The Assessment Of Small Fibre Neuropathy In Conditions Associated With Neuropathy

Sanjeev Sharma
Gerry Rayman

Diabetes Research Unit,
The Ipswich Hospital NHS Trust
Ipswich

Agenda

PART A:

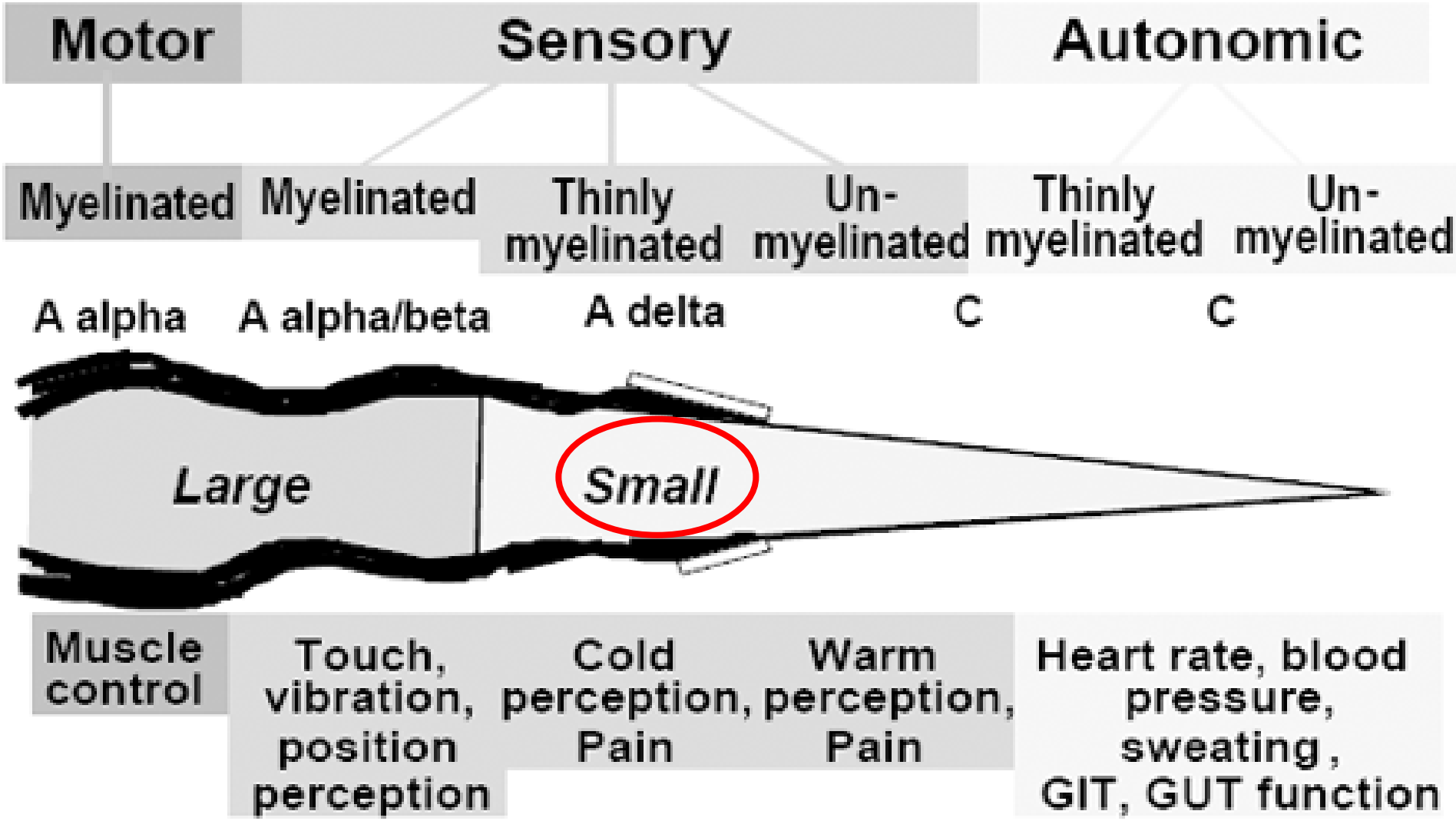
The assessment of small fibre neuropathy in diabetes: a cross-sectional comparison using methods of function and structure

PART B:

The assessment of small fibre neuropathy in other neuropathy states:

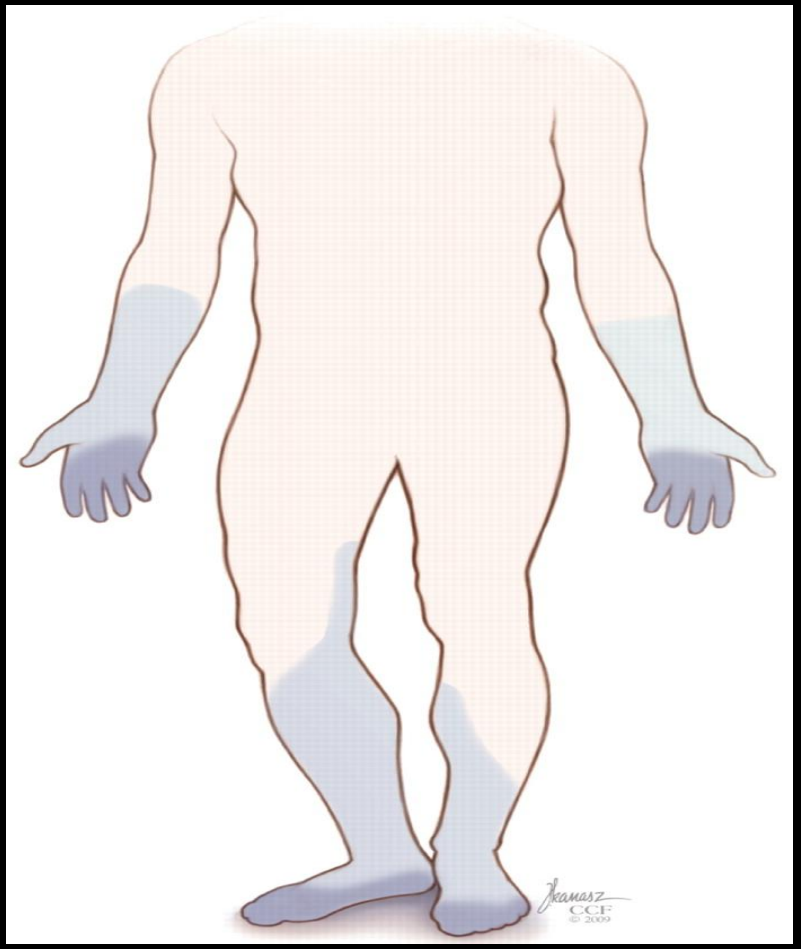
- Hypothyroidism
- CIPN
- Hypertriglyceridaemia

Small vs. Large fibre neuropathy

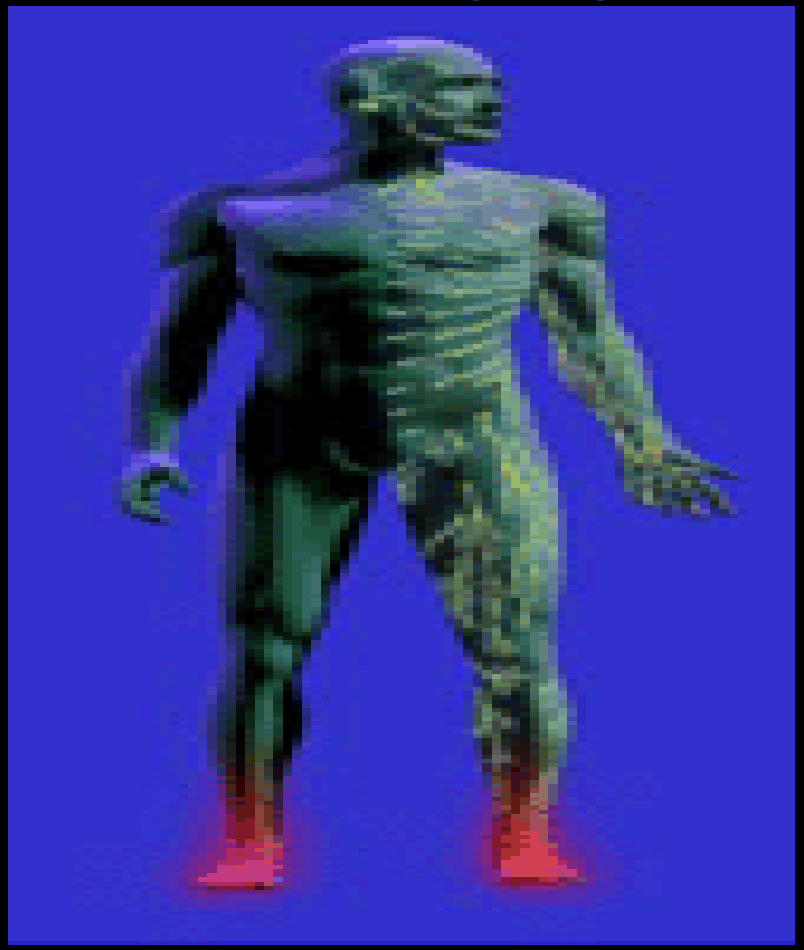


Small vs. Large fibre neuropathy

Large fibre neuropathy



Small fibre neuropathy



Introduction

- Small fibre neuropathy (SFN) in diabetes:
  - affects small unmyelinated C and Aδ fibres
  - damaged early in diabetes
  - usually cannot be detected by conventional /clinical methods
  - various functional and structural tests used in clinical practice and clinical research settings

SFN methods

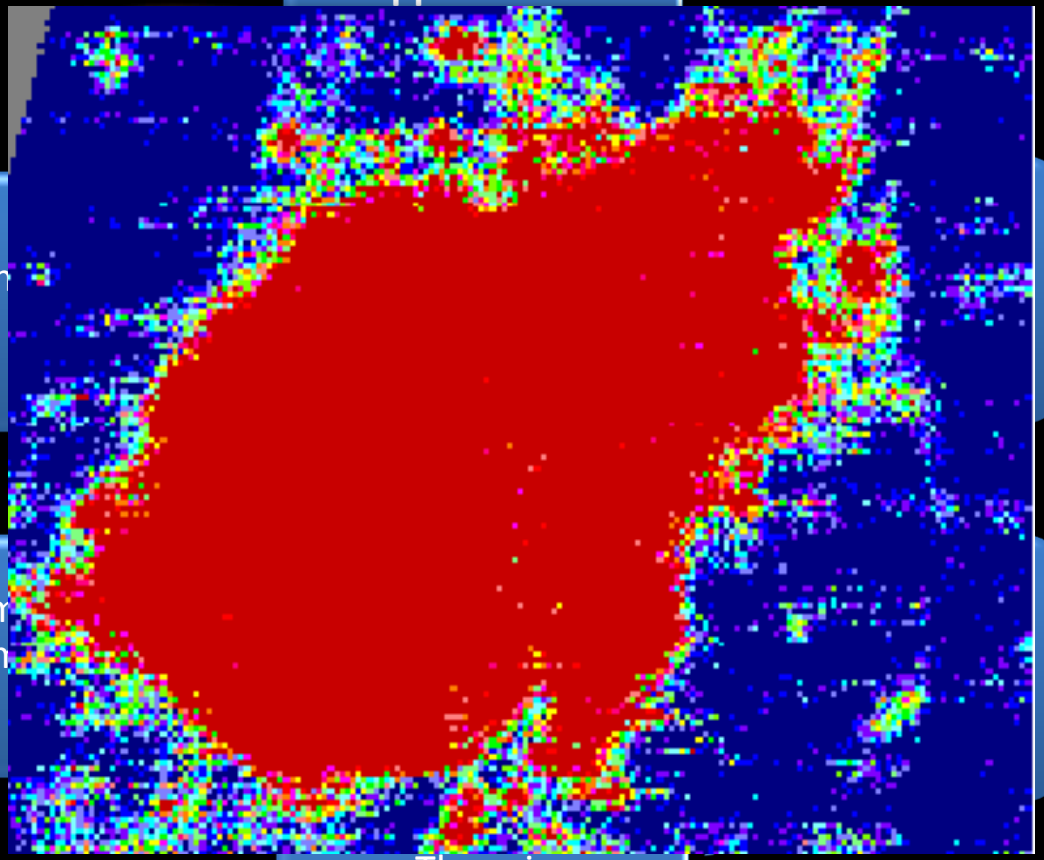
- Functional methods:
  - Laser Doppler Imager (LDI_{FLARE}) technique
  - Autonomic cardiac reflexes
  - Thermal threshold testing
- Structural methods:
  - Confocal microscopy (CCM)
  - Intraepidermal nerve fibre density (IENFD)

LDI_{FLARE} technique...

Doppler effect –

Ger

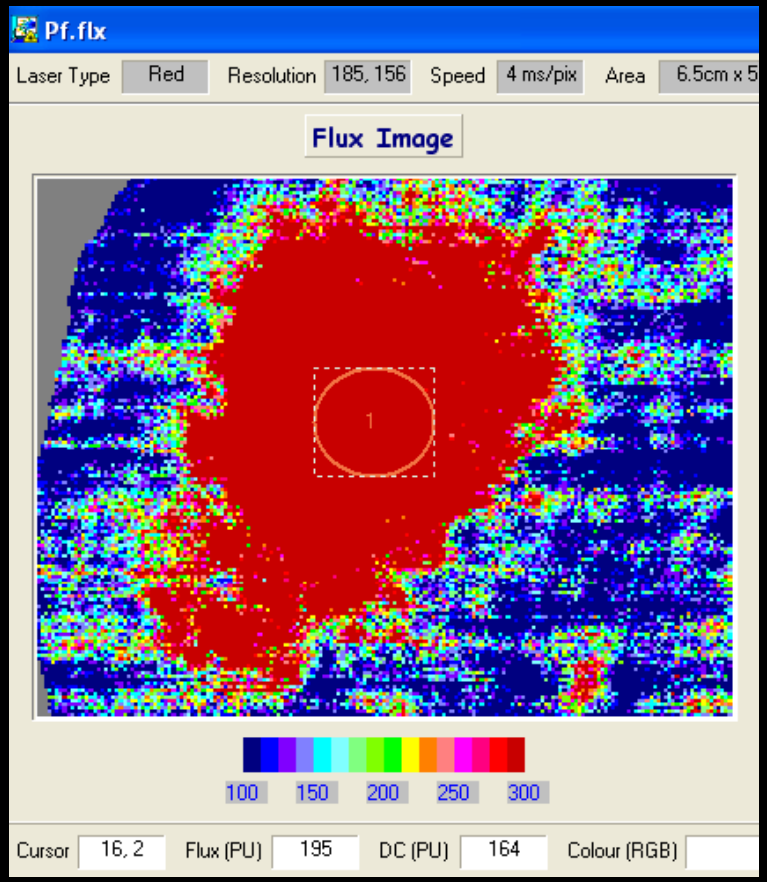
1-m
bean



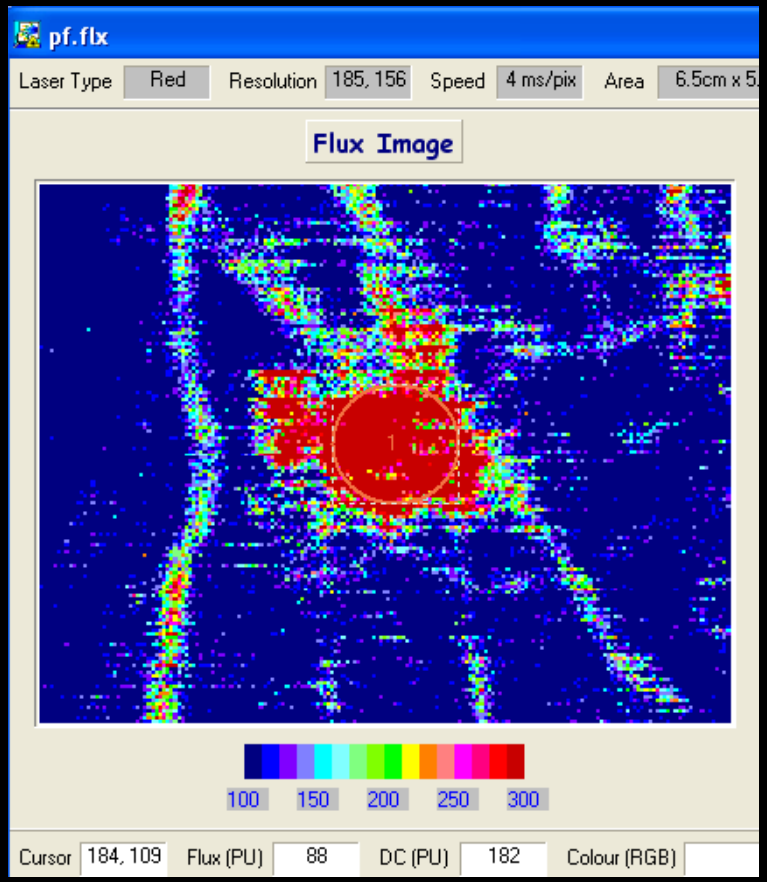
There is vasodilatation on the skin

LDI_{FLARE} outcomes...

- Healthy volunteer



- DM with SFN

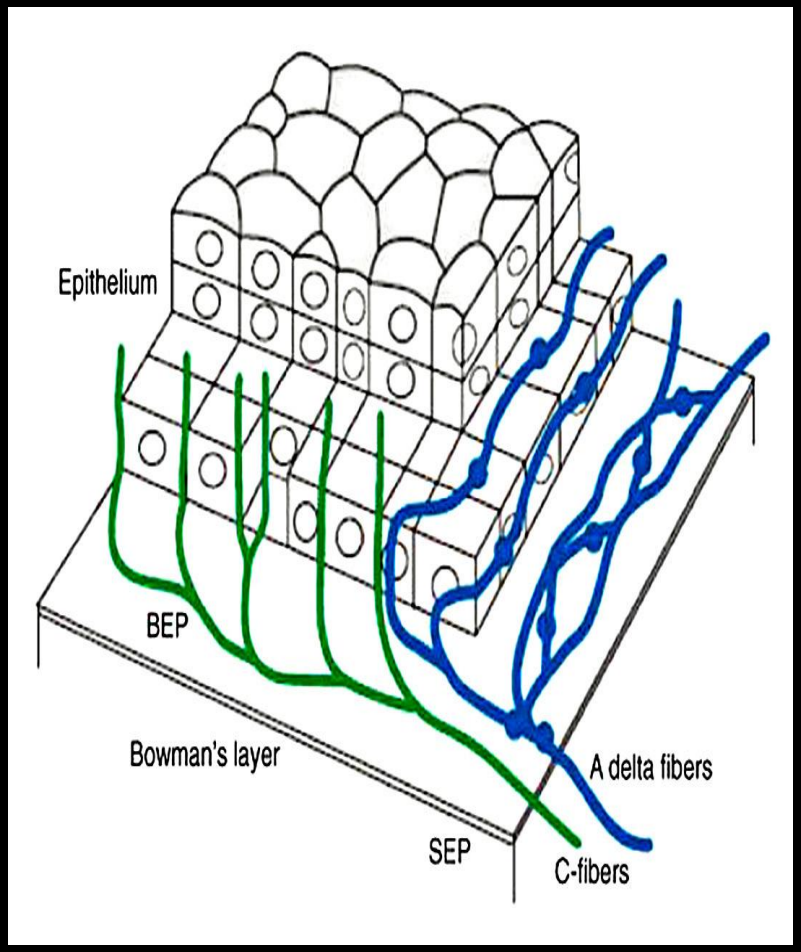


Efficacy of LDI_{FLARE} technique

- In T1DM:
  - glycaemic burden and microvascular complications are associated with SFN[1]
- In T2DM:
  - SFN precedes clinical neuropathy[2]
- In IGT:
  - Altered C-fibre function as an indicator of early peripheral neuropathy[3]
- In Painful SFN:
  - LDIflare correlates with IENFD[4]
- In Healthy volunteers:
  - Age related decline of small fibre function estimated by the use of age-related centile values[5]

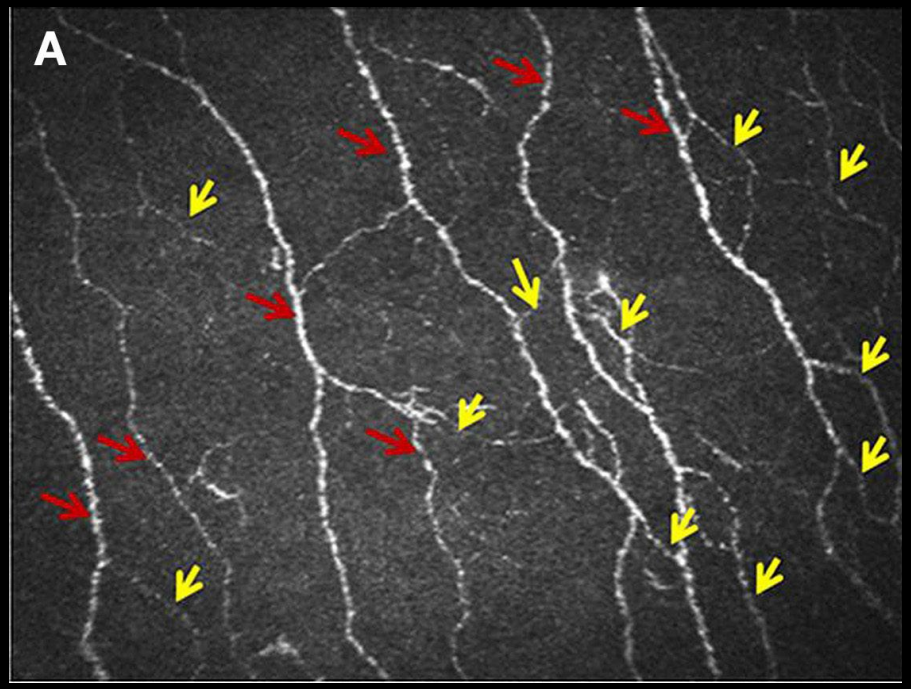
[1] Vas PRJ et al: Diabetologia. 2012; 55:795–800
[2] Krishnan M et al: Diabetes Care. 2004; 27(12):2930-5.
[3] Green AQ et al: Diabetes Care. 2010; 33:174–176.
[4] Krishnan M et al: Diabetes Care. 2009; 32(3):451-5
[5] Vas PRJ et al: PLoS ONE 8(7): e69920. doi:10.1371/journal.pone.

Corneal Confocal Microscopy (CCM)

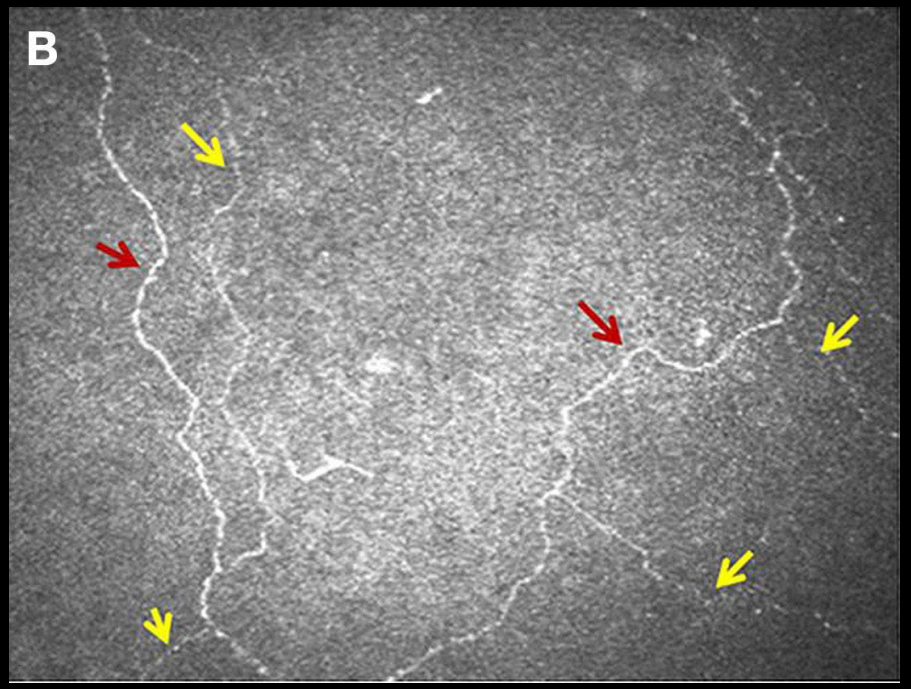


Corneal Confocal Microscopy (CCM)

Healthy volunteer



Type-1 DM

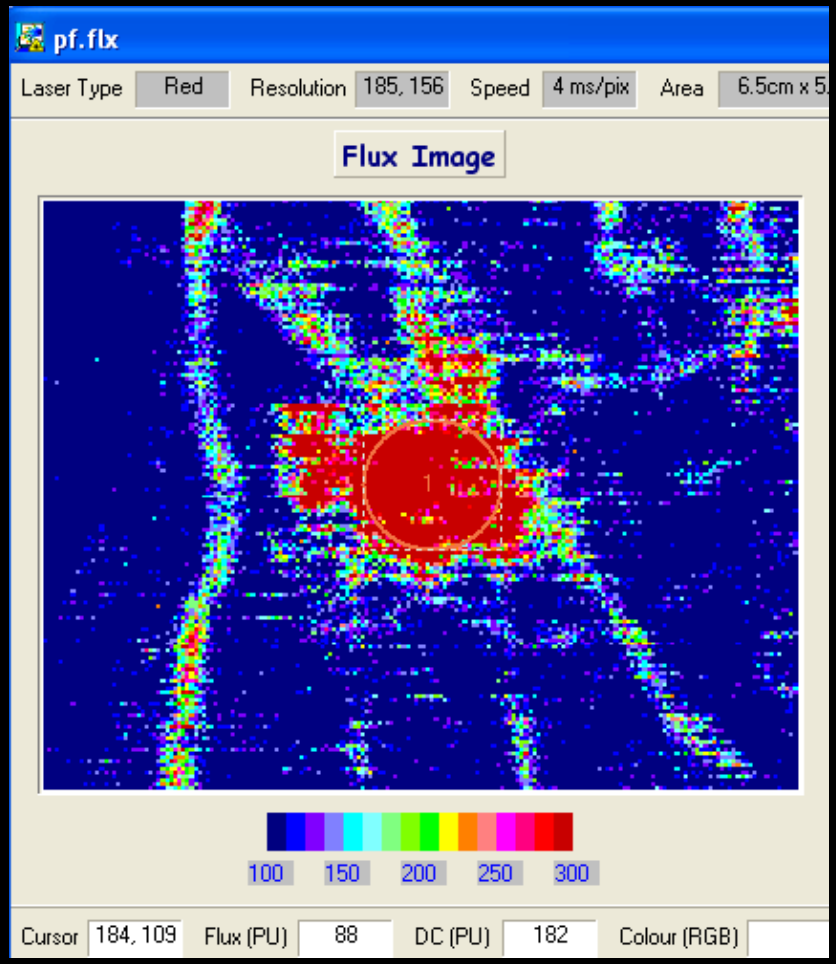


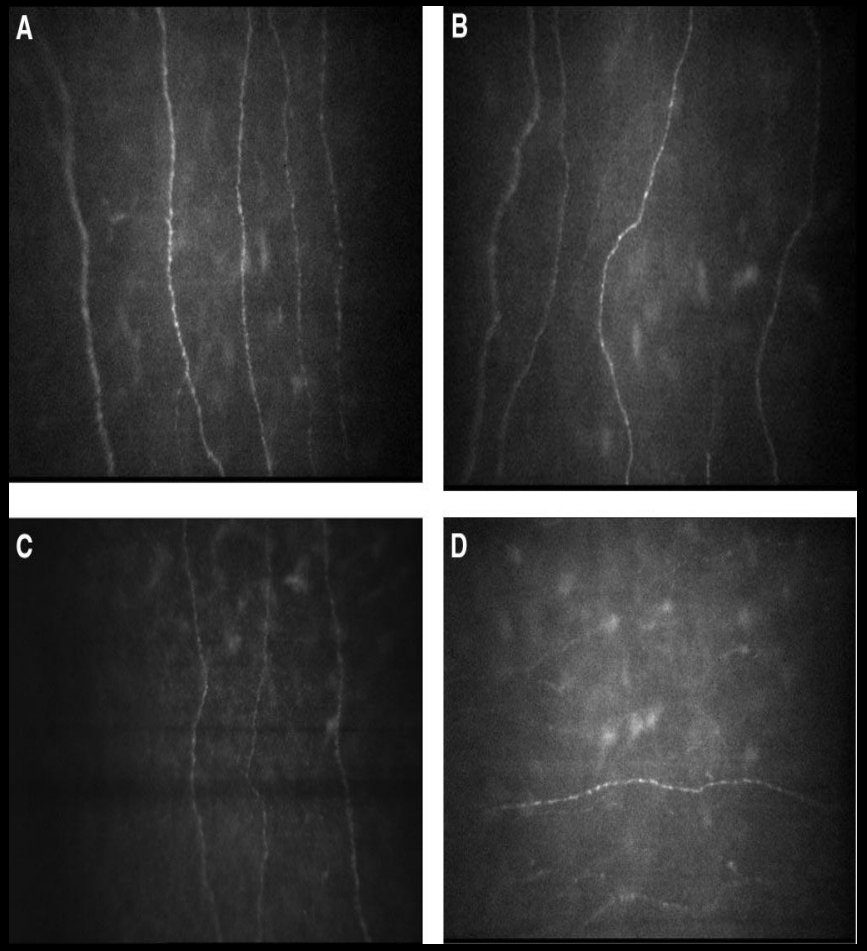
Corneal Confocal Microscopy (CCM)

- corneal nerve fibre abnormalities related to the severity of somatic neuropathy[1]
- reflects IENF loss in skin biopsies from the dorsum of the foot in diabetic patients[2]
- reasonable sensitivity and specificity to detect diabetic patients with minimal neuropathy and those at risk of foot ulceration[3]

[1] Hossain P et al. Lancet 2005;366:1340–1343.
[2] Quattrini C et al. Diabetes 2007;56:2148–2154.
[3] Tavakoli M et al. Diabetes Care 2010; 33:1792–1797.

Function vs Structure





Objective

- Compare the LDI_{FLARE} and CCM methods in:
  - Diabetes subjects (DM)
  - Health Controls (HC)

  to determine their relationship, reflecting their potential in detecting early diabetic neuropathy.

Methodology

- 162 Diabetes patients
  - 80 T_1DM *(47 males)*
  - 82 T_2DM *(44 males)*
- 80 Healthy controls *(45 males)*
- In all participants:
  - Biochemistry, Fasting lipids, HbA_{1c}, TFT
  - Neurology disability score (NDS)
  - LDIflare technique (modified method)
  - CCM
    - using Heidelberg Retina Tomograph 3 (HRT 3) with Rostock corneal module
    - ACCmetrix (ver. 2)
  - Sural nerve conduction velocity and amplitude

Results

	Healthy Controls *n=80*	Total Diabetes *n=162*	*p*
Age *(years ± SD)*	39.66 ± 15.17	47.96 ± 13.98	0.44
BMI *($kg.m^2$ ± SD)*	26.07 ± 4.38	29.16 ± 3.75	0.008
HbA_{1c} *(% ± SD)*	4.86 ± 0.31	7.9 ± 0.81	<0.0001
Triglycerides *(mmol/L ± SD)*	1.89 ± 0.56	2.39 ± 1.14	0.005
Total cholesterol *(mmol/L ± SD)*	4.36 ± 0.89	5.31 ± 0.99	0.009
Duration of diabetes *(years ± SD)*	-	11.32 ± 9.35	-

Results *(HV vs. Total diabetes)*

	LDI_{FLARE} (size/cm2)		CCM					
			CNFD		CNBD		CNFL	
	HC	TD	HC	TD	HC	TD	HC	TD
Age	<0.0001	<0.0001	<0.0001	0.005	<0.0001	0.009	<0.0001	0.21
BMI	0.015	<0.0001	0.005	<0.0001	0.019	<0.0001	0.024	0.014
HbA1c	0.50	<0.0001	0.12	<0.0001	0.29	<0.0001	0.54	0.029
Triglycerides	0.008	<0.0001	0.004	<0.0001	0.023	<0.0001	0.040	0.045
Total cholesterol	0.43	0.33	0.29	0.31	0.22	0.38	0.52	0.50
Duration of diabetes	-	0.059	-	0.055	-	0.13	-	0.19

HV=healthy controls; TD= total diabetes

CNFD= corneal nerve fibre density; CNBD= corneal nerve branch density; CNFL: corneal nerve fibre length

Results *(HC vs. Total diabetes)*

Category	Mean age *(yrs ± SD)*	LDI_{FLARE} *(cm^2 ± SD)*	CCM		
			CNFD *(fibres/mm^2 ± SD)*	**CNBD** *(branches/mm^2 ± SD)*	**CNFL** *(no/mm^2 ± SD)*
HC ***(n=80)***	39.66 ± 15.17	9.11 ± 2.17	43.91 ± 5.92	24.30 ± 3.69	9.47 ± 2.24
	p=0.44	***p<0.0001***	***p<0.0001***	***p<0.0001***	***p<0.0001***
Total Diabetes ***(n=162)***	47.96 ± 13.98	5.81 ± 2.09	22.58 ± 5.91	8.57 ± 5.33	4.32 ± 2.11

HC=healthy controls
CNFD= corneal nerve fibre density; CNBD= corneal nerve branch density; CNFL: corneal nerve fibre length

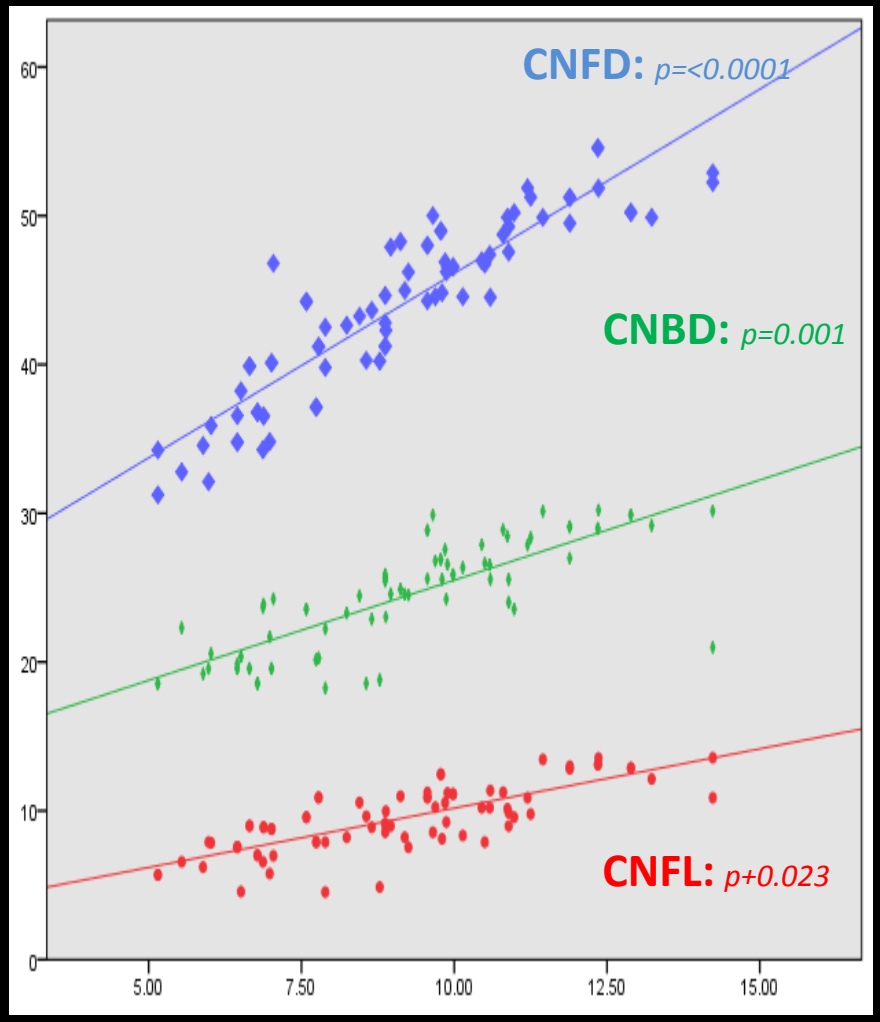
Results *(LDI_{FLARE} vs CCM)*

		HC *n=80*	Total diabetes *n=162*
LDI_{FLARE} *($cm^2 \pm SD$)*		9.11 ± 2.17	5.81 ± 2.09
CCM	**CNFD** *(fibres/$mm^2 \pm SD$)*	43.91 ± 5.92 *R^2=0.766; (p<0.0001)*	22.58 ± 5.91 *R^2=0.766; (p<0.0001)*
	CNBD *(branches/$mm^2 \pm SD$)*	24.30 ± 3.69 *R^2=0.789; (p=0.019)*	8.57 ± 5.33 *R^2=0.789; (p=0.001)*
	CNFL *(no/$mm^2 \pm SD$)*	9.47 ± 2.24 *R^2=0.760; (p=0.023)*	4.32 ± 2.11 *R^2=0.760; (p=0.011)*

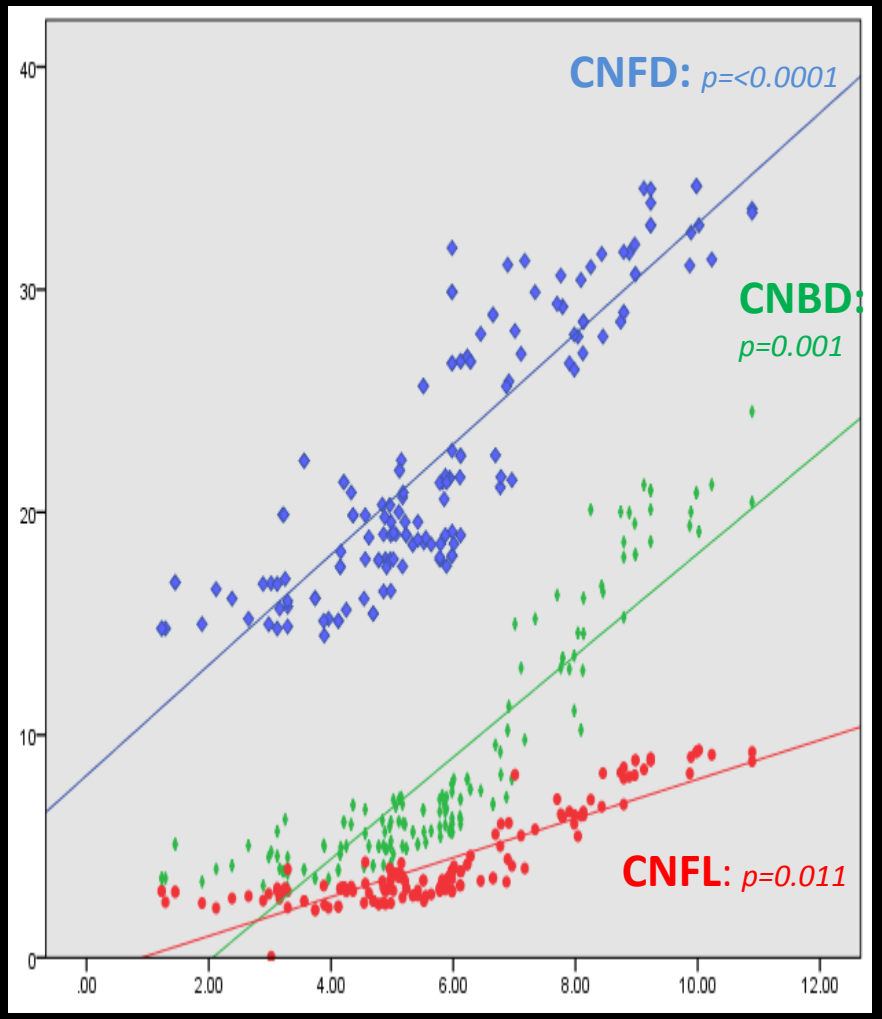
HC=healthy controls

CNFD= corneal nerve fibre density; CNBD= corneal nerve branch density; CNFL: corneal nerve fibre length

Results (LDI_{FLARE} vs CCM)



LDI_{FLARE} (cm^2) - HV



LDI_{FLARE} (cm^2) - Total Diabetes

Results *(LDI$_{FLARE}$ vs CCM)*

T_1DM *n=80*	T_2DM *n=82*

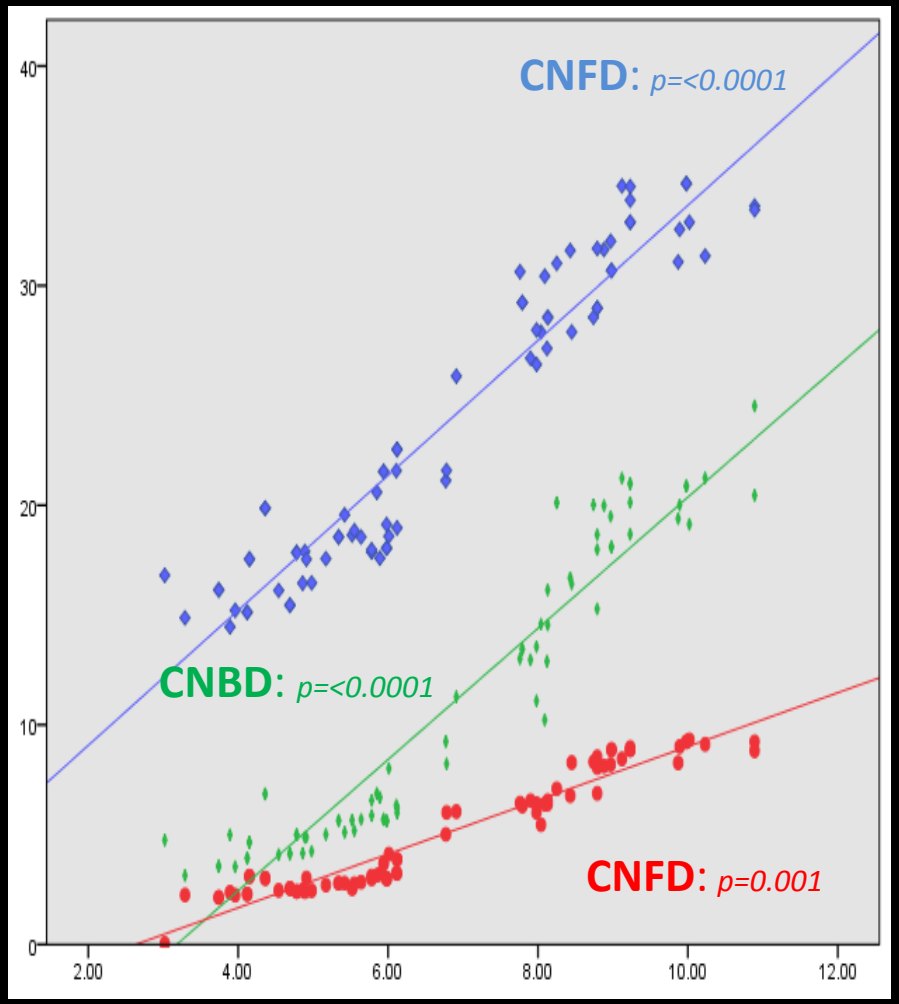
T1DM= type-1 diabetes; T2DM=type-2 diabetes
CNFD= corneal nerve fibre density; CNBD= corneal nerve branch density; CNFL: corneal nerve fibre length

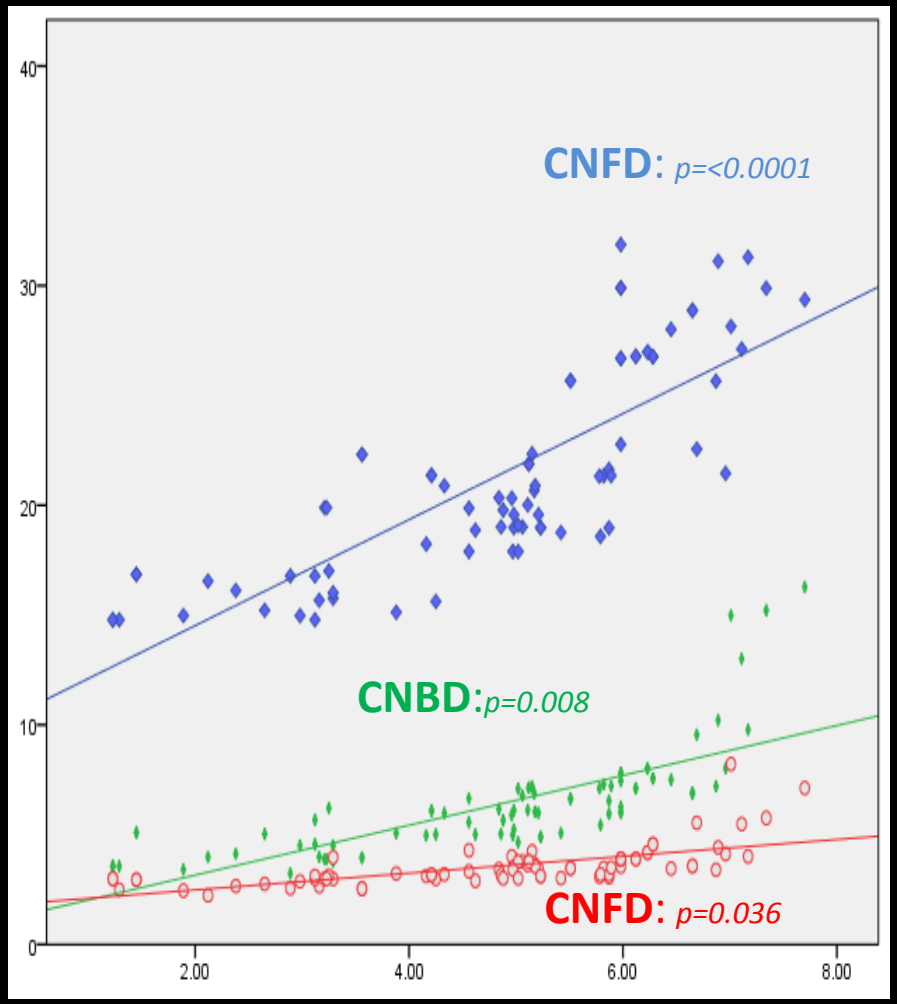
Results *(LDI_{FLARE} vs CCM)*

		T_1DM *n=80*	T_2DM *n=82*
LDI_{FLARE} *($cm^2 \pm SD$)*		6.95±2.07	4.84±1.57
CCM	**CNFD** *(fibres/$mm^2 \pm SD$)*	24.16±6.67 *R^2=0.930; (p<0.0001)*	20.96±4.71 *R^2=0.847; (p<0.0001)*
	CNBD *(branches/$mm^2 \pm SD$)*	11.20±6.53 *R^2=0.905; (p<0.0001)*	6.42±2.60 *R^2=0.546; (p=0.008)*
	CNFL *(no/$mm^2 \pm SD$)*	5.23±2.64 *R^2=0.818; (p=0.001)*	3.58±0.99 *R^2=0.430; (p=0.036)*

T1DM= type-1 diabetes; T2DM=type-2 diabetes
CNFD= corneal nerve fibre density; CNBD= corneal nerve branch density; CNFL: corneal nerve fibre length

Results *(LDI_{FLARE} vs CCM)*





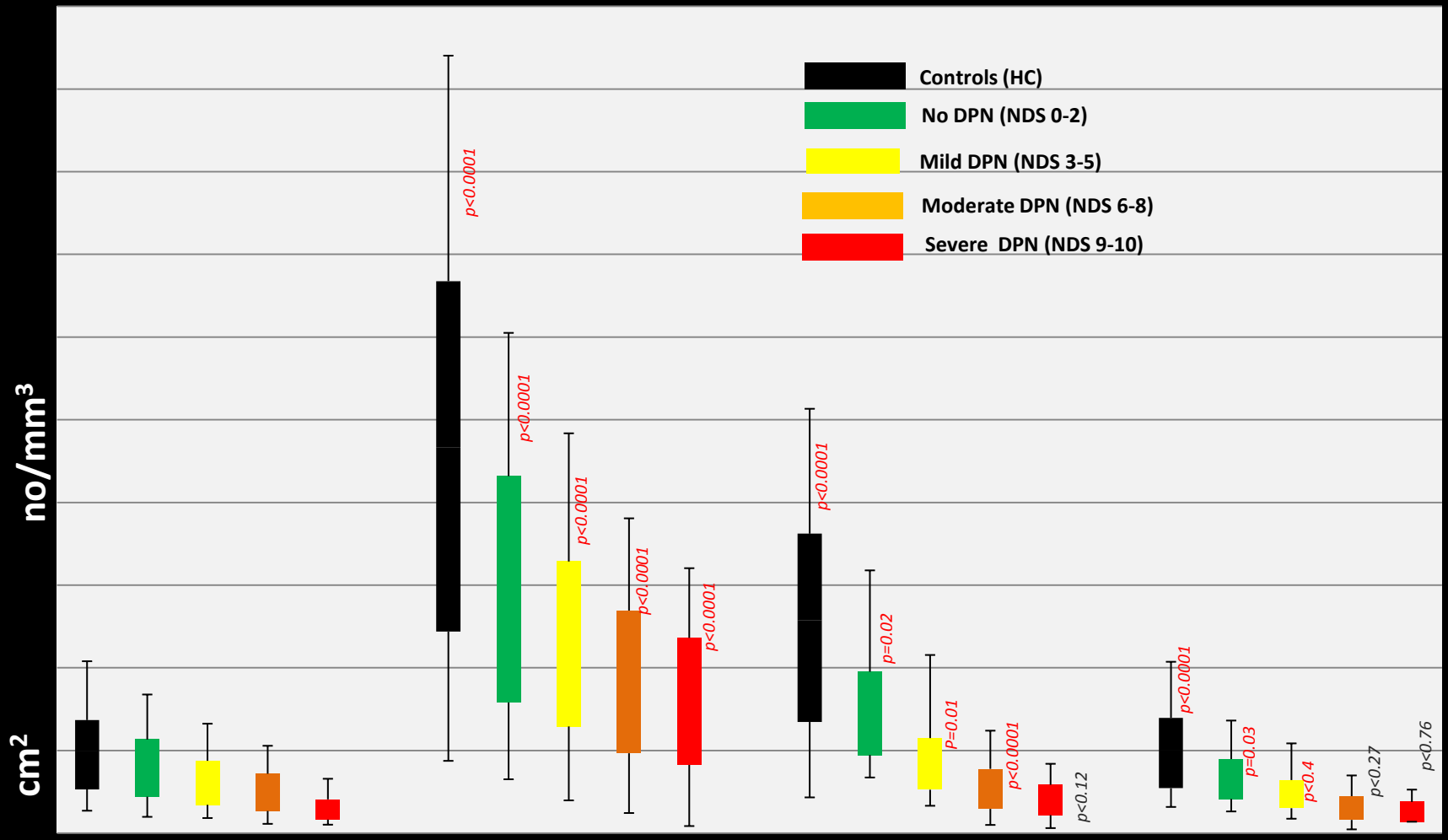
Results *(based on NDS)*

Category
Control *n=80*
No DPN (NDS=0-2) *n=60*
Mild DPN (NDS=3-5) *n=38*
Mod DPN (NDS=6-8) *n=46*
Sev DPN (NDS=9-10) *n=18*

Results *(based on NDS)*

Category)	LDI_{FLARE} *($cm^2 \pm SD$)*	CCM		
		CNFD *(fibres/$mm^2 \pm SD$)*	**CNBD** *(branches/$mm^2 \pm SD$)*	**CNFL** *(mm/$mm^2 \pm SD$)*
Control ***n=80***	9.17 ± 2.18	43.89±5.87 *R^2=0.764; (p<0.0001)*	24.36±3.60 *R^2=0.687; (p<0.0001)*	9.31±2.26 *R^2=0.647; (p<0.0001)*
No DPN (NDS=0-2) ***n=60***	7.52 ± 2.59	28.07±4.59 *R^2=0.677; (p<0.0001)*	12.96±5.84 *R^2=0.416; (p=0.02)*	5.96±2.23 *R^2=0.380; (p=0.03)*
Mild DPN (NDS=3-5) ***n=38***	5.98 ± 2.07	22.35±4.09 *R^2=0.620;(p<0.0001)*	8.51±4.29 *R^2=0.456; (p=0.01)*	4.46±1.76 *R^2=0.342; (p=0.04)*
Mod DPN (NDS=6-8) ***n=46***	5.01 ± 0.69	18.00±1.93 *R^2=0.664; (p<0.0001)*	5.30±1.04 *r=0.668; (p<0.0001)*	3.04±0.52 *R^2=0.215; (p=0.27)*
Sev DPN (NDS=9-10) ***n=18***	3.25 ± 1.12	15.75±0.81 *R^2=0.768; (p<0.0001)*	3.97±0.64 *R^2=0..223; (p=0.12)*	2.40±0.71 *R^2=0.186; (p=0.76)*

Results *(based on NDS)*



Conclusions

- Though assessing different aspects of neural integrity, in different anatomical sites, the LDIflare and CCM methods demonstrate excellent correlations in people with diabetes suggesting that they are both reliable methods to assess for disordered neural states.

Conclusions

- The very good correlation in apparently healthy controls is also interesting as this suggests a ubiquitous level of small fibre neural integrity in individual subjects which may relate to their general health.
- Further studies are required to understand the determinants of neural integrity in otherwise healthy individuals.

Conclusion

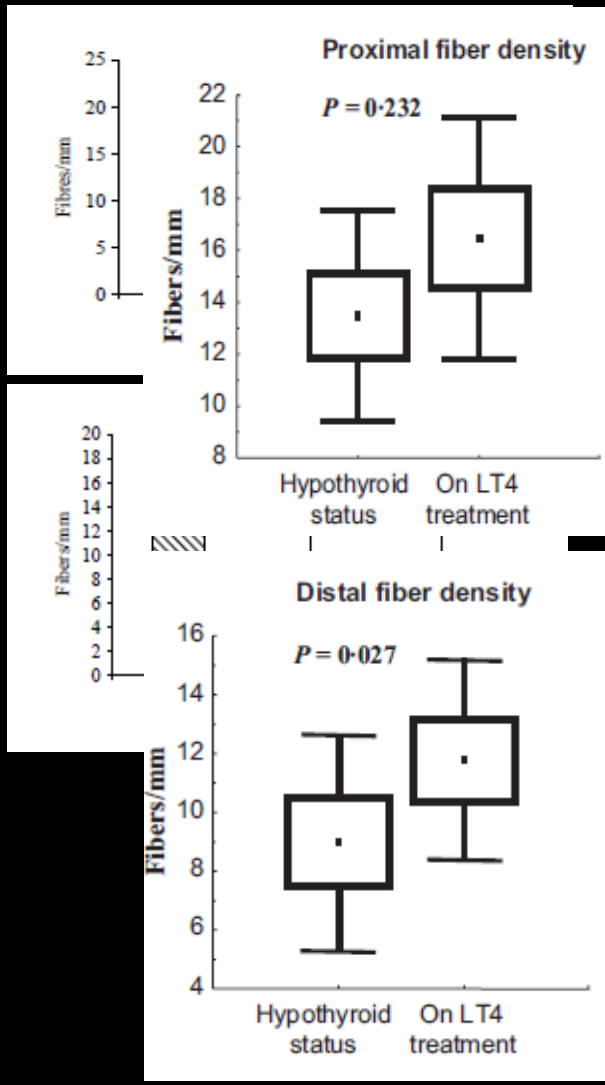
- Further longitudinal studies are required to assess :
  - if changes in small fibre function parallel changes in small fibre structure?
  - And if so, their pathophysiological determinants are similar across various disease states including diabetes?

SFN in other neuropathy states

- Hypothyroidism
- CIPN
- Hypertriglyceridaemia

SFN in Hypothyroidism

- Polyneuropathy: 42-72%[1]
  - 2-4% of neuropathy[2]
- Paucity of data regarding SFN
- Reduced IENFD[3]
- Improved IEFND on LT4 replacement[4]

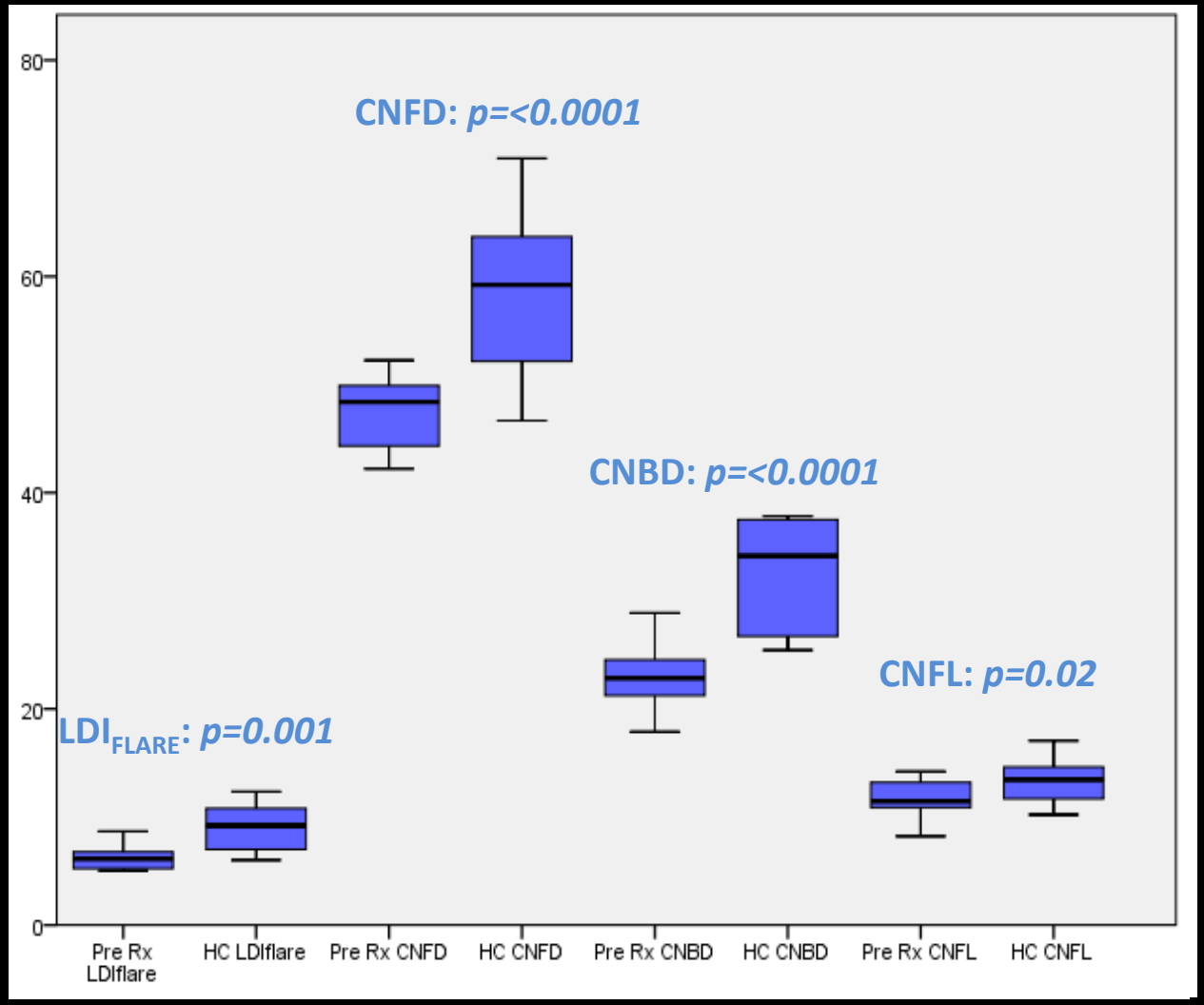


[1]Nemni R, et al. Journal of Neurology, Neurosurgery, and Psychiatry 1987; 50: 1454–1460.
[2]Beghi E et al. Journal of Neurology, Neurosurgery, and Psychiatry 1989; 52: 1420–1423.
[3]Magri F et al. European Journal of Endocrinology 2010; 163: 279–284
[4] Magri F et al. Clinical Endocrinology (2013) 78, 152–154

Preliminary data in Hypothyroidism (HT)

- 14 patients (10 Primary HT + 4 Post RAI) and age-matched healthy controls
- Hypothyroid at onset (*TSH = 74.38 ± SD 27.08*)
- All subjects underwent assessment
  - at baseline
  - 6-9 months after **both** LT_4dose and TSH stabilised
- Assessments included:
  - neurological assessment
  - large fibre assessments – VPT + Sural nerve CV/Amp
  - small fibre assessments – LDI_{FLARE} + CCM

Baseline HT data



Prospective data in HT

SFN assessment	Pre-Rx *(mean ± SD)*	Post-Rx *(mean ±S D)*	*p*
LDI_{FLARE}	6.32±1.20	7.42±1.02	*p=0.004*
CCM-CNFD	47.47±3.44	50.22±4.81	*p=0.004*
CCM-CNBD	22.93±3.14	24.13±2.62	*p=0.07*
CCM-CNFL	11.57±3.42	12.56±2.57	*p=0.09*

Chemotherapy-induced Peripheral Neuropathy (CIPN)

- Debilitating painful neuropathy
  - Platinum analogues, Taxanes and Vinca's
- Unmet need for assessing CIPN[1]
  - no correlation with symptom score or functional disability
  - Inconsistent correlation with NCS
- Lack of evidence[2]
  - neuroprotection
  - CIPN pharmacotherapy

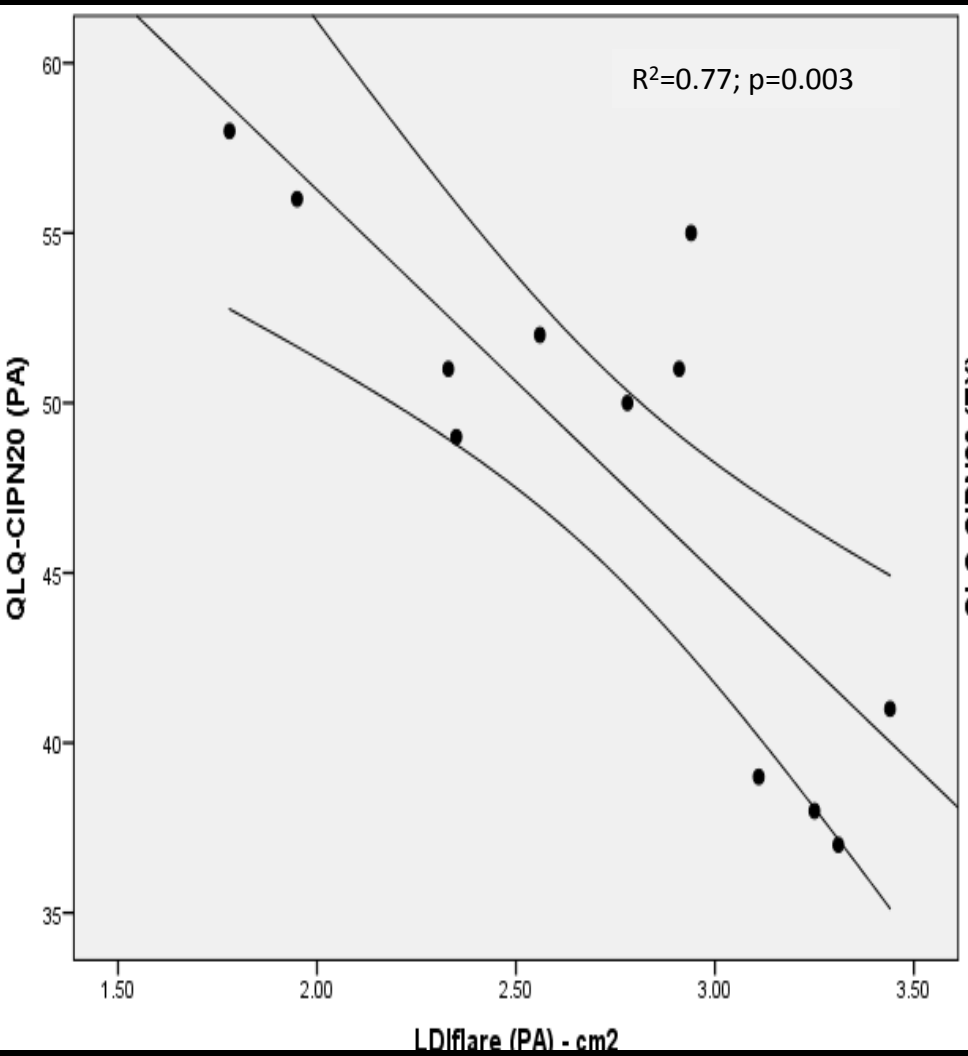
[1]Hausheer FH et al. Semin Oncol 2006: 33 (1):15-49.

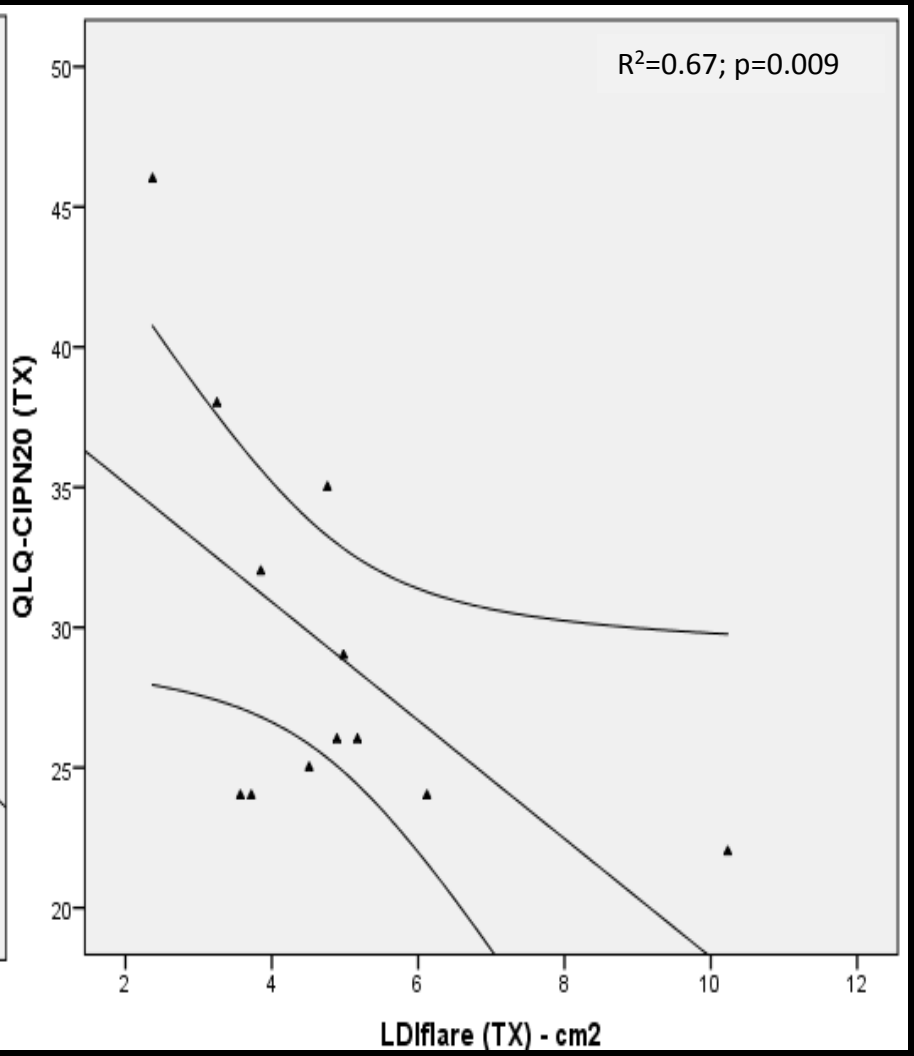
[2] Cavaletti G et al. Frontiers in bioscience : a journal and virtual library 2008: 13:3506-3524

Chemotherapy-induced Peripheral Neuropathy (CIPN)

- Two phases of study:
  - Initial validation phase: in established patients of CIPN
    - 12 platinums and 12 taxanes
  - Prospective study:
    - Before, midway and 8/52 after completion of chemotherapy
- Age & sex matched healthy comparators
- Assessments:
  - EORTC (European Organisation for Research and Treatment of Cancer) QLQ-CIPN20 questionnaire
  - SFN assessments – LDI_{FLARE}, CCM
  - Sural Never CV and Amp

Initial validation phase - CIPN





Prospective phase - CIPN

- Currently underway

Role of Hypertriglyceridaemia(TG) in SFN

- Diabetes
  - Type-1 Diabetes – EURODIAB IDDM Complications study [1]
  - Type-2 Diabetes – FIELD study [2, 3]
- Hypertriglyceridaemia states [4]
- Healthy subjects [5]

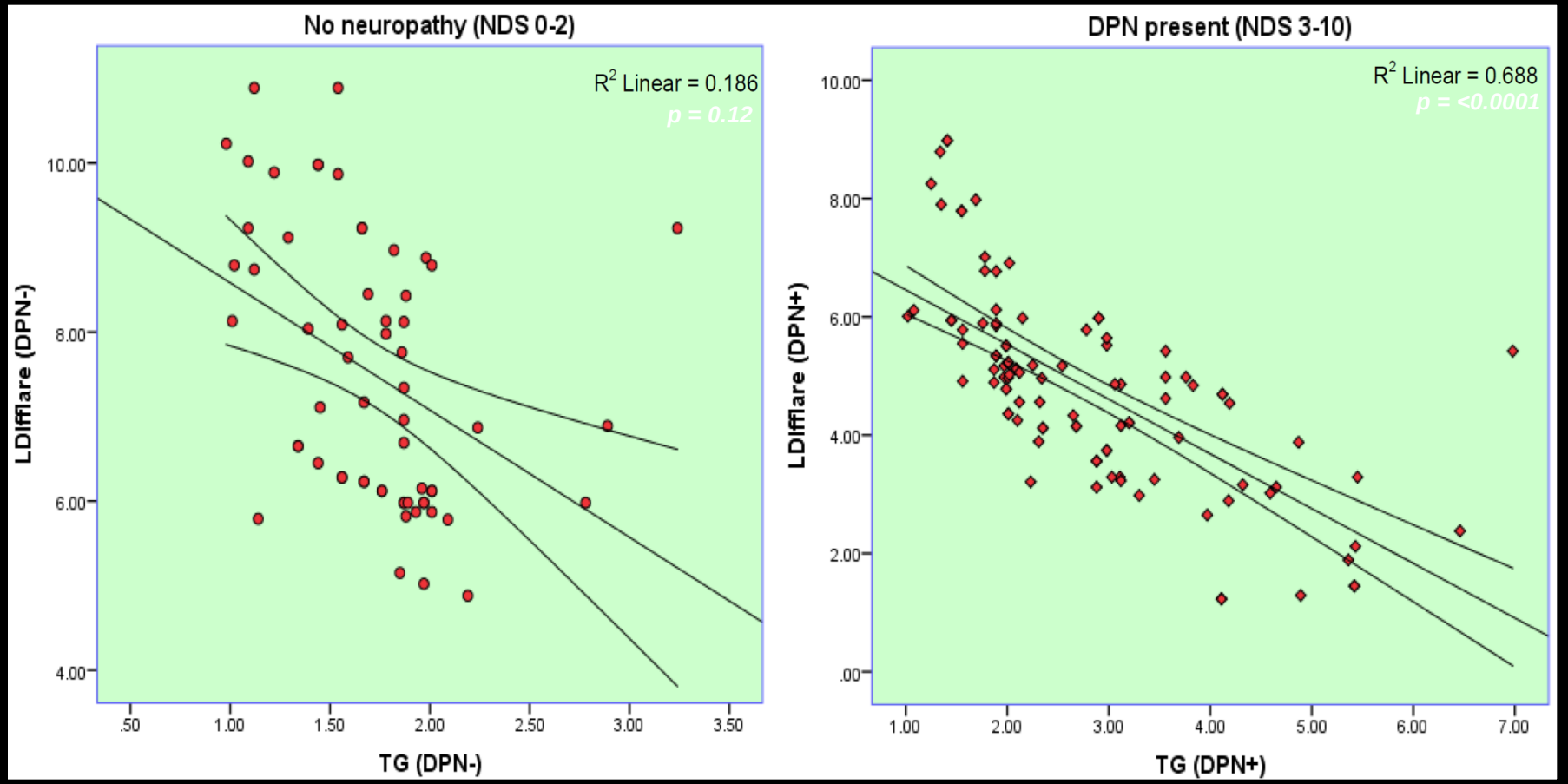
[1] Kempler P et al. The EURODIAB IDDM Complications Study. *Diabet Med* 19: 900-909
[2] Wiggin TD et al. *Diabetes* 58: 1634-1640
[3] Circulation. 2014 Mar 4;129(9):999-1008
[4] Drory VE et al. *Electromyogr Clin Neurophysiol* 39: 39-41
[5] Vas P et al. *Diab Obesity & Metabolism*(under review) 2014

TG in Diabetes

- The relationship between SFN and TG's in the following cohorts of patients:
  - diabetic subjects with and without polyneuropathy and
  - healthy controls (HC)

- Furthermore, to examine the influence of age, body mass index (BMI), glycaemic control (HbA_{1c}) and other lipids on SFF

TG in Diabetes



TG in Diabetes

- Our findings suggest an important relationship between TG levels and small fibre dysfunction.

- Additionally, the significant inverse correlation between TG and NDS in the neuropathic group (DPN+) but not in the non-neuropathic group (DPN-) suggests that TGs might play an important role in the development and progression of large fibre DPN.

- Prospective studies are required to further explore this relationship.

SFN in non-diabetes Hypertriglyceridaemia

- Baseline study
- Prospective study – after 6-9 months of treatment