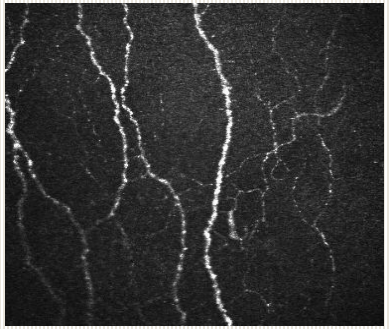
‘Corneal Confocal Microscopy: A new way of Screening & Early Detection of Diabetic Neuropathy



Mitra Tavakoli
BSc (Hons), MSc, PhD, MCOptom, FBCLA, FAAO

Senior Lecturer in Medicine,
University of Exeter Medical School

GOV.UK

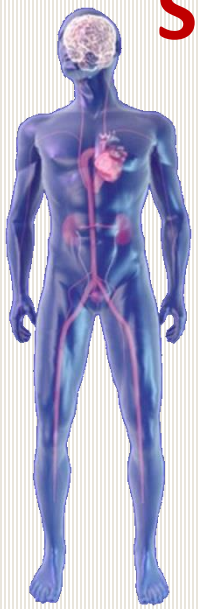
Press release

“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.”

Liew. G et al. BMJ Open 2014

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

mirror.co.uk

DAILY Mirror NEWSPAPER OF THE YEAR Wednesday, July 15, 2015 60P

EXCLUSIVE

Peter Andre in High Court..not on honeymoon

SEE PAGE 11

GROUNDED Peter Andre at court yesterday. Far left, ex-wife Katie Price

135 DIABETES VICTIMS EACH WEEK HAVE AMPUTATIONS

Obesity crisis fuels shock surge in disease-related ops costing NHS £2billion

BY MARTIN BAGOT

AMPUTATIONS due to diabetes have soared to 135 a week – yet four in five could be prevented, experts say.

As Type 2 diabetes rockets with the worsening obesity crisis, the NHS has spent £2billion in three years on amputations that could be avoided with better patient care.

Barbara Young of Diabetes UK said: "We need urgent action."

FULL STORY: PAGES 4&5

DIABETES UK
CARE. CONNECT. CAMPAIGN.

More than 135 diabetes amputations every week

Wednesday 15 July 2015

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.

Diabetes-related amputations figure rising

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.

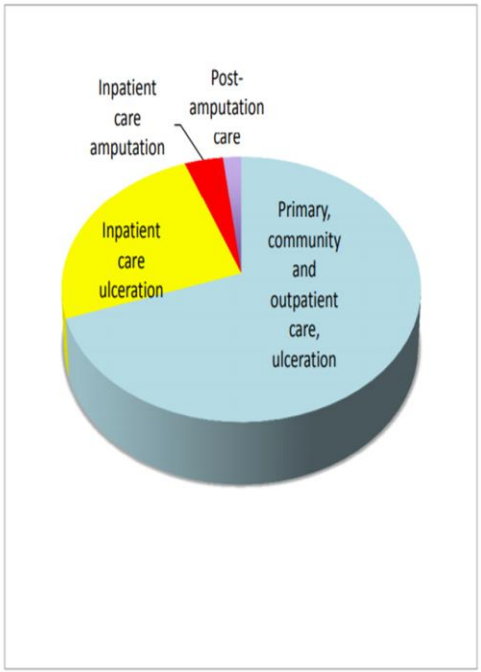
There is, though, some positive news in that the major amputation rate (classed as amputations above the ankle) has decreased slightly since Diabetes UK launched the Putting Feet First campaign in 2012.

Diabetes UK calls on Government and NHS to act

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

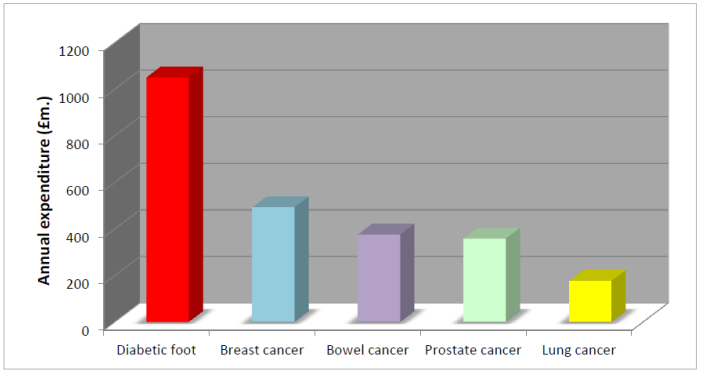
Only 50% of people with diabetes who have an amputation survive for two years.(2)

Costs in context

Insight Health Economics

Estimated NHS cost is higher than the combined annual cost of three of the four most common cancers

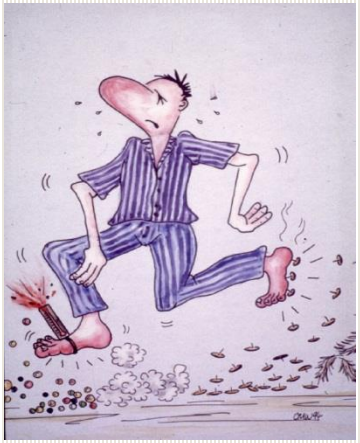
(Source for cancer costs: NHS Programme Budgeting 2012-13, inflation-adjusted)

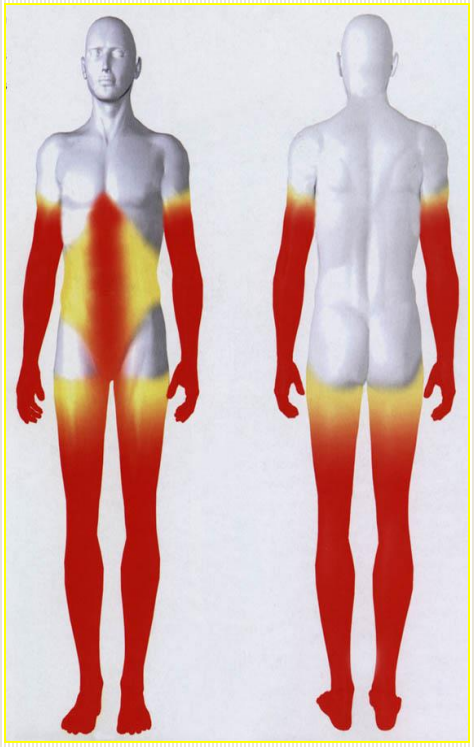


1. Kerr et al. Insight Health Economics 2017
2. Brownrigg JR et al. Diabetologia 2012; 55(11):2906-12

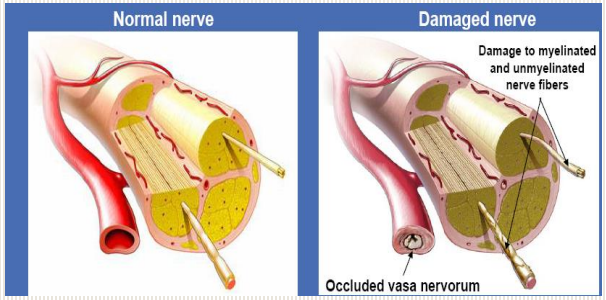
DIABETIC NEUROPATHY

PAIN





ULCERATION
AMPUTATION



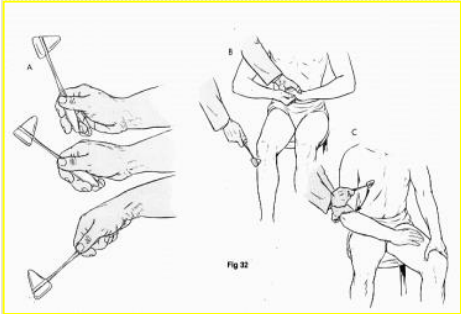
Tavakoli M. Expert Opinion on Pharmacotherapy 2008; 9 (17): 2969-78.

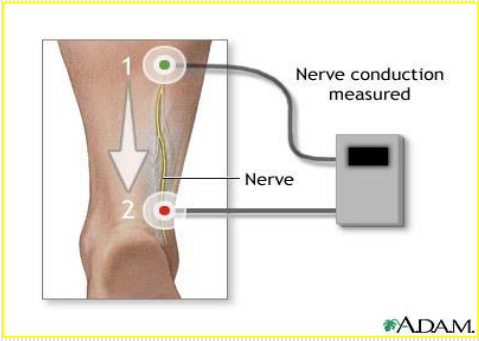
Which Test?

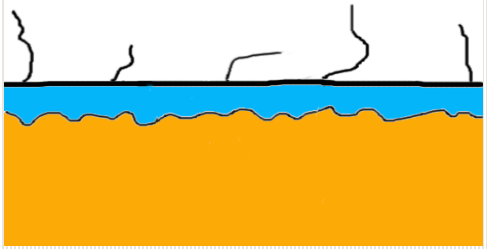
- Neurological examination
- 10g monofilament
- Vibration perception threshold
- Electrophysiology (NCS)

- **Relevance to end points?**

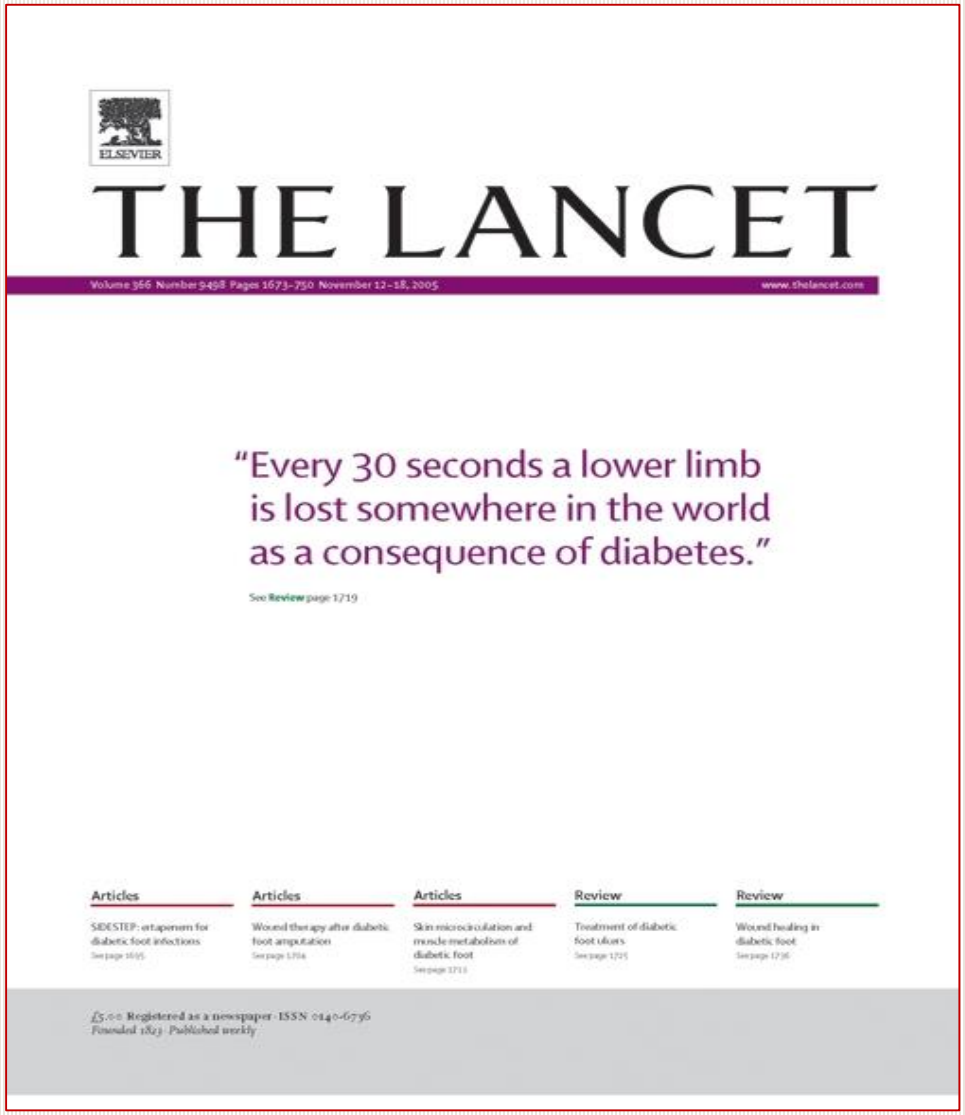
Pain/ulceration







Consequence of late Diagnosis



ELSEVIER

THE LANCET

Volume 366 Number 9498 Pages 1673–750 November 12–18, 2005 www.thelancet.com

"Every 30 seconds a lower limb is lost somewhere in the world as a consequence of diabetes."

See Review page 1719

Articles
SIDESTEP: ertapenem for diabetic foot infections

Articles
Wound therapy after diabetic foot amputation

Articles
Skin microcirculation and muscle metabolism of diabetic foot

Review
Treatment of diabetic foot ulcers

Review
Wound healing in diabetic foot

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Founded 1823 · Published weekly

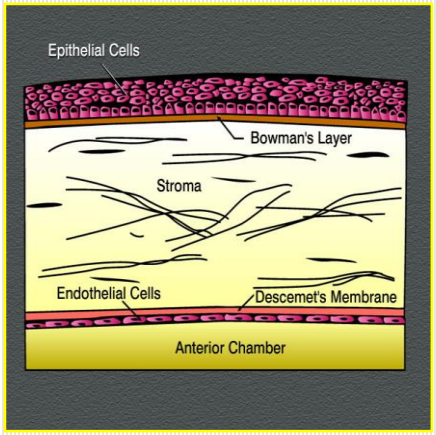
Boulton AJ, et al. *Lancet* 2005, 12; 366 (9498):1719-24

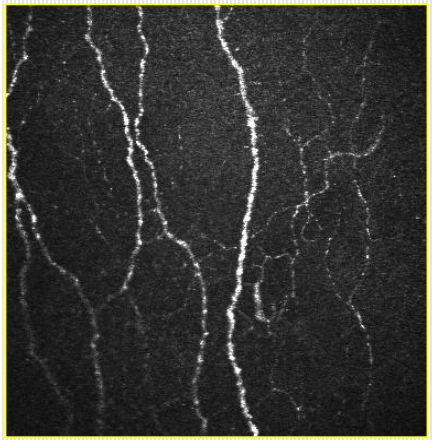
“How we think determines what we measure”

-A Einstein

A 21st Century Approach:
Corneal Confocal Microscopy

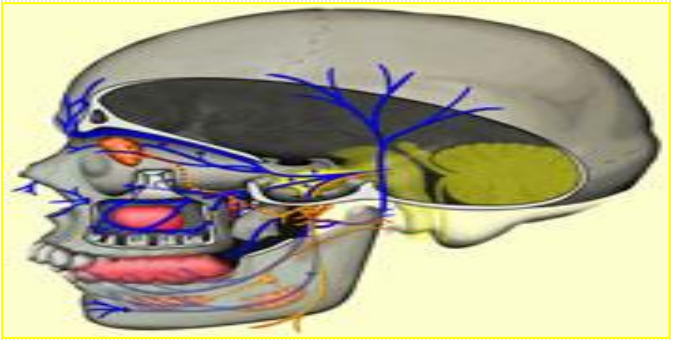
- Rapid (2 minutes)
- Non-invasive (in vivo)
- Reiterative
- en-face view images of corneal structure

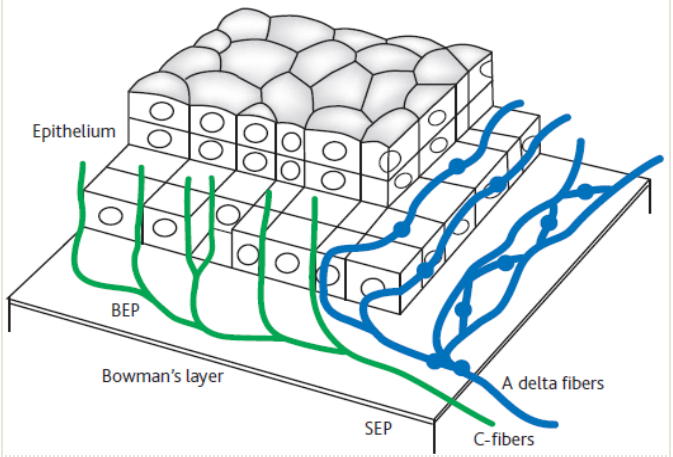


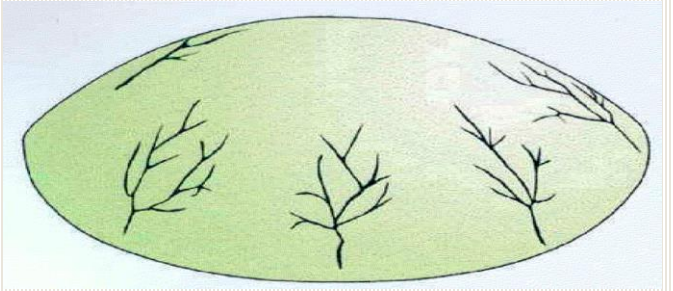


Corneal Innervation

- 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



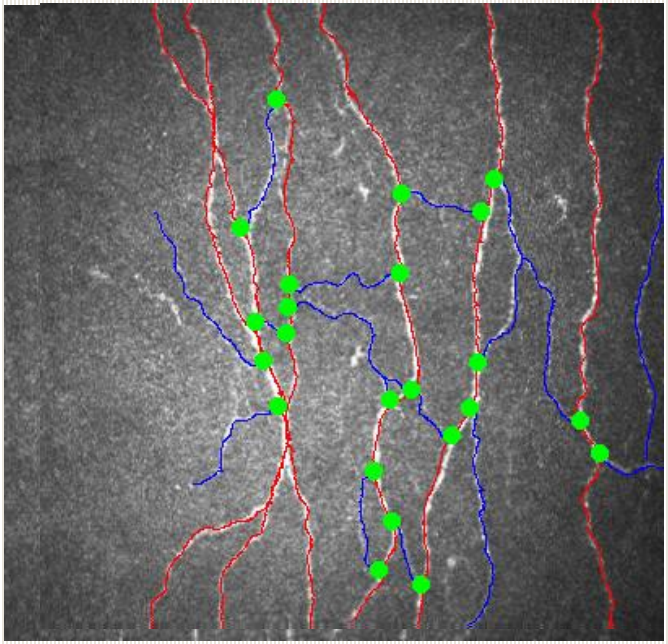




Müller et al. *Exp Eye Res* 2003;76(5):521-42
Tavakoli M, et al Clinical and Experimental Optometry, 2012; 95:338-347.

Corneal Nerve Quantification

- CCM (6 images/patient)
  CNFD (no./mm^2) + TC (Red)
  CNFL (mm/mm^2) (Red + Blue)
  CNBD (no./mm^2) (Green)



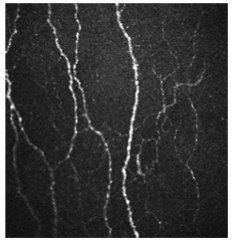
CCMetrics®, M. A. Dabbah, University of Manchester, Imaging Science and Biomedical Engineering, School of Cancer and Enabling Sciences.

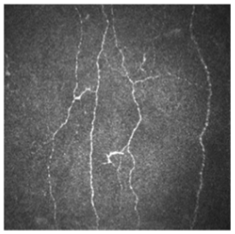
Intra observer variability-ICC-0.74-0.95
Inter observer variability-ICC-0.93-0.95

Tavakoli M, et al., Journal of Visualized Experiments (JOVE), 2011, 47, 2194
Petropolous I et al. Cornea. 2013;32(5):e83-9.

NHS
National Institute for Health Research

Corneal Confocal Microscopy: A Surrogate End Point





CCM has been clinically proven in adults for:

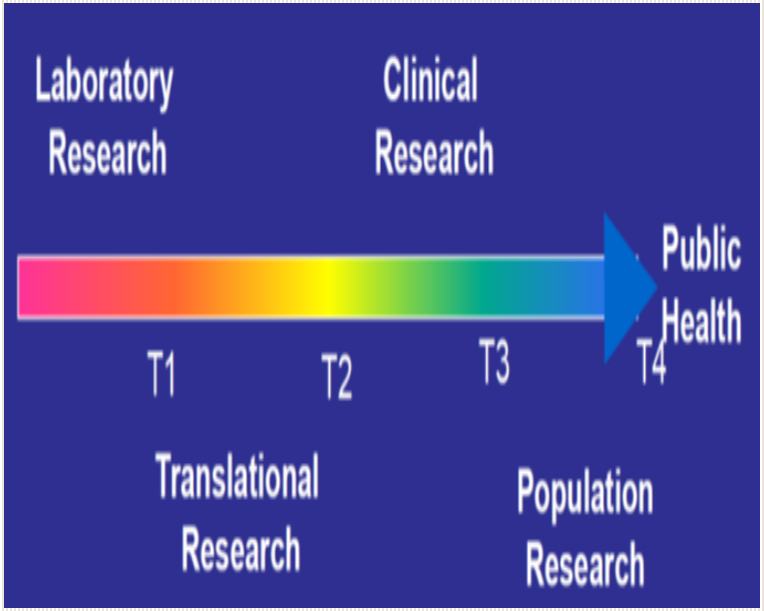
- Objective early diagnostic test of diabetic neuropathy (1-3)
- Assesses Intervention/therapeutic response (4-5)
- High Reproducibility & Sensitivity (6-7)
- Correlation with pathology (pathogenic process) (1,3,8, 9)
- Correlation with functional changes (biologic process) (10, 11)
- Other Neuropathies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

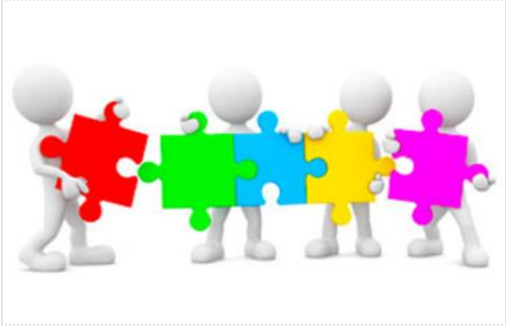
- Established Normative reference values (17)

1.**Tavakoli M**, et al. Diabetes Care. 2010; 33(8):1792-7. 2.Petropoulos IN, et al. Diabetes Care. 2013; 36(11):3646-51. 3. Ziegler D, et al. Diabetes. 2014; 63(7):2454-63 4. **Tavakoli M**, et al. Diabet Med. 2011; 28(10):1261-7. 5. **Tavakoli M**, et al. Diabetes. 2013; 62(1):254-60. 6. Petropoulos IN, Cornea. 2013;32(5):e83-9. 7. Hertz P, et al. Diabet Med. 2011; 28(10):1253-60; 8. Quattrini C, Diabetes. 2007; 56(8):2148-54. 9. Sivaskandarajah GA. Diabetes Care. 2013; 36(9):2748-55. 10.**Tavakoli M**, et al. Diabetes Care. 2007; 30(7):1895-7. 11.Pritchard N, et al. Clinical & experimental optometry. 2012;95(3):355-61. 12.**Tavakoli M**, et al. Muscle & nerve. 2012; 46(5):698-704. 13. **Tavakoli M**, et al. Exp Neurol. 2010; 223(1):245-50. 14. **Tavakoli M**, et al. Muscle Nerve.2009; 40(6):976-84; 15. Asghar O, et al. Diabetes Care. 2014; 37: 2643-; 16. Azmi et al. Diabetes Care 2015 (In Press); 17. **Tavakoli M**, et al. Diabetes Care, 2015;38:838-843

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

NHS National Institute for Health Research

Screening for Diabetic Neuropathy

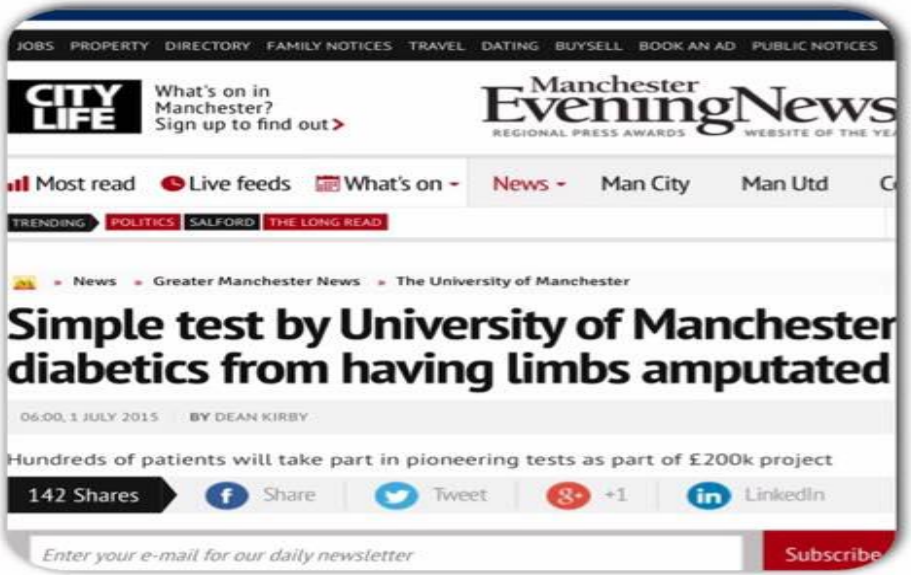
Implementation of Corneal Confocal Microscopy for Screening Diabetic Neuropathy alongside Diabetic Retinopathy Screening Programme

A Feasibility Study


High Court..not on honeymoon

135 DIABETES VICTIMS EACH WEEK HAVE AMPUTATIONS

besity crisis fuels shock surge in disease-related ops costing NHS £2billi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Simple test by University of Manchester diabetics from having limbs amputated

06:00, 1 JULY 2015 BY DEAN KIRBY

Hundreds of patients will take part in pioneering tests as part of £200k project

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The iScam: Con artists freeze iPad

Stormin' Corbyn on course to WIN the

Revealed: How Britain's image-

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 damag
- 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, 9 May 2015 | UPDATED: 13:03, 10 May 2015

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Optom trial to scan cornea for diabetic nerve damage

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APRIL 30 2015

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

Screening for Early Detection of Diabetic Neuropathy in Newly Diagnosed Type 2 Diabetes alongside of Retinopathy Screening

Study Population

NHS National Institute for Health Research

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)

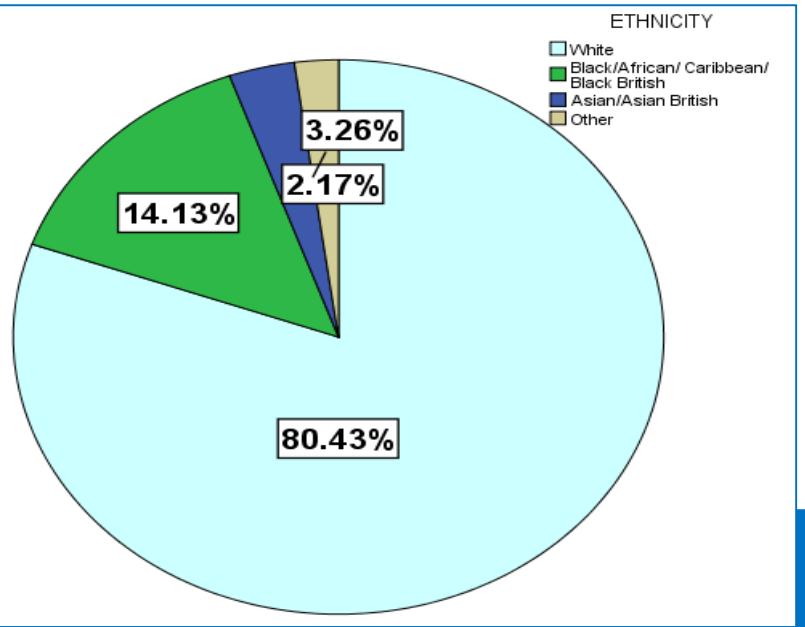
97 T2DM patients with Duration of Diabetes < 1.4 year

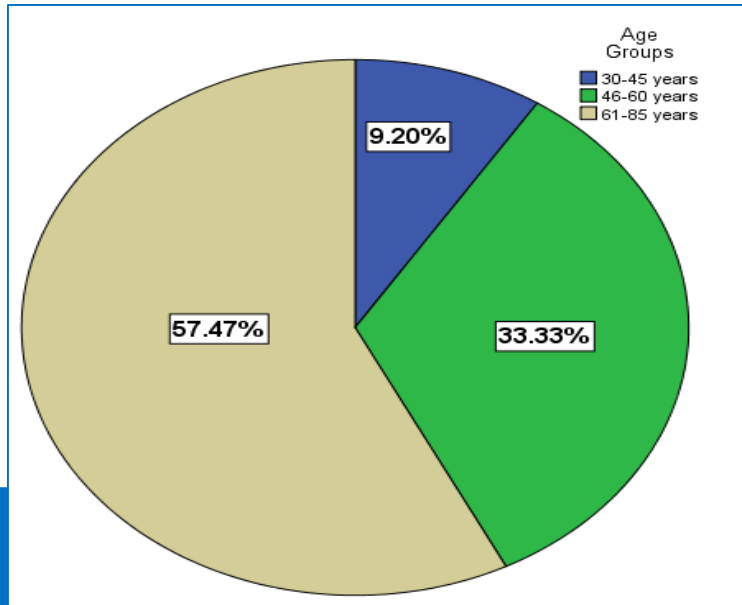
67 Healthy Control Subjects

Demographic Data

NHS National Institute for Health Research

	Controls	T2DM Patients	
NUMBER	67	97	
GENDER (F/M) (% male)	26/41 (61%)	35/62 (63%)	
DURATION DIABETES	0	1.04 ±0.07	
AGE (Years)	62±14	63±12	

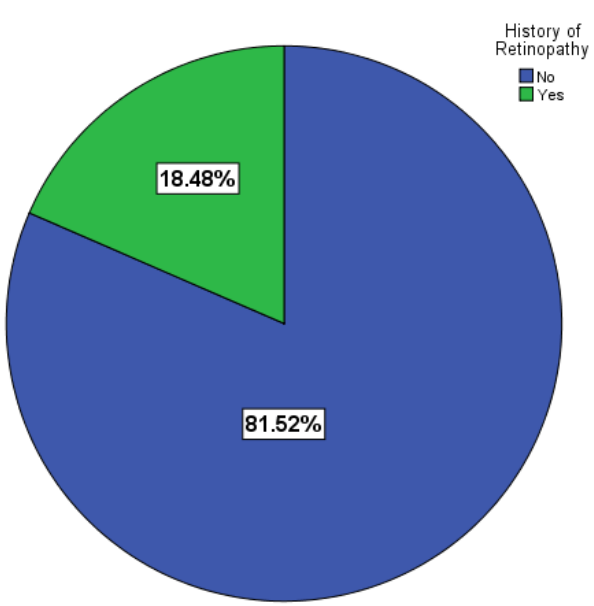




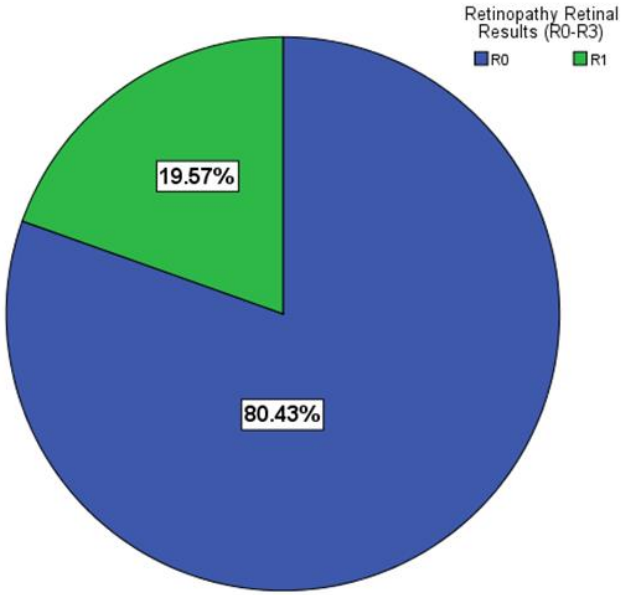
Retinopathy

NHS National Institute for Health Research

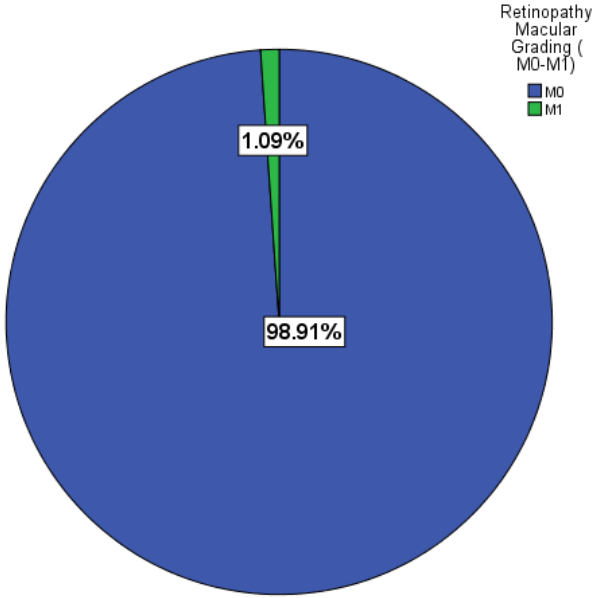
History of Retinopathy



Current Grade Retinopathy- R*



Current Grade Retinopathy- M*

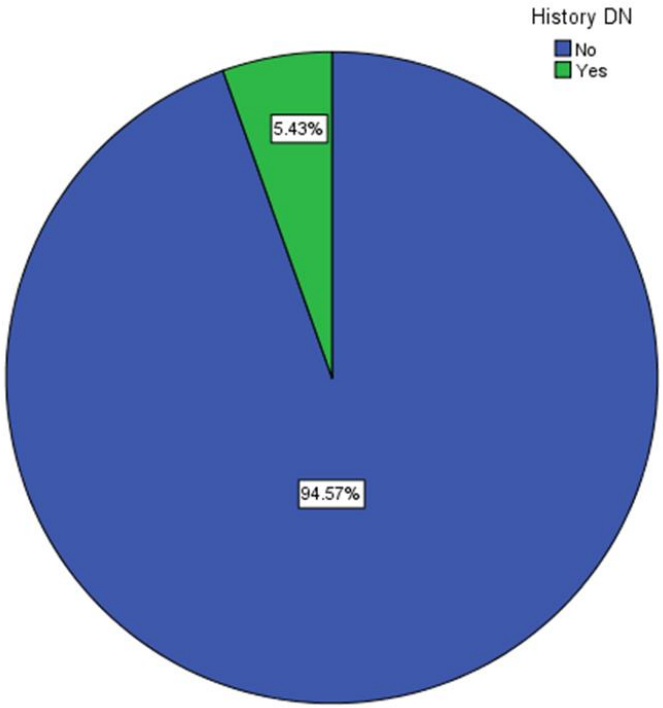


*Classification based on Early Treatment of Diabetic Retinopathy Study (ETDRS)

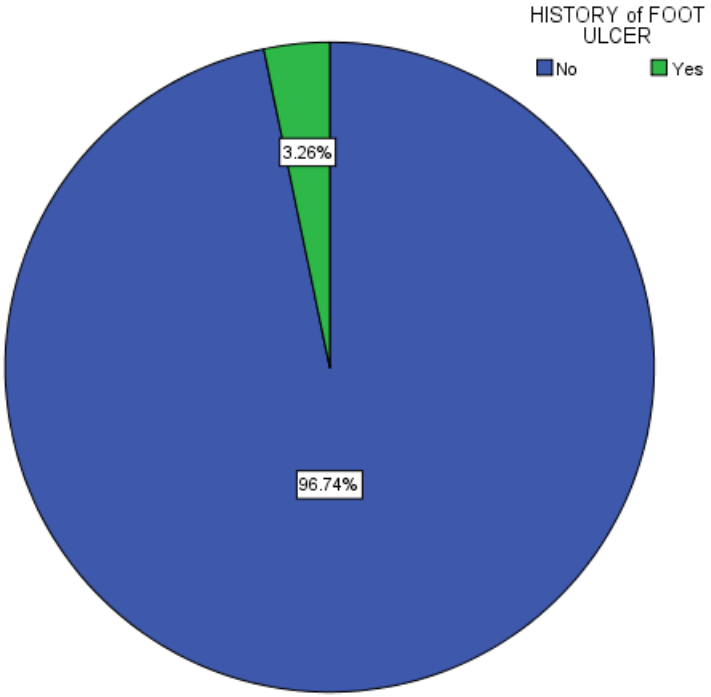
History of DN & Foot

National Institute for Health Research

History of Diabetic Neuropathy

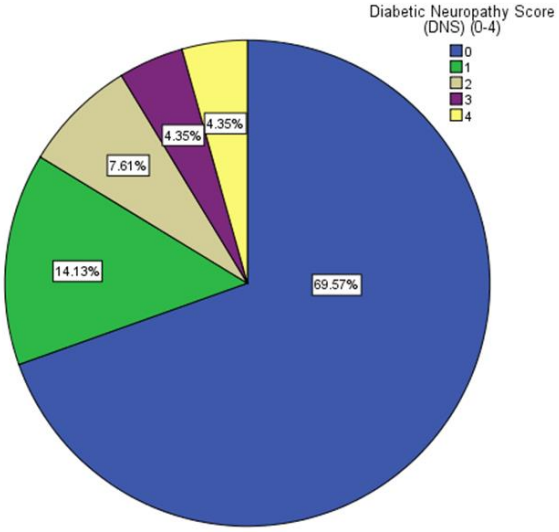


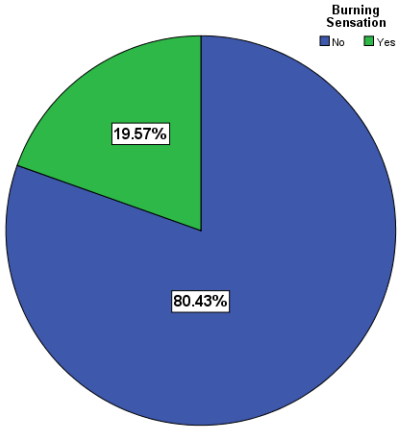
History of Foot Ulcer

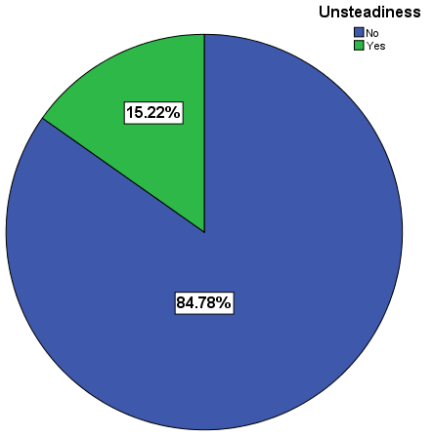


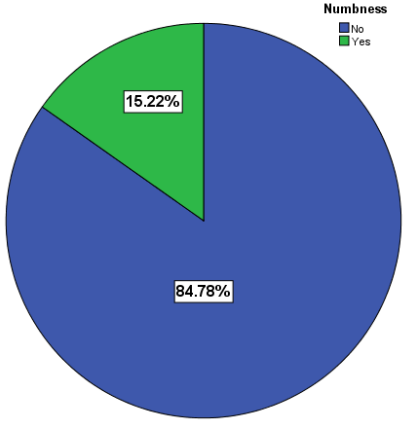
Neuropathy Symptoms (DNS)

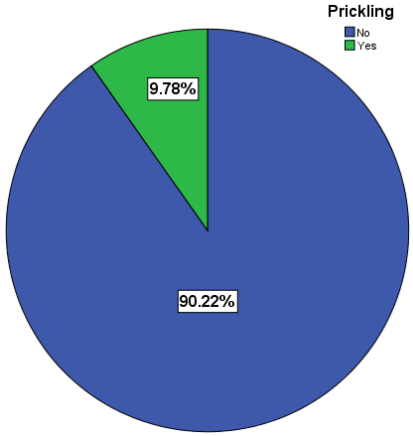
National Institute for Health Research







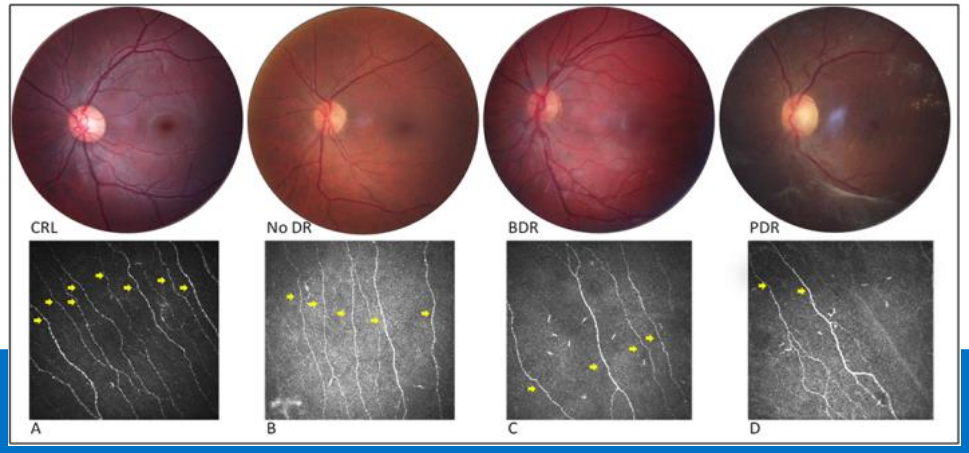




CCM Results

NHS National Institute for Health Research

	Controls	Diabetes	P-Value
A-CNFD (no/mm2)	29.14 ±6.81	23.83 ±7.85	<0.0001
A- CNBD (no/mm2)	41.14 ±18.56	33.42 ±16.36	0.007
A-CNFL (mm/mm2)	17.40 ±3.36	14.39 ±3.34	<0.0001
BEADING Pixel Size	184.11±4.49	237.59±19.91	<0.0001



Corneal Nerves

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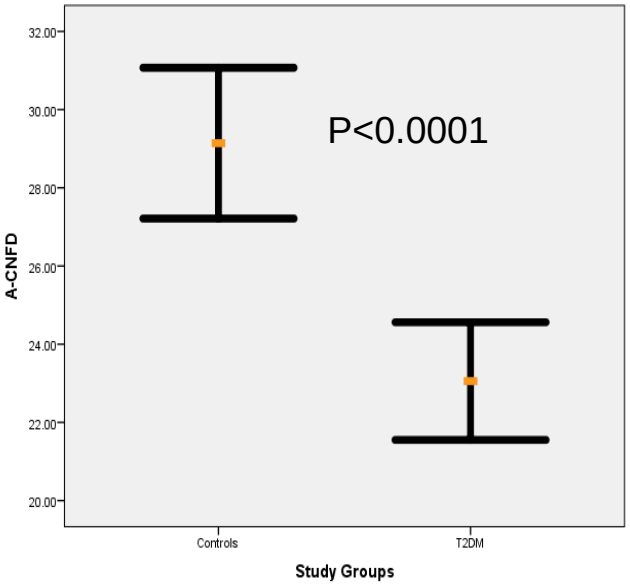

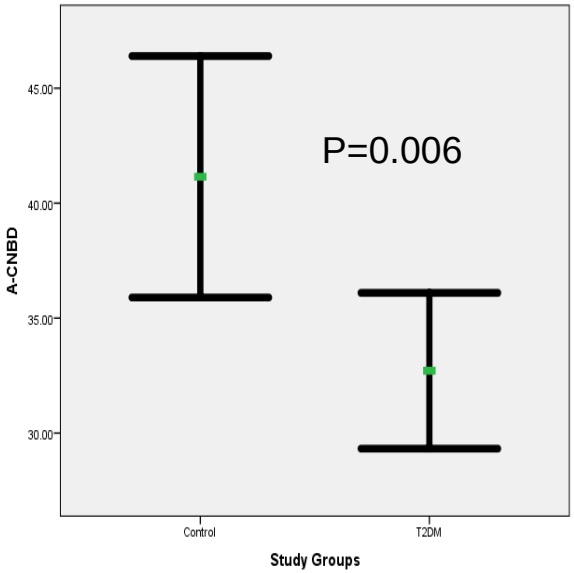

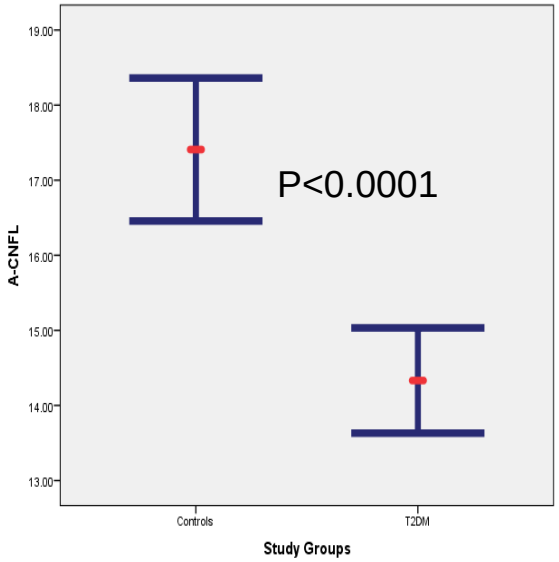

Corneal Nerve Fibre Density

Corneal Nerve Branch Density

Corneal Nerve Fibre Length

Prevalence of Abnormality

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

	Controls (No)	T2DM (No)	Percentage abnormal cases (%)
A-CNFD	1 (1.4%)	14	14.43%
A-CNBD	0	3	3.02%
A-CNFL	1	17	17.52%

Lessons from other studies

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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 3—Percentages of CCM measures, IENFD, NCS, quantitative sensory testing, and cardiovascular autonomic nerve function tests below the 2.5th or above the 97.5th percentile limit of normal in the diabetic and control groups studied

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

Conclusion

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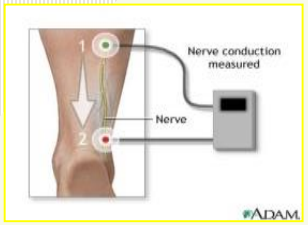
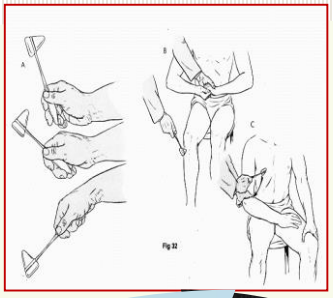
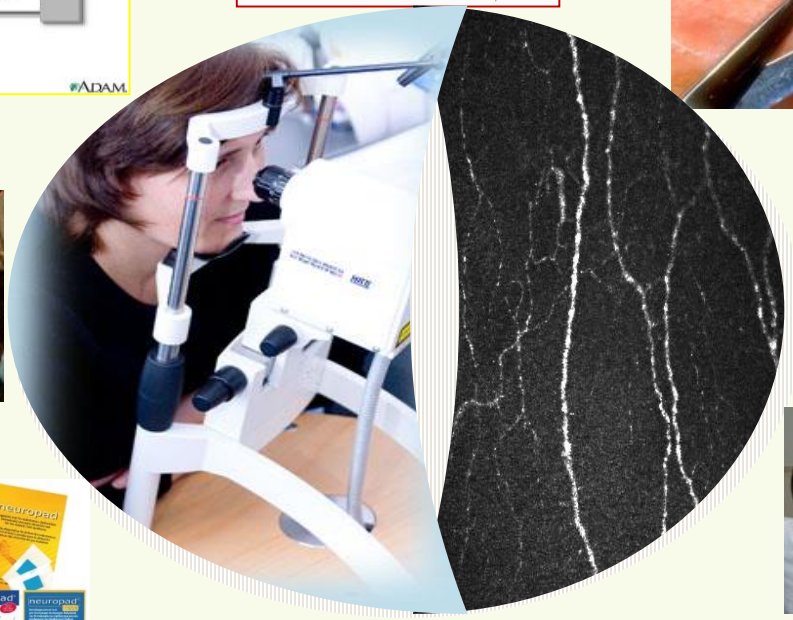
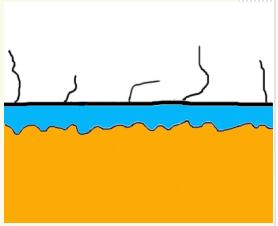
- The level of neuropathy symptoms that reported by newly diagnosed T2DM patients was interestingly high.
- The prevalence of background retinopathy was considerably high.
- There was a significant level of small fibre damage at corneal nerves of this cohort of newly diagnosed T2DM.
- Corneal Confocal 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

Thank You

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