Diabetic Neuropathy: Early Diagnosis and Prevention

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Rayaz A Malik

I DO NOT have a financial interest in commercial products or services referred to in this lecture.
## Conflict of Interest

<table>
<thead>
<tr>
<th>City</th>
<th>United</th>
</tr>
</thead>
<tbody>
<tr>
<td>45</td>
<td>Wins</td>
</tr>
<tr>
<td>50</td>
<td>Draws</td>
</tr>
<tr>
<td>6-1 (2011)</td>
<td>Biggest win</td>
</tr>
<tr>
<td>3</td>
<td>League titles</td>
</tr>
<tr>
<td>5</td>
<td>FA Cups</td>
</tr>
<tr>
<td>0</td>
<td>European Cups</td>
</tr>
<tr>
<td>2</td>
<td>League Cups</td>
</tr>
</tbody>
</table>
Overview

• Current Issues with Diabetic Neuropathy.
• Need for a Biomarker for DPN.
• Development of a Biomarker DPN
• Development of a Surrogate End Point for DPN.
“Progress in the development of disease modifying agents in diabetic neuropathy has completely stalled”
FDA (Feb 2013)

“Diabetic neuropathy is a nightmare
No clear endpoints, so we focus on nephropathy”
Head of late complications
Big Pharma (Sep 2012)
### Failure after failure... 2015

<table>
<thead>
<tr>
<th>Abnormality</th>
<th>Compound</th>
<th>Aim of treatment</th>
<th>Status of RCTs</th>
</tr>
</thead>
<tbody>
<tr>
<td>Polyol pathway ↑</td>
<td>Aldose reductase inhibitors</td>
<td>Nerve sorbitol ↓</td>
<td>Withdrawn (AE)</td>
</tr>
<tr>
<td></td>
<td>Sorbinil</td>
<td></td>
<td>Withdrawn (AE)</td>
</tr>
<tr>
<td></td>
<td>Tolrestat</td>
<td></td>
<td>Ineffective</td>
</tr>
<tr>
<td></td>
<td>Ponalrestat</td>
<td></td>
<td>Withdrawn (marginal effects)</td>
</tr>
<tr>
<td></td>
<td>Zopolrestat</td>
<td></td>
<td>Withdrawn (AE)</td>
</tr>
<tr>
<td></td>
<td>Zenares</td>
<td></td>
<td>Withdrawn (AE)</td>
</tr>
<tr>
<td></td>
<td>Lidores</td>
<td></td>
<td>Effective in phase II trial</td>
</tr>
<tr>
<td></td>
<td>Fidares</td>
<td></td>
<td>Effective in phase II trials (studies halted)</td>
</tr>
<tr>
<td></td>
<td>Ranires</td>
<td></td>
<td>Effective in phase II trial</td>
</tr>
<tr>
<td></td>
<td>Epalrest</td>
<td></td>
<td>Marketed in Japan</td>
</tr>
<tr>
<td>mυο-inositol ↑</td>
<td>Mυο-inositol</td>
<td></td>
<td>Effective in phase II trial</td>
</tr>
<tr>
<td>GLA synthesis ↓</td>
<td>γ-Linolenic acid</td>
<td></td>
<td>Effective in phase II trial</td>
</tr>
<tr>
<td>Oxidative stress ↑</td>
<td>α-Lipoic acid</td>
<td></td>
<td>Effective in phase II trial</td>
</tr>
<tr>
<td>Nerve hypoxia ↑</td>
<td>Vasodilators</td>
<td></td>
<td>Effective in phase II trial</td>
</tr>
<tr>
<td>ACE inhibitor</td>
<td></td>
<td></td>
<td>Effective in phase II trial</td>
</tr>
<tr>
<td>Prostaglandin</td>
<td></td>
<td></td>
<td>Effective in phase II trial</td>
</tr>
<tr>
<td>PhVEGF</td>
<td></td>
<td></td>
<td>Effective in phase III trial ongoing</td>
</tr>
<tr>
<td>Protein kinase C ↑</td>
<td>PKC-β inhibitors</td>
<td></td>
<td>Effective in phase III trial ongoing</td>
</tr>
<tr>
<td>C-peptide ↓</td>
<td>C-peptide</td>
<td></td>
<td>Effective in phase II trials</td>
</tr>
<tr>
<td>Neurotrophism ↓</td>
<td>Nerve growth factor</td>
<td></td>
<td>Effective</td>
</tr>
<tr>
<td></td>
<td>BDNF</td>
<td></td>
<td>Effective</td>
</tr>
<tr>
<td>LCFA metabolism ↓</td>
<td>Acetyl-L-carnitine</td>
<td>LCFA accumulation ↓</td>
<td>Ineffective</td>
</tr>
<tr>
<td>NEG ↑</td>
<td>Aminoguanidine</td>
<td>AGE accumulation ↓</td>
<td>Withdrawn</td>
</tr>
</tbody>
</table>

NEG = non-enzymatic glycation; AGE = advanced glycation end products; EFA = essential fatty acids; LCFA = long-chain fatty acids; AE = adverse events; NBF = nerve blood flow; RCTs = randomized clinical trials; BDNF = brain-derived neurotrophic factor.
FDA End Point?

1. **Biomarker:** a physical sign or laboratory measurement that occurs in association with a **pathological process** and has **diagnostic** or **prognostic** utility.

2. **Clinical endpoint:** A clinically meaningful measure of how a patient feels, functions or survives.

3. **Surrogate Endpoint:** Biomarker intended to substitute for a clinical endpoint and is expected to predict the effect of **therapeutic intervention**.
Diabetic Neuropathies: Update on Definitions, Diagnostic Criteria, Estimation of Severity, and Treatments

- Possible- Symptoms or Signs (↓ sensation, reflexes).
- Probable- Symptoms & Signs.
- Confirmed- Abnormal NC + symptom(s) or sign(s).

Tefsaye et al. Diabetes Care 2010; 33: 2285-2293
Neurological examination

- 10g monofilament
- Vibration perception threshold
- Electrophysiology (NCS)

**FDA: Pathological Relevance**

![Graph showing fiber diameters and types](image)

- **Unmyelinated C fibers**
  - Polymodal Nociceptive, Temperature, Slow Pain, Postganglionic Sympathetic

- **Myelinated**
  - **Aδ fibers**
    - Mechanoreceptive, Pressure, Temperature, Fast Pain
  - **Aβ fibers**
    - Cutaneous Touch Pressure

![Diagram of nerve conduction](image)
FDA: Diagnostic Utility?

12 ‘experts’ assessed 24 diabetic patients on consecutive days, physical features and voice disguised for symptoms and signs.

Study physician dx from signs and symptoms were excessively variable, often overestimating DSPN. Specific approaches to improving clinical proficiency should be tested.

A TRIAL OF PROFICIENCY OF NERVE CONDUCTION: GREATER STANDARDIZATION STILL NEEDED

4 Expert clinical neurophysiologists, assessed NCV in 24 patients with diabetes on consecutive days. Significant inter-observer differences were seen

FDA: Clinical End Point

Pain, Skin Blood flow, Inflammation, Ulceration
FDA: Diagnostic Utility

Normal NCS  Normal NCS

Control  Diabetic  P<0.001

P<0.01

Control  Diabetic -  Diabetic +  P<0.001

Ignore Small Fibres!

As the doctors say of a wasting disease, to start with it is easy to cure but difficult to diagnose; after a time, unless it has been diagnosed and treated at the outset, it becomes easy to diagnose but difficult to cure.

Niccolo Machiavelli
The Prince
“We need to learn to measure what we value, not value what we can easily measure”

Roman Emperor & Philosopher
Marcus Aurelius AD 120

“Open mind and the courage to throw out yesterday’s ideas when they don’t appear to be working”
Skin Biopsy for all?
Infection/bleeding: 1.9/1000
Perhaps not
Conversation with a Prof of Optometry about a Corneal confocal microscope!

Oliveira Soto & Efron: Morphology of Corneal Nerves
Cornea 2001; 20: 374-384
Conventional Wisdom

“How we think determines what we measure”
A Einstein
Anatomy

• Derived from the ophthalmic division of the Trigeminal nerve.

• Skin 200 nociceptors/mm².

• Cornea most dense innervation in body 7000 nociceptors/mm².

• Biopsy the Cornea!
Corneal Confocal Microscopy

- Utilises CONFOCAL principle increases resolution (Minsky 1957).
- Scanning gives a wide field of view (Thomas & Christoph Cremer 1978).
- Cornea transparent use white light/lasers and no stains.
- 10 um optical sectioning at x760.
Corneal Confocal Microscopy

- Rapid (2 min)
- Non-invasive (in vivo)
- Reiterative

- Images Corneal Structure.
Corneal tomography
Corneal nerves

In vitro

CGRP whole mount

In vivo

CCM
Corneal Structure and Sensitivity in Type 1 Diabetes Mellitus

Maria E. Rosenberg,\textsuperscript{1} Timo M. T. Tervo,\textsuperscript{1} Ilkka J. Immonen,\textsuperscript{1} Linda J. Müller,\textsuperscript{2} Carola Grönbägen-Riska,\textsuperscript{3} and Minna H. Vesaluoma\textsuperscript{1}

From the \textsuperscript{1}Department of Ophthalmology, University of Helsinki, Finland; \textsuperscript{2}The Netherlands Ophthalmic Research Institute, Amsterdam, The Netherlands; and the \textsuperscript{3}Department of Internal Medicine, Division of Nephrology, University of Helsinki, Finland.

<table>
<thead>
<tr>
<th>No diabetes ($n = 9$)</th>
<th>Corneal Sensitivity (mm)</th>
<th>Number of Long NFBs per Image</th>
</tr>
</thead>
<tbody>
<tr>
<td>No neuropathy ($n = 11$)</td>
<td>57.8 ± 4.9</td>
<td>4.0 ± 1.2</td>
</tr>
<tr>
<td>Mild to moderate neuropathy ($n = 7$)</td>
<td>56.9 ± 7.5</td>
<td>2.6 ± 1.4</td>
</tr>
<tr>
<td>Severe neuropathy ($n = 5$)</td>
<td>26.0 ± 27.9</td>
<td>1.8 ± 0.8</td>
</tr>
</tbody>
</table>

$P = 0.027$, M–W$^*$ $P = 0.048$, M–W$^*$ $P = 0.30$, t-test$^*$.
Corneal Nerve Quantification

CCM (6 images/patient)
- CNFD (no./mm²) + TC (Red)
- CNFL (mm/mm²) (Red + Blue)
- CNBD (no./mm²) (Green)

CCMetrics®, M. A. Dabbah, University of Manchester, Imaging Science and Biomedical Engineering, School of Cancer and Enabling Sciences.

Malik et al. Diabetologia 2003; 46: 683-688
Kallinikos et al. IOVS 2004; 45: 418-422
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3. Surrogate Endpoint: Biomarker intended to substitute for a clinical endpoint and is expected to predict the effect of therapeutic intervention.
Corneal confocal microscopy: a non-invasive surrogate of nerve fibre damage and repair in diabetic patients

R. A. Malik¹, P. Kallinikos², C.A. Abbott¹, C.H.M. van Schie¹, P. Morgan², N. Efron², A. J. M. Boulton¹

Diabetic Neuropathy

P=0.04

P=0.0001

Diagnostic efficiency of corneal nerve parameters against the NDS > 5 (101 diabetic patients & 17 controls)

<table>
<thead>
<tr>
<th></th>
<th>NCCA(&gt;1.01)</th>
<th>NFD(&lt;31.5)</th>
<th>NBD(&lt;17.5)</th>
<th>NFL(&lt;8.30)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Sensitivity</strong></td>
<td>70%</td>
<td>90%</td>
<td>96%</td>
<td>100%</td>
</tr>
<tr>
<td><strong>Specificity</strong></td>
<td>51%</td>
<td>54%</td>
<td>63%</td>
<td>62%</td>
</tr>
</tbody>
</table>

Tavakoli et al. Diabetes Care 2010; 33: 1792-97
Detection of Diabetic Sensorimotor Polyneuropathy by Corneal Confocal Microscopy in Type 1 Diabetes

CNFL: AUC-0.88, Sensitivity-85%, Specificity-84% for DPN

Corneal Nerve Loss Detected With Corneal Confocal Microscopy Is Symmetrical and Related to the Severity of Diabetic Polyneuropathy
### N=1680 (DPN-559, no DPN-592, Controls 529)

**Corneal Confocal Microscopy for Assessment of Diabetic Peripheral Neuropathy: A Meta-analysis**

#### CNFD

<table>
<thead>
<tr>
<th>Study</th>
<th>Subgroup</th>
<th>Control</th>
<th>DPN</th>
<th>IV. Random. 95% CI</th>
<th>Mean Difference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ahmad A 2012</td>
<td>28</td>
<td>9</td>
<td>33</td>
<td>43</td>
<td>11</td>
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<tr>
<td>Hertz P 2011</td>
<td>20.64</td>
<td>12.8</td>
<td>14</td>
<td>31.6</td>
<td>5.4</td>
</tr>
<tr>
<td>Malik RA 2003</td>
<td>26</td>
<td>5.4</td>
<td>18</td>
<td>44.5</td>
<td>14.1</td>
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<tr>
<td>Mehri S 2007</td>
<td>13.88</td>
<td>5.4</td>
<td>20</td>
<td>42.04</td>
<td>12.4</td>
</tr>
<tr>
<td>Perkinsoula IN 2014</td>
<td>20.5</td>
<td>6.4</td>
<td>193</td>
<td>37.2</td>
<td>8.7</td>
</tr>
<tr>
<td>Quatieri C 2007</td>
<td>22.12</td>
<td>12.42</td>
<td>44</td>
<td>43.2</td>
<td>10.66</td>
</tr>
<tr>
<td>Sivakosamagoh Oa 2013</td>
<td>25.1</td>
<td>14.6</td>
<td>33</td>
<td>45.3</td>
<td>12</td>
</tr>
<tr>
<td>Tarak M 2010</td>
<td>23.8</td>
<td>12.1</td>
<td>97</td>
<td>45.6</td>
<td>18.43</td>
</tr>
<tr>
<td>Tarak M 2011</td>
<td>18.6</td>
<td>10.5</td>
<td>25</td>
<td>46</td>
<td>18.1</td>
</tr>
</tbody>
</table>

**Total (95% CI):**

- CNFD: 354
- CNBD: 286
- CNFL: 100.9%

**Heterogeneity:** Tau² = 0.08, Chi² = 6.92, df = 5 (P = 0.5973), I² = 0%

**Test for overall effect:** Z = 9.17 (P < 0.00001)

- C v DPN: P < 0.00001
- DPN v no-DPN: P < 0.00001
- C v no-DPN: P < 0.02

---

### DPN v no-DPN, P < 0.01

- C v DPN: P < 0.00001
- DPN v no-DPN: P < 0.0001
- C v no-DPN: P < 0.02

---

### C v no-DPN, P < 0.004

- C v DPN: P < 0.00001
- DPN v no-DPN: P < 0.0001
- C v no-DPN: P < 0.004
NIH: $750k

Prove that CCM is as good as Skin Biopsies!
Skin biopsy v CCM

Corneal confocal microscopy

Control

Diabetic

Skin biopsy v CCM

Skin biopsy v CCM for DPN

<table>
<thead>
<tr>
<th>Method</th>
<th>Sensitivity</th>
<th>Specificity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Auto CNFD</td>
<td>0.64</td>
<td>0.79</td>
</tr>
<tr>
<td>Manual CNFD</td>
<td>0.79</td>
<td>0.71</td>
</tr>
<tr>
<td>IENFD</td>
<td>0.53</td>
<td>0.77</td>
</tr>
</tbody>
</table>

Chen et al. Diabetes Care (Positive review)
FDA End Point?

1. Biomarker: a physical sign or laboratory measurement that occurs in association with a pathological process and has diagnostic or prognostic utility.

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Autonomic Neuropathy

**ROC Curve**

<table>
<thead>
<tr>
<th></th>
<th>AUC</th>
<th>Sensitivity</th>
<th>Specificity</th>
</tr>
</thead>
<tbody>
<tr>
<td>NFD</td>
<td>0.915</td>
<td>86%</td>
<td>78%</td>
</tr>
<tr>
<td>NFL</td>
<td>0.907</td>
<td>86%</td>
<td>78%</td>
</tr>
<tr>
<td>NBD</td>
<td>0.889</td>
<td>100%</td>
<td>56%</td>
</tr>
</tbody>
</table>

Painful v Painless

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Control (n=50)</th>
<th>Painless (n=50)</th>
<th>Painful (n=41)</th>
</tr>
</thead>
<tbody>
<tr>
<td>CNFD (no./mm²)</td>
<td>37.0±6.3</td>
<td>26.2±8.02*</td>
<td>20.2±10.7#</td>
</tr>
<tr>
<td>CNBD (no./mm²)</td>
<td>87.1±34.4</td>
<td>58.1±30.5*</td>
<td>46.4±32.5</td>
</tr>
<tr>
<td>CNFL (mm/mm²)</td>
<td>26.06±5.2</td>
<td>19.8±5.6*</td>
<td>15.7±7.8#</td>
</tr>
</tbody>
</table>
“Look into my eyes to predict my amputation risk”
March 2011
Retinopathy is the earliest Microvascular Complication
Correlation of Diabetic Retinopathy and Corneal Neuropathy Using Confocal Microscopy

<table>
<thead>
<tr>
<th></th>
<th>Control (n = 47)</th>
<th>NDR (n = 46)</th>
<th>NPDR (n = 47)</th>
<th>PDR (n = 46)</th>
<th>ANCOVA Test statistic</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>NFD (fibers/mm²)</td>
<td>31.3 (1)</td>
<td>27.4 (0.8)</td>
<td>23.7 (0.8)</td>
<td>18.8 (0.8)</td>
<td>35.5</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>NBD (branches/mm²)</td>
<td>45.1 (2.8)</td>
<td>39.9 (3)</td>
<td>30.6 (2.7)</td>
<td>25.0 (2.1)</td>
<td>9.1</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>NFL (mm/mm²)</td>
<td>16.6 (0.6)</td>
<td>14.8 (0.6)</td>
<td>12.3 (0.5)</td>
<td>10.4 (0.5)</td>
<td>23.7</td>
<td>&lt;0.0001</td>
</tr>
</tbody>
</table>

**P = 0.008**

**P < 0.0001**
Corneal nerve fibre damage precedes diabetic retinopathy in patients with Type 2 diabetes mellitus

Bitirgen G et al. Diabetic Medicine 2014; 31: 431-8
Neuropathy precedes Retinopathy & Microalbuminuria

53 T1DM

PloS 1 (positive review)
Corneal Confocal Microscopy Detects Neuropathy in Subjects With Impaired Glucose Tolerance.

CONTROLS

IGT

P < 0.01

Neuropathy cut-off

Asghar, Petropoulos et al. Diabetes Care 2014; 37: 2643-46
Early Detection of Nerve Fiber Loss by Corneal Confocal Microscopy and Skin Biopsy in Recently Diagnosed Type 2 Diabetes

Diabetes Duration- 2.1 yrs, HbA1c- 6.8%

<table>
<thead>
<tr>
<th></th>
<th>Diabetic group (n = 86)</th>
<th>Control group (n = 48)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>CNFL (mm/mm²)</td>
<td>19.7 ± 7.5</td>
<td>24.9 ± 6.5</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>CNFL-MNF (mm/mm²)</td>
<td>9.8 ± 3.6</td>
<td>11.9 ± 2.9</td>
<td>0.001</td>
</tr>
<tr>
<td>CNFD (n/mm²)</td>
<td>299.2 ± 152.8</td>
<td>397.3 ± 165.3</td>
<td>0.001</td>
</tr>
<tr>
<td>CNFD-MNF (n/mm²)</td>
<td>58.2 ± 23.4</td>
<td>73.1 ± 17.9</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>CNBD (n/mm²)</td>
<td>165.2 ± 96.4</td>
<td>226.7 ± 103.1</td>
<td>0.001</td>
</tr>
<tr>
<td>IENFD (n/mm)</td>
<td>8.3 ± 3.0</td>
<td>10.6 ± 3.6</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

Ziegler et al. Diabetes 2014; 63: 2454-2463
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JDRF: $3.5M
Normative Values (6 centre study: n=343)

CNFD $\sim -1.6/mm^2/\text{decade}, P<0.01$

CNFL $\sim -0.5/mm^2/\text{decade}, P<0.02$

CNBD $\sim +1.9/mm^2/\text{decade}, P=0.26$

Tavakoli et al Diabetes Care (under review)
Natural History of Corneal Nerve Morphology in Mild Neuropathy Associated with Type 1 Diabetes: Development of a Potential Measure of Diabetic Peripheral Neuropathy

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NIH- $1.5M

Prove that CCM improves with intervention!
Conversation in the corridor with a friend and colleague: Transplant Surgeon
Pancreas Transplantation

Corneal Confocal Microscopy Detects Early Nerve Regeneration After Pancreas Transplantation in Patients With Type 1 Diabetes

ORIGINAL ARTICLE

Corneal Confocal Microscopy Detects Early Nerve Regeneration in Diabetic Neuropathy After Simultaneous Pancreas and Kidney Transplantation
Corneal confocal microscopy detects improvement in corneal nerve morphology with an improvement in risk factors for diabetic neuropathy


Multiple Risk Factor improvement

- **P=0.08**
- **P=0.01**
- **P=0.05**
- **P=0.09**
- **P=0.03**
- **P=0.008**
Almost 2 years ago...

On 21 Feb 2013, at 12:17, "A Cerami" <acarami@araimpharma.com> wrote:

Dear Dr Malik-- Dr Duncan McGrouther of the Department of Surgery at Manchester with whom we collaborate suggested that I write you about a clinical program that we are pursuing. I have followed your work on CCM for a number of years and appreciate its potential for studying small fiber neuropathy, especially with regard to therapeutics. For a number of years we have been developing a new agent, ARA290, which has the ability to turn off inflammation and turn on repair in many tissues in a number of different animal models. During the last two years we have been studying patients with sarcoidosis and diabetes at the Leiden University Medical Center in the Netherlands. I have attached a paper which describes our first phase 2 study in sarcoidosis. We have recently completed another trial using a subcutaneous formulation in which we measured CCM at the beginning and after thirty days of daily administration and observe a difference between the treated and placebo groups. We would be most interested in discussing our results with you since we are planning to carry out a new trial in diabetes in the near future. Your insights would be gratefully received.

With best wishes,

Tony Cerami
Automated Analysis (CCMetrics/ACCMetrics)
http://www.click2go.umip.com/i/software/Biomedical_Software/ccmetrics.html


30 min

25 sec

Scatter Plot of Manually and Automatically Extracted NFL

- Controls
- Non-neuropathic
- Neuropathic

$r = 0.9656$
ARA 290, a non-erythropoietic peptide engineered from erythropoietin, improves metabolic control and neuropathic symptoms in patients with type 2 diabetes.

ARA-290: +2.6 ± 1.0 fibers/mm², P=0.02
Placebo: 0.7 ± 1.3 fibers/mm², P=ns
**Other Peripheral Neuropathies**

**CORNEAL CONFOCAL MICROSCOPY: A NOVEL NONINVASIVE MEANS TO DIAGNOSE NEUROPATHY IN PATIENTS WITH FABRY DISEASE**

MITRA TAVAKOLI, PhD, MSc, ANDREW MARSHALL, MRCP, LORRAINE THOMPSON, BSc, MARGARET KENNY, BSc, STEPHEN WALDEK, MD, NATHAN EFRON, PhD, DSc, and RAYAZ A. MALIK, PhD, FRCP


**Corneal confocal microscopy: A novel means to detect nerve fibre damage in idiopathic small fibre neuropathy**

Mitra Tavakoli, Andrew Marshall, Robert Pitcaithy, Hassan Fadavi, David Gow, Mark E. Roberts, Nathan Efron, Andrew JM Boulton, Rayaz A. Malik

**CORNEAL CONFOCAL MICROSCOPY DETECTS SMALL-FIBER NEUROPATHY IN CHARCOT-MARIE-TOOTH DISEASE TYPE 1A PATIENTS**

MITRA TAVAKOLI, MSc, PhD, ANDY MARSHALL, MD, FRCP, SIDDHARTH BANKA, MBBS, MRCPCh, IOANNNIS N. PETROPOULOS, MSc, HASSAN FADAVI, MD, HELEN KINGSTON, MD, FRCP, and RAYAZ A. MALIK, MBChB, PhD

Sarcoid Neuropathy

**CNFD**

Nerve Fibers/mm²

**CNFL**

Nerve Fiber length [mm/mm²]

**CNBD**

Nerve Branches/mm²

**IENFD foot vs CNFL**

IENFD = 0.37 * CNFL; p < 0.0001

**BPI pain interference**

BPI pain interference = -1.4 * CNFL + 52.3; p < 0.0005
Central Neurological Conditions?
Corneal confocal microscopy reveals trigeminal small sensory fiber neuropathy in amyotrophic lateral sclerosis

**ALS-FRS Bulbar score**

$r=0.764$, $P<0.02$

Ferrari et al. Front Age Neurosci 2014; 6: 1-4
Parkinson’s Disease

PD Controls

CNFD (no./mm²)  P = 0.002

CNFL (no./mm²)  P = 0.025

P = 0.002

P = 0.025
Control

MS with no optic neuritis
MS with no optic neuritis (RE)  

MS with optic neuritis (LE)
Reverse Translation

Sprague Dawley rat

NOD mouse/ZDF rat

Chen DK et al. Neurodiab 2011, UCSD
Reichard et al EASD 2011, ARVO 2012
Future Projects

Chemotherapy Induced Neuropathy ✔
Sarcoidosis ✔
Parkinson’s ✔
CIDP ✔
Obesity (Bariatric Surgery) ✔
Freidrich’s Ataxia
Dementia
Stroke
MS
HIV neuropathy
ARA 290 Phase 2b
......
Translational Impact
FDA End Point?

1. **Biomarker**: a physical sign or laboratory measurement that occurs in association with a pathological process and has **diagnostic** or **prognostic** utility.

2. **Clinical endpoint**: A clinically meaningful measure of how a patient feels, functions or survives.

3. **Surrogate Endpoint**: Biomarker intended to substitute for a clinical endpoint and is expected to predict the effect of **therapeutic intervention**.
“He who is not courageous enough to take risks will accomplish nothing in life”

Muhammad Ali
Thank you

JD Ward
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G Sundkvist
N Efron
M Jeziorska
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M Tavakoli
P Kallinikos
C Quattrini
H Fadavi
M Dabbah
M Mojaddidi
A Al-Sunni
U Alam
I Petropoulos
O Asghar
G Ponirakis
S Ahmed
X Chen

http://qatar-weill.cornell.edu
http://www.medicine.manchester.ac.uk/ena/