (both phenotypes.)

American Diabetes Association.
Cure • Care • Commitment®

ADA 2016: Clinical Pearls

- Most common forms of DN are DSPN and AN.
- DSPN is a length-dependent symmetrical disorder and most commonly predominantly sensory.
- Neuropathy may be present in patients with metabolic syndrome, and/or impaired glucose tolerance.
- Non-diabetic neuropathies may occur in diabetes, may be more prevalent than in non- diabetic populations (e.g., higher incidence of B12 deficiency with long-term metformin treatment; CIDP), and should be actively excluded.

Atypical Neuropathy

- Rapid progression ☒
- Asymmetry ☒
- Motor > Sensory ☑
- Other Complications ☒
- Family History ☑
- Drugs ☒

A swollen foot

- 52 yr old male
- T1D for 25yrs
- Retinopathy: PRP
- HTN 5yrs, eGFR 56
- Long term Urinary Catheter
- Swelling foot 2 months

Presentation

A&E: Diagnosis?

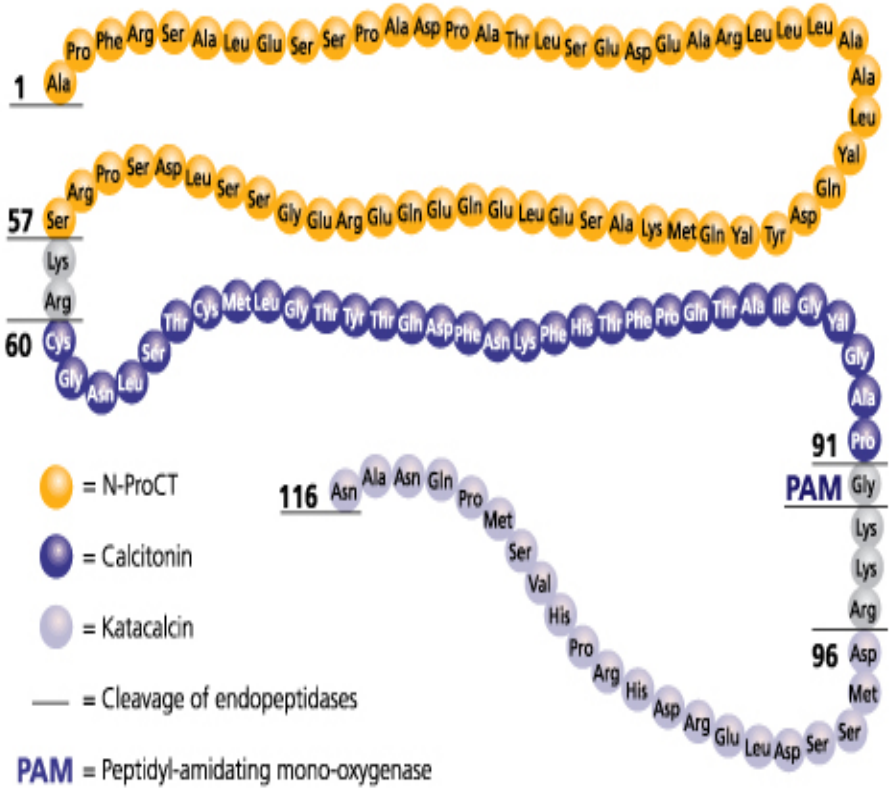
1. Cellulitis
2. DVT
3. Gout
4. Charcot
5. Osteomyelitis

Investigations

- ESR 80
- CRP 142
- Pro-calcitonin 4.6 ng/mL

Procalcitonin

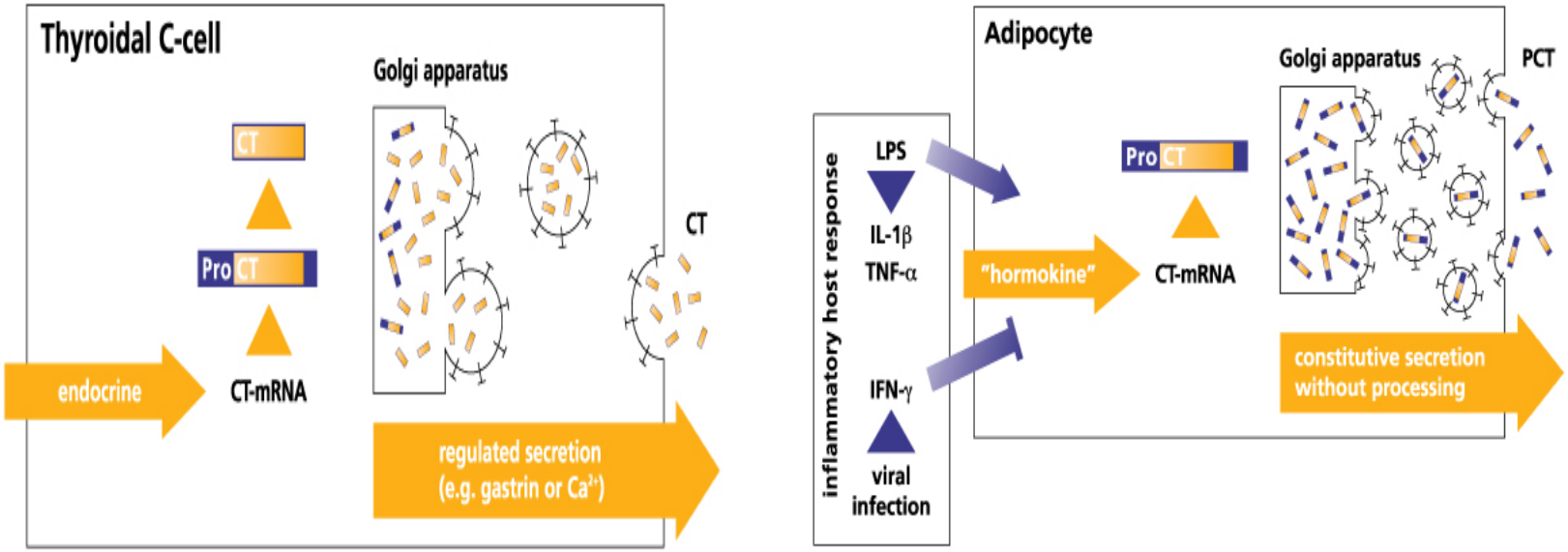
- Procalcitonin is a 116 amino-acid peptide - precursor of the hormone calcitonin



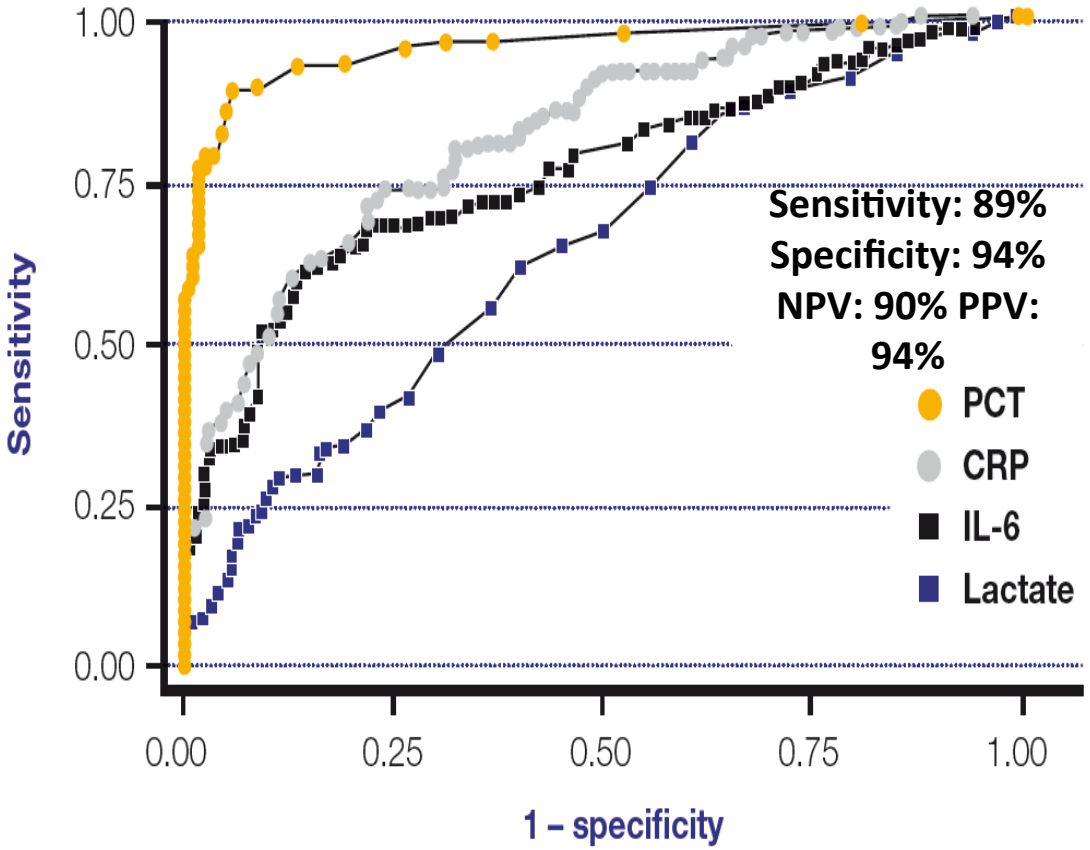
Procalcitonin in sepsis

- **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**



PCT: Sepsis diagnosis



- PCT levels accurately differentiate sepsis from noninfectious inflammation*
- PCT has been demonstrated to be the best marker for differentiating patients with sepsis from those with systemic inflammatory reaction not related to infectious cause

Simon L. *et al. Clin Infect Dis*. 2004; 39:206-17

DFU vs Osteomyelitis

DFU vs osteomyelitis

- ESR >67 mm/hr (sensitivity 84%; specificity 75%)
- CRP >14 mg/L (sensitivity 85%; specificity 83%)
- Pro-calcitonin >0.3 ng/mL (sensitivity 81%; specificity 71%)

The value of inflammatory markers to diagnose and monitor diabetic foot osteomyelitis

- Osteo (n=24) v DFU (n=11).
- ESR, CRP, IL-6, IL-8, TNFα, MCP-1, MIP1α
- **Pro-calcitonin (PCT) (P<0.049).**

Khodaee *et al. J Fam Pract.* 2015; 64: 309-310
Van Asten *et al. Int Wound J* 2015;

Imaging?

Probe to Bone

X-Ray

Bone Scan

CT

MRI

Which test?

TABLE

Diagnosing osteomyelitis: How the tests stack up*

Type of evidence	Number of patients	Diagnostic test	Gold standard comparison	Pooled results
Meta-analysis of 9 cohort trials[3] (8 prospective, 1 retrospective)	Total N=612			
	4 trials; N=177	Plain film	Histopathology or bone culture	Sensitivity 54% Specificity 68% LR+=1.7 LR–=0.68
	4 trials; N=135	MRI	Histopathology or bone culture	Sensitivity 90% Specificity 79% LR+=4.3 LR–=0.13
	6 trials; N=185	Bone scan	Histopathology or bone culture	Sensitivity 81% Specificity 28% LR+=1.1 LR–=0.68
	2 trials; N=288	PTB	Histopathology or bone culture	Sensitivity 60% Specificity 91% LR+=6.7 LR–=0.44
Meta-analysis† of 21 cohort trials[4] (8 prospective, 13 retrospective)	Total N=1027			
	1 trial; N=35	Ulcer >2 cm²	Bone biopsy	LR+=7.2 LR–=0.48
	3 trials; N=75	PTB	Bone biopsy	LR+=6.4 LR–=0.39
	4 trials; N=108	ESR >70 mm/hr	Bone biopsy	LR+=11 LR–=0.34
	16 trials; N= 567 (data pooled for 7 trials; N=217)	Plain film	Bone biopsy	LR+=2.3 LR–=0.63

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.

Khodaee *et al. J Fam Pract.* 2015; 64: 309-310

Diagnosis?

1. Cellulitis
2. DVT
3. Gout
4. Charcot
5. Osteomyelitis

Case 2

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

- CRP 2
- ESR 5
- Pro-calcitinon 0.1ng/ml

Is There a Systemic Inflammatory Response in the Acute Charcot Foot?

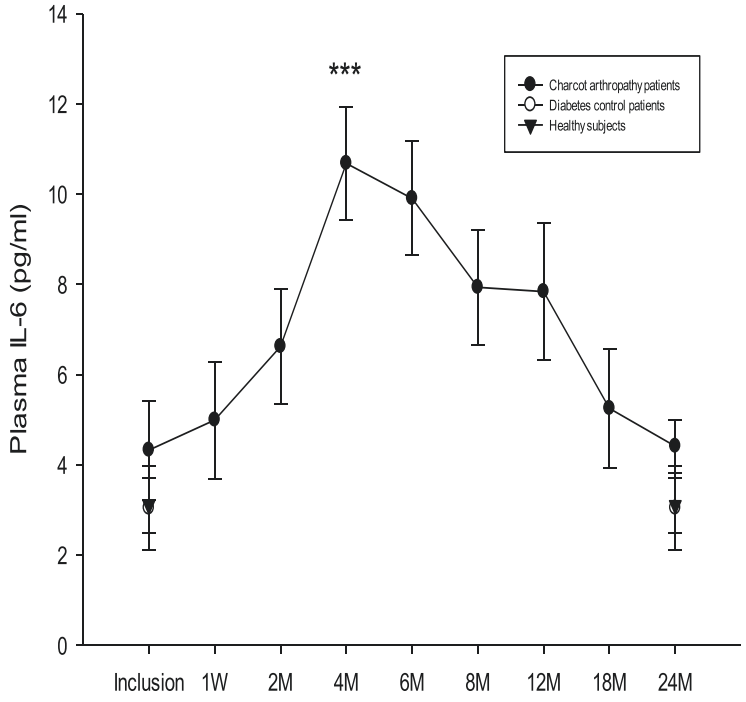
- 36 consecutive patients who presented to the Diabetic Foot Clinic with a red, hot swollen foot
- Skin foot temperature 3.1°C (2.4 – 4.2) > in the Charcot compared with the contralateral foot

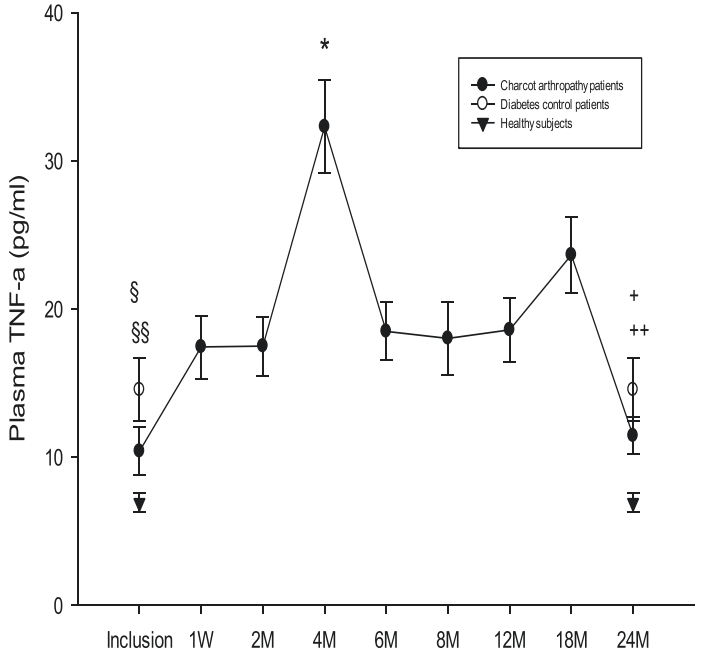
HOWEVER

- 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).

Petrova *et al. Diabetes Care* 2007; 30:997-998

Offloading treatment is linked to activation of proinflammatory cytokines and start of bone repair and remodeling in Charcot arthropathy patients





Folestad et al. Foot & Ankle Research 2015; 8: 72-84

Imaging

Diagnosis

1. Cellulitis
2. DVT
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5. Osteomyelitis

Charcot: Pathogenesis

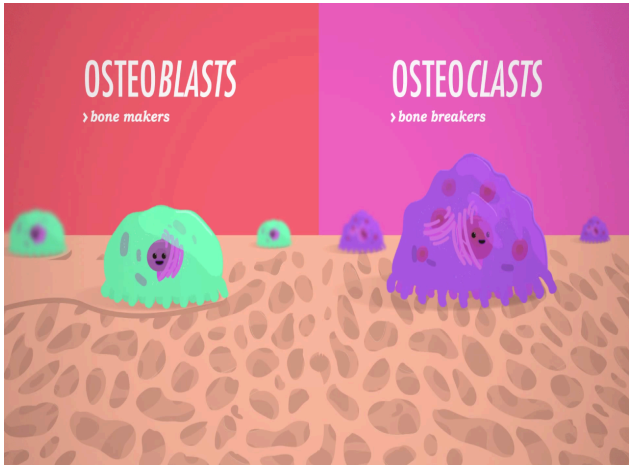
Neurovascular

Charcot 1868

Neurotraumatic

Volkman 1870

Pro-inflammatory cytokines (IL-1ß, TNF-α)
Activation (RANKL- NFκB)
OSTEOCLASTS (CGRP/VIP)

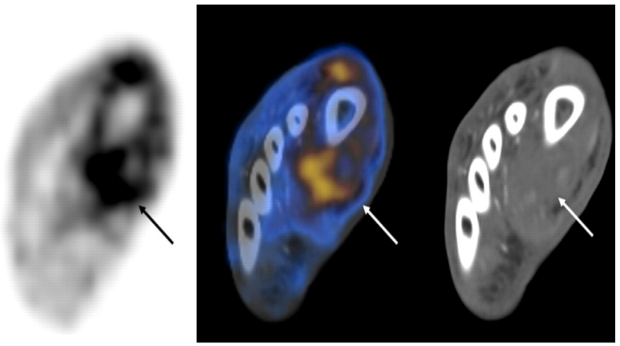


Wnt/β-catenin pathway, sclerostin and dickkopf-1.
OSTEOBLASTS (SP/CGRP)

Charcot: Imaging

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

F^{18} FDG PET:
Sen-100%, Spec-93%



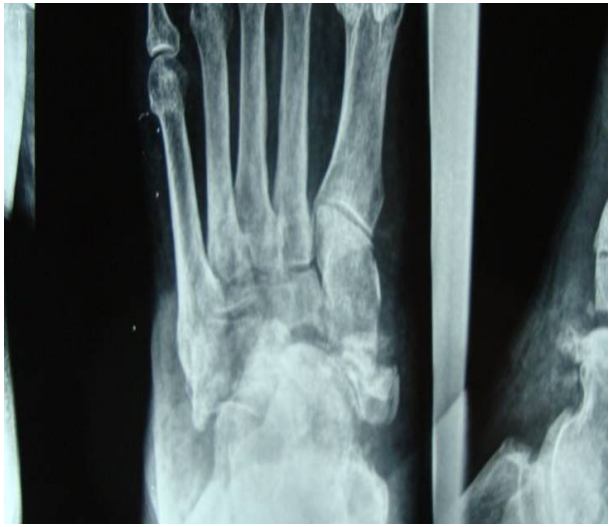
Management?

Off-loading

Bisphosphonates

Calcitonin

5 yr malignancy: 4.1 v 2.9%



Denosumab

RANK-L inhibitor (Osteoclasts)

Teriparatide

Recombinant PTH (Osteoblasts)

Surgery

Exostectomy, Arthrodesis

Thank you