‘Corneal Confocal Microscopy: A new way of Screening & Early Detection of Diabetic Neuropathy

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Press release

“Diabetes no longer leading cause of blindness thanks to screening”

“For the first time in over 50 years diabetic eye disease is no longer the leading cause of blindness in adults of working age. Although many factors have likely contributed to the results, it is safe to say that public health interventions such as screening have played a key role.”

Screening for Microvascular Complications

- Defines at risk patients
- Anticipates deterioration
- Enables assessment of new therapies

- **Retinopathy** (fundus photography/OCT)
  - **NOT** the Leading cause of blindness in working age adults in the UK

- **Nephropathy** (microalbuminuria/eGFR)
  - Leading cause of end-stage renal disease

- **Neuropathy** *(No similar surrogate)*
  - Leading cause of non-traumatic lower extremity amputations
New figures have revealed that the number of diabetes-related amputations each week in England has now reached an all-time record high of 135, according to new analysis by Diabetes UK.

The figures, calculated using new Public Health England data, show that the annual number of diabetes-related amputations in England is now more than 7,000, compared to the previous figure of 6,677. This equates to seven more amputations each week. Yet, with good diabetes and footcare, up to 80 per cent of these amputations can be avoided.

The figures show that despite a big focus on preventing these amputations, the amputation rate for major and minor amputations combined in people with diabetes has stayed the same. And because of the sharp increase in the number of people with diabetes in the past 20 years, the number of diabetes-related amputations is rising.

There is, though, some positive news in that the major amputation rate (classed as amputations above the ankle) has decreased slightly since Diabetes UK launched the Putting Feet First campaign in 2012.

Diabetes UK is calling on the Government and the NHS to do more to tackle the problem of diabetes-related amputation by improving diabetes footcare. This includes ensuring everyone with diabetes gets good quality annual foot checks and that anyone who has a foot problem gets the right care to prevent or treat it. It is particularly important that if anyone with diabetes has a foot infection they get urgent attention from a team of specialists.
The Financial Cost of Diabetic Foot

Estimated NHS cost in England = £972m.-£1.13 bn. in 2014-15

£1 in every £140 the NHS spends

Only 50% of people with diabetes who have an amputation survive for two years.(2)

1. Kerr et al. Insight Health Economics 2017
PAIN

ULCERATION AMPUTATION

Which Test?

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

- Relevance to end points?
  Pain/ulceration
Consequence of late Diagnosis

“How we think determines what we measure”
-A Einstein
A 21st Century Approach: Corneal Confocal Microscopy

- Rapid (2 minutes)
- Non-invasive (in vivo)
- Reiterative
- en-face view images of corneal structure
Corneal Innervation

• Cornea is the most densely innervated tissue of the human body.

• Corneal innervation is derived from the Trigeminal nerve.

• Unmyelinated C nerve fibres & Myelinated A-δ

Corneal Nerve Quantification

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

Intra observer variability-ICC-0.74-0.95
Inter observer variability-ICC-0.93-0.95

Tavakoli M, et al., Journal of Visualized Experiments (JOVE), 2011, 47, 2194
Corneal Confocal Microscopy: A Surrogate End Point

CCM has been clinically proven in adults for:

- Objective early diagnostic test of diabetic neuropathy (1-3)
- Assesses Intervention/therapeutic response (4-5)
- High Reproducibility & Sensitivity (6-7)
- Correlation with pathology (pathogenic process) (1,3,8, 9)
- Correlation with functional changes (biologic process) (10, 11)
- Other Neuropathies (12-16)

- Established Normative reference values (17)

CCM: Neuropathy Screening tool
The Wilson-Jungner Criteria (WJC)

1. An important health problem.
2. Treatment at an early stage more beneficial than at a later stage.
3. Physical and psychological risks - less than the benefits.
4. The costs - balanced against the benefits.
5. Adequate health service resources provided for the extra workload resulting from screening.
6. The condition’s natural history – to be well understood.
7. Detectable early stage.
8. Suitable test - devised for the early stage.
9. The test - acceptable.
10. Intervals for repeating the test – to be determined.

Adapted from World Health Organisation 1968
From Research to Practice:

Screening for Diabetic Neuropathy
Implementation of Corneal Confocal Microscopy for Screening Diabetic Neuropathy alongside Diabetic Retinopathy Screening Programme

A Feasibility Study
135 DIABETES VICTIMS EACH WEEK HAVE AMPUTATIONS

Some crisis fuels shock surge in disease-related ones costing NHS £2billion

Diabetic? One quick trip to the optician’s could save your...leg: Two-minute eye test detects early signs of nerve damage

- Test uses a probe with a camera to scan the eye for early signs of damage
- Diabetics are at particularly high risk of condition known as neuropathy
- They suffer damage to nerves that transmit impulses from brain to body
- Can lead to complications in limbs and amputations if not caught early

By KATHERINE KEOGH FOR THE MAIL ON SUNDAY
PUBLISHED: 22.02.15 | UPDATED: 13.03.10 May 2015

Optom trial to scan cornea for diabetic nerve damage

Researchers at the University of Manchester are embarking on a six-month project to screen patients for diabetic nerve damage by scanning the nerves of the cornea. If successful, the technique could form part of the diagnostic arsenal of community optometrists. The £200,000 project, which is part-funded by Heidelberg Engineering, will be carried out at four optometry practices in Greater Manchester and aims to assess the feasibility of a community approach, alongside diabetic retinopathy screening.

Diabetic neuropathy is a common long-term complication of diabetes which affects the nerves. It mainly affects the legs and feet and can lead to ulceration and even amputation of a limb.
Screening for Early Detection of Diabetic Neuropathy in Newly Diagnosed Type 2 Diabetes alongside of Retinopathy Screening
450 DM Patients and 70 Healthy Subjects have been screened with CCM for Diabetic Neuropathy in 4 primary care optometry practices

(South Manchester Screening Programme)

97 T2DM patients with Duration of Diabetes < 1.4 year

67 Healthy Control Subjects
## Demographic Data

<table>
<thead>
<tr>
<th></th>
<th>Controls</th>
<th>T2DM Patients</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>NUMBER</strong></td>
<td>67</td>
<td>97</td>
</tr>
<tr>
<td><strong>GENDER (F/M) (% male)</strong></td>
<td>26/41 (61%)</td>
<td>35/62 (63%)</td>
</tr>
<tr>
<td><strong>DURATION DIABETES</strong></td>
<td>0</td>
<td>1.04 ±0.07</td>
</tr>
<tr>
<td><strong>AGE (Years)</strong></td>
<td>62±14</td>
<td>63±12</td>
</tr>
</tbody>
</table>

### Ethnicity Diagram

- White: 80.43%
- Black/African/Caribbean: 14.13%
- Other: 3.26%
- Black British: 2.17%
- Asian/Asian British: 9.20%

### Age Groups

- 30-45 years: 57.47%
- 46-60 years: 33.33%
- 61-85 years: 9.20%
Retinopathy

History of Retinopathy

Current Grade Retinopathy - R*

Current Grade Retinopathy - M*

*Classification based on Early Treatment of Diabetic Retinopathy Study (ETDRS)
History of DN & Foot

History of Diabetic Neuropathy

- History DN
  - No: 94.57%
  - Yes: 5.43%

History of Foot Ulcer

- History of Foot Ulcer
  - No: 93.74%
  - Yes: 3.26%
Neuropathy Symptoms (DNS)

- Burning Sensation
  - No: 0.43%
  - Yes: 19.57%

- Unsteadiness
  - No: 84.78%
  - Yes: 15.22%

- Numbness
  - No: 84.78%
  - Yes: 15.22%

- Prickling
  - No: 90.22%
  - Yes: 9.78%
## CCM Results

<table>
<thead>
<tr>
<th></th>
<th>Controls</th>
<th>Diabetes</th>
<th>P-Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>A-CNFD (no/mm²)</td>
<td>29.14 ±6.81</td>
<td>23.83 ±7.85</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>A-CNBD (no/mm²)</td>
<td>41.14 ±18.56</td>
<td>33.42 ±16.36</td>
<td>0.007</td>
</tr>
<tr>
<td>A-CNFL (mm/mm²)</td>
<td>17.40 ±3.36</td>
<td>14.39 ±3.34</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>BEADING Pixel Size</td>
<td>184.11±4.49</td>
<td>237.59±19.91</td>
<td>&lt;0.0001</td>
</tr>
</tbody>
</table>

![Image of retina with labels CRL, No DR, BDR, PDR]
Corneal Nerves

- Corneal Nerve Fibre Density: P<0.0001
- Corneal Nerve Branch Density: P=0.006
- Corneal Nerve Fibre Length: P<0.0001
Prevalence of Abnormality

- Percentages of CCM measures below the 2.5th percentile limit of normal in the diabetic and control groups studied

<table>
<thead>
<tr>
<th></th>
<th>Controls (No)</th>
<th>T2DM (No)</th>
<th>Percentage abnormal cases (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>A-CNFD</td>
<td>1 (1.4%)</td>
<td>14</td>
<td>14.43%</td>
</tr>
<tr>
<td>A-CNBD</td>
<td>0</td>
<td>3</td>
<td>3.02%</td>
</tr>
<tr>
<td>A-CNFL</td>
<td>1</td>
<td>17</td>
<td>17.52%</td>
</tr>
</tbody>
</table>
Lessons from other studies

Dan Ziegler,1,2 Nikolaos Papanas,1 Andrey Zhirov,3 Stephan Allgeier,4 Karsten Winter,5 Iris Ziegler,1 Jutta Brüggenmann,1 Alexander Strom,1 Sabine Peschel,3 Bernd Köhler,6 Oliver Stachs,3 Rudolf F. Guthoff,3 and Michael Roden,1,2 for the German Diabetes Study (GDS) Group*

Early Detection of Nerve Fiber Loss by Corneal Confocal Microscopy and Skin Biopsy in Recently Diagnosed Type 2 Diabetes

Diabetes 2014;63:2454–2463 | DOI: 10.2337/db13-1819

<table>
<thead>
<tr>
<th></th>
<th>Diabetic group, % (95% CI)</th>
<th>Control group, % (95% CI)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>CNFL</td>
<td>18.6 (12.0–26.9)</td>
<td>4.2 (0.8–12.5)</td>
<td>0.019</td>
</tr>
<tr>
<td>CNFL-MNF</td>
<td>17.4 (11.1–25.6)</td>
<td>6.3 (1.7–15.4)</td>
<td>0.111</td>
</tr>
<tr>
<td>CNFD</td>
<td>5.8 (2.3–11.8)</td>
<td>0</td>
<td>0.160</td>
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<tr>
<td>CNFD-MNF</td>
<td>20.9 (14.0–29.4)</td>
<td>6.3 (1.7–15.4)</td>
<td>0.027</td>
</tr>
<tr>
<td>CNBD</td>
<td>4.7 (1.6–10.3)</td>
<td>0</td>
<td>0.296</td>
</tr>
</tbody>
</table>
Conclusion

- The level of neuropathy symptoms that reported by newly diagnosed T2DM patients was interestingly high.

- The prevalence of background retinopathy was considerably high.

- There was a significant level of small fibre damage at corneal nerves of this cohort of newly diagnosed T2DM.

- Corneal Confocal microscopy can detect neuropathy at early stages and be used as screening method.
“We must learn to measure what we value rather than valuing what we can easily measure”. - Unknown
“I marvel that society would pay a surgeon a large sum of money to remove a person’s leg— but nothing to save it.”

- George Bernard Shaw