

## **NEURODIAB 2015** Annual Meeting

25th Annual Meeting of the  
Diabetic Neuropathy Study Group  
of the EASD

11 - 13 September 2015  
Elsinore · Denmark

**Programme and Abstracts**



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**NEURODIAB**

Society for  
Diabetic  
Neuropathy

## INFORMATION

## WELCOME TO NEURODIAB 2015

Dear Friends and Colleagues,

It is our great pleasure to welcome you to the 25th Annual Scientific Meeting of NEURODIAB at Konventum Conference Centre and Hotel in Elsinore, Denmark.

NEURODIAB continues to be considered the most important annual event in the field of diabetic neuropathy. This year we will take the opportunity to celebrate NEURODIAB as this is the 25th meeting since the early start in 1991. We look forward to our anniversary meeting and invite you to celebrate NEURODIAB with us.

At this year's meeting we will stick to our tradition with focus on original research work. There will be oral and poster sessions, keynote lectures and symposia. The meeting will provide clinicians and basic science investigators with the opportunity to present and discuss novel ideas on causation, assessment and treatment of diabetic neuropathy. This year we will also introduce the new young investigators awards for the best oral and poster presentation encouraging young scientists to present their latest scientific discoveries.

The social programme includes a get-together dinner at Konventum followed by a visit to Louisiana Museum of Modern art on Friday. Saturday there will be an unforgettable dinner at the impressive Kronborg castle known as the setting of Shakespeare's Hamlet. We hope you will enjoy the meeting together with us.

On behalf of the local organizing committee,



Chairman, NEURODIAB  
**Professor Henning Andersen**  
Aarhus University Hospital



Professor  
**Johannes Klitgaard Jakobsen**  
Copenhagen University Hospital



Chief Medical Officer  
**Jannik Hilsted**  
Copenhagen University Hospital

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## GENERAL INFORMATION

### LOCAL ORGANISING COMMITTEE

Professor Henning Andersen  
NEURODIAB Chairman,  
Professor of Neurology  
Department of Neurology Aarhus  
University Hospital  
Nørrebrogade 44  
8000 Aarhus C, Denmark

Chief Medical Officer Jannik Hilsted  
Copenhagen University Hospital  
Blegdamsvej 9,  
2100 Copenhagen Ø, Denmark

Professor Johannes Klitgaard Jakobsen  
Copenhagen University Hospital  
Blegdamsvej 9  
2100 Copenhagen Ø, Denmark

### 2015 CONGRESS SECRETARIAT

CAP Partner  
Contact: Maiken Barsøe-Sayers  
Nordre Fasanvej 113, 2nd floor  
2000 Frederiksberg C, Denmark  
+45 70 20 03 05  
mbs@cap-partner.eu  
www.cap-partner.eu

### VENUE

Konventum Conference Centre  
and Hotel (LO-Skolen)  
Gl. Hellebækvej 70  
3000 Helsingør, Denmark  
+45 49 28 09 00  
www.konventum.dk

### WEBSITE

Website of the conference:  
www.neurodiab2015.org

### OPENING HOURS OF REGISTRATION DESK

Friday 11 Sep.: 10.00 – 18.30  
Saturday 12 Sep.: 07.30 – 18.00  
Sunday 13 Sep.: 08.00 – 16.00

The conference badge and final programme/abstract book will be given at the registration desk. The registration includes access to scientific sessions, coffee breaks and lunches as well as welcome dinner & gala dinner.

### LANGUAGE

The official language of the conference is English. Simultaneous translation will not be provided.

### INTERNET

Wi-Fi is available in all areas and is free of charge.

### PARKING

Free parking is available in the hotel's outdoor parking.

### HOW TO GET TO THE CONFERENCE VENUE

#### From Copenhagen Airport:

From Copenhagen Airport (below Terminal 3, platform 2), there are direct trains to Elsinore, (Helsingør) Station every 20 minutes. The train journey itself takes approx. 1 hour, and tickets can be bought in Terminal 3 (please buy a ticket for all zones). Once you arrive at Helsingør Station a free bus shuttle service between Helsingør (Elsinore) Station and Konventum Conference Center will be provided at the times mentioned below. Outside these times public bus number 803 towards Ålsgårde St. runs 1-2 times an hour. Get off at Hellebo Park stop and from there it is approx. 500 meters walk to the venue.

Alternatively take a taxi to Konventum Hotel and Conference Center (contact details below).

#### From Copenhagen Central Station:

From Copenhagen Central Station there are direct trains to Elsinore (Helsingør) Station every 20 mins. The journey takes approx. 45 mins., and tickets can be bought at the station (please buy a ticket for all zones). Once you arrive at Helsingør Station a free bus shuttle service between Helsingør (Elsinore) Station and Konventum Conference Center will be provided at the times mentioned below. Outside these times public bus number 803 towards Ålsgårde St. runs 1-2 times an hour. Get off at Hellebo Park stop and from there it is approximately 500 meters walk to the venue. Alternatively take a taxi to Konventum Hotel and Conference Center (contact details below).

For a detailed travel planner according to your arrival/departure times please visit [www.rejseplanen.dk](http://www.rejseplanen.dk) – you can choose your language in the top right corner.

### FREE BUS SHUTTLE FROM ELSINORE (HESINGØR) STATION

A free bus shuttle service between Helsingør (Elsinore) Station and Konventum Conference Center will be provided during these hours:

Friday 11 September	10:00 – 13:00
Sunday 13 September	16:15 – 19:00

Please note that the shuttle bus will be returning to/departing from the station approx. every 20 minutes.

### TAXI

The hotel reception at Konventum Conference Centre can assist with ordering of taxis. The taxi company (4x48) can be contacted at phone: +45 48 48 48 48  
The price is approx. 11-14 EUR (80-100 DKK) from Elsinore Station (Helsingør Station) to the Conference venue, and approx. 135 EUR (1,000 DKK) from Konventum Conference venue to Copenhagen Airport. Prices may vary depending on time of day, waiting time etc.

### HEALTH AND SAFETY

Emergency telephone numbers in Denmark:  
Ambulance/emergency: 112  
Police (general): 114  
Fire Department: 112

### POSTER SESSIONS

Please refer to the programme for the times of the poster sessions.  
The poster boards will be identified with numbers as stated in the program. Materials for putting up the posters will be provided. Please make sure to remove all the posters and materials from the board by Sunday 13 September at 16:30.

WELCOME DINNER

11 September 2015

- 18:30 - 20:00 Welcome Dinner held at Konventum Conference Centre and Hotel
- 20:00 Bus transfer to LOUISIANA Museum of Modern Art
- 20:30 - 22:00 Welcome reception and introduction to LOUISIANA Museum of Modern Art followed by a chance to explore the museum.
- 22:00 Busses departing from LOUISIANA to Konventum Conference Centre and Hotel

GALA DINNER

12 September 2015

at Kronborg Castle - Hamlet's Historic Castle' in Elsinore, a world heritage site.

- 18:30 Bus transfer leaves from Konventum Conference Centre and Hotel for Kronborg Castle
- 19:00 - 23:00 Dinner
- 23:00 Bus transfer leaves from Kronborg Castle to Konventum Conference Centre and Hotel



ABOUT NEURODIAB

NEURODIAB is a study group of the European Association for the Study of Diabetes (EASD) which focuses on clinical and experimental aspects of diabetic neuropathy.

Its primary aim is to promote the advance of knowledge on all aspects of diabetic neuropathy through an active cooperation between interested diabetologists and other specialists such as neurologists, neurophysiologists, urologists, gastroenterologists, etc. In pursuit of this aim it will also encourage appropriate surveys and clinical trials.

NEURODIAB celebrates its 25th anniversary at the 2015 Annual meeting in Elsinore, Denmark.



## FRIDAY 11 SEPTEMBER 2015

10.00	REGISTRATION OPENS
13.00 - 14.00	WELCOME BUFFET
14.00 - 15.00	REGISTRATION & COFFEE
15.00 - 15.45	WELCOME
15.45 - 16.15	KEYNOTE SESSION Autonomic dysfunction in obesity and the role of bariatric surgery
16.15 - 17.45	ORAL SESSION YOUNG INVESTIGATORS ORAL PRESENTATIONS
17.45 - 18.30	GØRAN SUNDKVIST CLINICAL AWARD
18:30 - 19:50	WELCOME DINNER at Konventum Conference Center and Hotel
20:00	BUSSES DEPARTING from Konventum Conference Center for visit to LOUISIANA Museum of Modern Art
22:00	BUSSES DEPARTING from LOUISIANA Museum of Modern Art

## SATURDAY 12 SEPTEMBER 2015

08.00 - 08.30	KEYNOTE SESSION Pharmacological treatment of painful diabetic neuropathy: Recent recommendations
08.30 - 10.00	ORAL SESSION PAIN AND SMALL FIBER
10.00 - 10.30	COFFEE BREAK
10.30 - 11.00	KEYNOTE SESSION Neuropathy in prediabetes - prevention and treatment
11.00 - 12.00	ORAL SESSION INFLAMMATION AND NEUROTROPHIC SUPPORT
12.00 - 13.00	LUNCH
13.00 - 14.45	POSTER SESSION YOUNG INVESTIGATORS PRESENTATIONS POSTER SESSION AUTONOMIC AND EXPERIMENTAL NEUROPATHY
14.45 - 15.15	COFFEE BREAK
15.15 - 16.45	ORAL SESSION AUTONOMIC NEUROPATHY
16.45 - 17.00	25th. ANNUAL MEETING - COMMEMORATIVE SESSION
17.00 - 17.30	GENERAL ASSEMBLY
18.30	BUS DEPARTURE FOR GALA DINNER AT KRONBORG CASTLE

## SUNDAY 13 SEPTEMBER 2015

08.00 - 09.00	ORAL SESSION TREATMENT AND MONITORING
09.00 - 10.00	MEDA SYMPOSIUM Oxidative stress: biomarker and treatment target in diabetic neuropathy
10.00 - 10.30	COFFEE BREAK
10.30 - 11.00	KEYNOTE SESSION Capillary dysfunction in diabetic neuropathy: A hypothesis
11.00 - 12.30	ORAL SESSION PATHOPHYSIOLOGY
12.30 - 13.30	LUNCH
13.30 - 15.00	POSTER SESSION PATHOPHYSIOLOGY AND TREATMENT POSTER SESSION ASSESSMENT
15.00 - 16.00	ORAL SESSION CLINICAL STUDIES



## DETAILED PROGRAMME

## FRIDAY 11 SEPTEMBER 2015

10.00	<b>REGISTRATION OPENS</b>	
13.00 - 14.00	<b>WELCOME BUFFET</b>	
14.00 - 15.00	<b>REGISTRATION &amp; COFFEE</b>	
15.00 - 15.45	<b>WELCOME</b> Welcome by Prof. Henning Andersen, Chairman NEURODIAB Welcome Address by Prof. Andrew Boulton, President, the European Association for the Study of Diabetes (EASD)	
15.45 - 16.15	<b>KEYNOTE SESSION</b> Autonomic dysfunction in obesity and the role of bariatric surgery Chairs: Simona Frontoni and Henning Andersen	<i>Jim Lenhard, Center for Diabetes &amp; Metabolic Diseases, Christiana Care Health System; Weight Management Center, United States</i>
16.15 - 17.45	<b>ORAL SESSION</b> YOUNG INVESTIGATORS ORAL PRESENTATIONS Chairs: Simona Frontoni and Henning Andersen	
	O1 Reduced Thalamic $\gamma$ -aminobutyric Acid (GABA) in Painless Diabetic Peripheral Neuropathy	<i>Pallai Rappai Shillo, United Kingdom</i>
	O2 Magnetic Resonance Diffusion Tensor Imaging for evaluation of Diabetic Polyneuropathy	<i>Michael Vaeggemose, Denmark</i>
	O3 Corneal Confocal Microscopy detects early small nerve fiber repair after Bariatric Surgery	<i>Shazli Azmi, United Kingdom</i>
	O4 Impact of Glycemic Variability on Neurosensory Retina in patients with Type 1 Diabetes Mellitus	<i>Fabiana Picconi, Italy</i>
	O5 Validation of the Composite Autonomic Symptom Score 31 (COMPASS 31) for the autonomic symptoms of diabetic neuropathy	<i>Federica Di Gennaro, Italy</i>
	O6 Vitamin B12 deficiency associated with Cardiovascular Autonomic Neuropathy in patients with Type 2 Diabetes	<i>Christian Stevns Hansen, Denmark</i>
17.45 - 18.30	<b>GÖRAN SUNDKVIST CLINICAL AWARD</b> Chairs: Simona Frontoni and Henning Andersen	
18.30 - 19.50	<b>WELCOME DINNER</b> at Konventum Conference Center and Hotel	
20:00	<b>BUSSES DEPARTING</b> from Konventum Conference Center for visit to LOUISIANA Museum of Modern Art	
22:00	<b>BUSSES DEPARTING</b> from LOUISIANA Museum of Modern Art	

SATURDAY 12 SEPTEMBER 2015

08.00 - 08.30	<b>KEYNOTE SESSION</b> Pharmacological treatment of painful diabetic neuropathy: Recent recommendations Chairs: Solomon Tesfaye and James Russell	<i>Nanna Finnerup, The Danish Pain Research Center, Aarhus University Hospital, Denmark</i>
08.30 - 10.00	<b>ORAL SESSION: PAIN AND SMALL FIBER</b> Chairs: Solomon Tesfaye and James Russell	
O7	Vitamin D levels are reduced in subjects with painful Diabetic Peripheral Neuropathy	<i>Pallai Rappai Shillo, United Kingdom</i>
O8	Congenital Insensitivity to Pain evidences by lack of c-nerve fibres at the cornea	<i>Mitra Tavakoli, United Kingdom</i>
O9	Corneal Confocal Microscopy detects early small fibre damage and increased Langerhans cell density in children with type 1 DM	<i>Maryam Ferdousi, United Kingdom</i>
O10	Agreement between automated and manual quantification of Corneal Nerve Fiber length: Implications for Diabetic Neuropathy research	<i>Bruce Perkins, Canada</i>
O11	Small nerve fiber structure and function in painful Distal Polyneuropathy	<i>Páll Karlsson, Denmark</i>
O12	Factors influencing diabetes polyneuropathy – assessment using methods of small fibre function and structure	<i>Sanjeev Sharma, United Kingdom</i>
10.00 - 10.30	<b>COFFEE BREAK</b>	
10.30 - 11.00	<b>KEYNOTE SESSION</b> Neuropathy in prediabetes - prevention and treatment Chairs: Vera Brill and Bruce Perkins	<i>John Robinson Singleton, Department of Neurology and Center for Clinical and Translational Sciences, University of Utah, United States</i>
11.00 - 12.00	<b>ORAL SESSION: INFLAMMATION AND NEUROTROPHIC SUPPORT</b> Chairs: Vera Brill and Bruce Perkins	
O13	Modulating molecular chaperones improves Mitochondrial bioenergetics and decreases the Inflammatory Transcriptome in Diabetic Sensory Neurons	<i>Rick Dobrowsky, United States</i>
O14	The Macrophage Activation Marker soluble CD163 is associated to Diabetic Neuropathy	<i>Signe Toft Andersen, Denmark</i>
O15	Brain-derived neurotrophic factor in the Cerebrospinal fluid is related to Peripheral Nerve Function in Type 2 Diabetic patients	<i>Mia-Maiken Kallestrup, Denmark</i>
O16	Role of macrophages in the pathogenesis of diabetic polyneuropathy	<i>Hiroki Mizukami, Japan</i>
12.00 - 13.00	<b>LUNCH</b>	
13.00 - 14.45	<b>POSTER SESSION: YOUNG INVESTIGATORS PRESENTATIONS</b> Chairs: Dan Ziegler and Tamas Varkonyi	
P1	Longitudinal changes of sudomotor function in type 1 Diabetes (T1D)	<i>Lynn Ang, United States</i>
P2	Cardiovascular autonomic neuropathy predicts development of Diabetic Foot Ulcer in patients with type 2 Diabetes Mellitus	<i>Eun Young Lee, Rep. of South Korea</i>
P3	Validation of cooling detection threshold as a marker of sensorimotor polyneuropathy in type 2 Diabetes	<i>Erik Lovblom, Canada</i>
P4	Nondipping is a major predictor of obstructive sleep apnoea syndrome in diabetes	<i>Cinzia D'Amato, Italy</i>
P5	Association between risk factors and cognitive impairment in patients with type 2 diabetes mellitus	<i>Nadiia Zherdova, Ukraine</i>
P6	Changes in left ventricle contractility in obese patients with impaired glucose tolerance. Role of autonomic function	<i>Amel Rezki, France</i>
P7	Left ventricle hyperkinesia in obese patients with impaired glucose tolerance. Relations with glucose variability and the autonomic nervous system function	<i>Amel Rezki, France</i>
P8	The diagnostic validity of NerveCheck: From functional and structural damage of small and large nerve fibres to neuropathic pain	<i>Georgios Ponirakis, Qatar</i>
P9	Corneal Confocal Microscopy demonstrates severe small fibre Neuropathy in Diabetic patients with Charcot Foot in Qatar	<i>Ioannis Petropoulos, Qatar</i>

P10	Pharmacological modulation of AMPK in experimental diabetic peripheral neuropathy	<i>Ashutosh Kumar, India</i>
P11	The diagnostic performance of Neuropad against different composite tests of Diabetic Neuropathy	<i>Georgios Ponirakis, Qatar</i>
P12	Cholecystokinin as a marker of motor-evacuation function of assessment of the stomach in patients with Diabetes	<i>Iryna Kostitska, Ukraine</i>
P13	Corneal Confocal Microscopy - a reliable method to assess Diabetic Peripheral Neuropathy	<i>Georgeta Inceu, Romania</i>
P14	Peripheral neuropathy and Wernicke's encephalopathy after bariatric restrictive surgery	<i>Sarah Bathaei, France</i>
P15	Changes in heart rate and cardiac time intervals in obese patients with impaired glucose tolerance. Role of autonomic function	<i>Amel Rezki, France</i>
P16	The characteristics of complete blood count in the type 2 diabetic patients with peripheral polyneuropathy	<i>Hyun Ae Seo, Rep. of South Korea</i>
P17	Influence of changes in vago-sympathetic activity on heart rate and insulin response to oral glucose load	<i>Sarah Bathaei, France</i>
P18	Electroneuromyographical monitoring children with IDDM who apply insulin pump	<i>Roza Abedimova, Kazakhstan</i>
P19	Relationship between glucose variability and peripheral nerves parameters in patients with type 1 Diabetes	<i>Sara Coluzzi, Italy</i>
	<b>POSTER SESSION: AUTONOMIC AND EXPERIMENTAL NEUROPATHY</b> Chair: Fabiana Picconi	
P20	Reactive hypoglycemia and counterregulatory response after bariatric surgery	<i>Sabrina Chiheb, France</i>
P21	Autonomic testing: a study on the diagnostic value of each test in real world	<i>Giuseppe Bax, Italy</i>
P22	Associations with Cardiovascular Autonomic Neuropathy and Arterial Oxygen Saturation during Sleep in Patients with Type 2 Diabetes	<i>KyuChang Won, Rep. of South Korea</i>
P23	The handgrip test in the assessment of cardiovascular autonomic neuropathy: to use or not to use?	<i>Anna Korei, Hungary</i>
P24	Day and night heart rate variability for detection of cardiac autonomic neuropathy	<i>Irena Kurcalte, Latvia</i>
P25	Blood Pressure Variability in Subjects with Type 1 Diabetes	<i>Rodica Pop-Busui, United States</i>
P26	Characteristics of cardiovascular autonomic and central afferent function in patients with recently diagnosed type 1 or type 2 diabetes	<i>Tamás Várkonyi, Hungary</i>
P27	High fat fed mouse models of Neuropathy	<i>John Hayes, United States</i>
P28	Cabexolone prevents ER stress induced Hypothalamic Neuronal Apoptosis	<i>Seong-Su Moon, Rep. Of South Korea</i>
P29	Dietary reversal improves peripheral nerve function in pre-diabetic C57BL/6J mice	<i>John Hayes, United States</i>
14.45 - 15.15	<b>COFFEE BREAK</b>	
15.15 - 16.45	<b>ORAL SESSION: AUTONOMIC NEUROPATHY</b> Chairs: Luciano Bernardi and Vincenza Spallone	
O17	Nocturnal antihypertensive treatment restores 24 hour blood pressure profile in type 1 diabetic patients with autonomic neuropathy	<i>Jannik Hilsted, Denmark</i>
O18	Bariatric surgery restores autonomic nerve function towards normal in obese subjects with diabetes	<i>Aaron Vinik, United States</i>
O19	Role of Glucose variability on Sympatho-Vagal balance in patients with Metabolic Syndrome and Diabetes	<i>Sara Coluzzi, Italy</i>
O20	Cardiac autonomic neuropathy predicts the occurrence of hypertension in type 2 diabetic patients	<i>Fatima Ayad, France</i>
O21	Integrated cardiovascular/respiratory control in type 1 diabetes	<i>Luciano Bernardi, Italy</i>
O22	Cardiovascular autonomic neuropathy and coronary artery calcifications in asymptomatic patients with type 2 diabetes	<i>Paul Valensi, France</i>
16.45 - 17.00	<b>25th. ANNUAL MEETING - COMMEMORATIVE SESSION</b>	
17.00 - 17.30	<b>GENERAL ASSEMBLY</b>	
18.30	<b>BUS DEPARTURE FOR GALA DINNER AT KRONBORG CASTLE</b>	

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SUNDAY 13 SEPTEMBER 2015

<b>08.00 - 09.00</b>		
<b>ORAL SESSION: TREATMENT AND MONITORING</b>		
Chairs: Eva Feldman and Johannes Jakobsen		
O23	Cognitive Impairment in Subjects with Impaired Glucose Tolerance Improves with a Lifestyle Intervention	James Russell, United States
O24	Effects of long-acting c-peptide on peripheral neuropathy in Type 1 Diabetes – Clinical Trial results	John Wahren, Sweden
O25	Impact of Diabetic Neuropathy on Diabetes distress and depression in longstanding T1DM: Results from the Canadian study of longevity in type 1 Diabetes	Bruce Perkins, Canada
O26	Progressive decline of compound muscle action potentials in motor nerve conduction studies in Japanese type 2 diabetic patients-Four year follow-up study	Soroku Yagihashi, Japan
<b>09.00 - 10.00</b>		
<b>MEDA SYMPOSIUM</b>		
Oxidative stress: biomarker and treatment target in diabetic neuropathy		
Chair: Peter Kempler		
<b>10.00 - 10.30</b>		
<b>COFFEE BREAK</b>		
<b>10.30 - 11.00</b>		
<b>KEYNOTE SESSION</b> Capillary dysfunction in diabetic neuropathy: A hypothesis		
Chairs: John Wahren and Rayaz Malik		
<b>11.00 - 12.30</b>		
<b>ORAL SESSION: PATHOPHYSIOLOGY</b>		
Chairs: John Wahren and Rayaz Malik		
O27	Muscarinic Toxin 7 enhances sensory nerve growth in vitro and in vivo in normal and Diabetic rodents	Paul Fernyhough, Canada
O28	Clinical Neuropathy Phenotyping and Assessment of Biomarkers in Painful Diabetic Peripheral Neuropathy	Pallai Rappai Shillo, United Kingdom
O29	High Glucose concentration down-regulates SIRT2 expression in sensory neurons via a Sorbitol Dehydrogenase-dependent pathway	Paul Fernyhough, Canada
O30	Systemic Extracellular Superoxide Dismutase (SOD3) levels in relation to nerve conduction over two years in recently diagnosed Type 1 and Type 2 Diabetes	Alexander Strom, Germany
O31	Involvement of insulin and RhoA in the neuroprotective activities of exendin-4 in vitro	Kazunori Sango, Japan
O32	Oxidative and carbonyl stress in relation to polyneuropathy in subjects with recently diagnosed type 1 and type 2 diabetes	Dan Ziegler, Germany
<b>12.30 - 13.30</b>		
<b>LUNCH</b>		
<b>13.30 - 15.00</b>		
<b>POSTER SESSION: PATHOPHYSIOLOGY AND TREATMENT</b>		
Chair: Mitra Tavakoli		
P30	Targeting painful diabetic neuropathy in a rat model of type 1 Diabetes: Therapeutic efficacy of novel mesenchymal stem cell populations	Isaura Tavares, Portugal
P31	IVIg therapy markedly ameliorates small fiber function in diabetic painful neuropathy	Mikiko Kamijo, Japan
P32	Reduced lower limb muscle strength and volume in patients with Type 2 diabetes: Relationship to neuropathy, intramuscular fat and vitamin D levels	Monirah Almurhdi, United Kingdom
P33	Glucosamine induced neuropathy and its association with nerve insulin resistance	Hiroki Mizukami, Japan
P34	The effects of Angiotensin II Receptor Blocker (ARB) on Neuropathy in spontaneously hypertensive rats (SHR)	Hitoshi Nukada, Japan
P35	Mitochondrial transcription factor a regulation of mitochondrial degeneration in experimental diabetic neuropathy	James Russell, United States
P36	Reduced induction of gp130 cytokines and neuropeptides in axotomized sympathetic and sensory neurons in a mouse model of type 1 diabetes	Richard Zigmond, United States
P37	The identification of the tissue-specific gene expression signatures of Pioglitazone treatment in a murine model of type 2 Diabetes	Eva Feldman, United States
P38	Is IGT-associated sensory neuropathy driven only by glycemia?	Zsuzsanna Putz, Hungary
P39	Role of transient receptor potential channels TRPV1 and TRPM8 in Diabetic Peripheral Neuropathy	Louis Premkumar, United States
P40	N-3 Polyunsaturated fatty acids protect oxidative stress-induced Cytotoxicity by induction of antioxidant enzymes in immortalized adult mouse schwann (IMS-32) cells	Koichi Kato, Japan

P41	Treatment responsiveness in CIDP patients with Diabetes is associated with higher degrees of Demyelination	Vera Bril, Canada
P42	Glycemia impacts survival of glioblastoma patients treated with radiation and Temozolomide	Bruce Perkins, Canada
P43	Early lower limb muscle abnormalities in subjects with impaired glucose tolerance in relation to intramuscular fat and vitamin D levels	Monirah Almurhdi, United Kingdom
P44	Peripheral neuropathy is related to reduced sudomotor function in adult patients with type 1 Diabetes	Aleksandra Araszkievicz, Poland
P45	Changes in hypodermic adipose tissue could affect skin wound occurrence during obesity	Noelle Remoue, France
P46	Natural history of neuropathy in type 2 diabetic patients with mild neuropathy: A 3 years follow up study	Hassan Fadavi, United Kingdom
<b>POSTER SESSION: ASSESSMENT</b>		
Chair: Rodica Pop Busui		
P47	Comparison of quality of life in painful and painless diabetic peripheral neuropathy	Chong Hwa Kim, Rep. of South Korea
P48	Skin autofluorescence is related to intraepidermal nerve fiber density in type 1 Diabetic patients with long disease duration	Aleksandra Araszkievicz, Poland
P49	Validity of an automated protocol of in vivo corneal confocal microscopy for diabetic sensorimotor polyneuropathy detection in type 1 Diabetes	Bruce Perkins, Canada
P50	Sensitive diabetic neuropathy and an early clinical diagnostic accuracy are associated with quantitative detection of subtypes nerves fibers dysfunction in diabetes: Assessment of a new device vs standardized clinical tools	Ariel Odriozola, Spain
P51	MIBG Imaging and left ventricular dysfunction patients with Diabetes Mellitus type 1	Triantafillos Didangelos, Greece
P52	The quantitative assessment of nerve fibers in internal organs in comparison with cutaneous small nerve fibers in STZ induced diabetic rats	Tae Sun Park, Rep. of South Korea
P53	Reproducibility of in vivo corneal confocal microscopy using an automated analysis program for detection of Diabetic Sensorimotor Polyneuropathy	Bruce Perkins, Canada
P54	Elevated pain threshold in painful Diabetic Neuropathy: A study by Intraepidermal Electrical Stimulation	Chieko Suzuki, Japan
P55	Usefulness of MNSI to Screen Symptomatic Diabetic Peripheral Neuropathy	Dongsun Kim, Rep. of South Korea
P56	Assessing Corneal Nerve Morphology with Visual Analysis	Martin Röhlig, Germany
P57	Staging system of Diabetic Neuropathy by nerve conduction study	Masayuki Baba, Japan
P58	Sudoscans as a tool for early screening of Diabetic Microvascular complications: Experience of a french hospital	Jean-Henri Calvet, France
P59	The largest study on the impact of neuropathy on quality of life (QOL) in different age groups of Romanian patients with self-reported Diabetes	Ioan Veresiu, Romania
P60	Different impairment of peripheral nervous system fibers: a clinical study in type 1 and 2 diabetes	Federico Bellavere, Italy
P61	Characteristics of diabetic foot ulcers by etiologic classification in hospitalized patients	Jihyun Lee, Rep. of South Korea
P62	Hemorrhological approach for early detection of diabetic microangiopathy	So Yeon Park, Rep. of South Korea
<b>15.00 - 16.00</b>		
<b>ORAL SESSION: CLINICAL STUDIES</b>		
Chairs: Jannik Hilsted and Soroku Yagihashi		
O33	Neuropathy prevalence compared to other complications in longstanding T1DM: Preliminary analysis of the Canadian study of longevity in Diabetes cohort	Bruce Perkins, Canada
O34	A Multi National Normative Dataset for Corneal Nerve Morphology Assessed Using Corneal Confocal Microscopy	Mitra Tavakoli, United Kingdom
O35	The prevalence of Diabetes Mellitus (DM) is increased in older subjects with chronic inflammatory Demyelinating Polyneuropathy (CIDP)	James Russell, United States
O36	Diabetic Nephropathy Lesions Associate with Cardiovascular Autonomic Neuropathy (CAN) in Pima Indians with Type 2 Diabetes	Rodica Pop-Busui, United States
<b>16.15</b>		
<b>DEPARTURE</b>		

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ORAL ABSTRACTS



## [O1] REDUCED THALAMIC $\Gamma$ -AMINO BUTYRIC ACID (GABA) IN PAINLESS DIABETIC PERIPHERAL NEUROPATHY

Pallai Rappai Shillo<sup>1</sup>, Dinesh Selvarajah<sup>1</sup>, Marni Greig<sup>1</sup>, Ganesh D Rao<sup>2</sup>, Iain Wilkinson<sup>3</sup>, Richard A Edden<sup>4</sup>, Solomon Tesfaye<sup>5</sup>

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**Objective:** We have previously demonstrated reduction in thalamic N-Acetyl Aspartate to Choline ratio on Proton Magnetic Resonance Spectroscopy (H-MRS) indicating neuronal dysfunction in patients with painless diabetic peripheral neuropathy (Painless-DPN). In this study, we assessed thalamic GABA (inhibitory neurotransmitter) in carefully phenotyped patients with and without DPN using novel H-MRS editing techniques.

**Method:** 44 type 2 diabetes (T2DM) subjects (14 Painful-DPN, 15 Painless-DPN and 15 No-DPN) and 15 healthy volunteers (HV) underwent clinical and neurophysiological assessments. T2DM subjects were grouped according to the results of the neuropathy composite score [NIS(LL)+7] and Douleur Neuropathique 4 (DN4). All groups underwent H-MRS at 3 Tesla to assess GABA relative to unsuppressed water and creatine using a single-voxel, spin-echo, spectral editing technique (MEGA-PRESS; echo time=68ms) centred over the thalami. GABA resonance signal was obtained relative to that of parenchymal water.

**Results:** Subjects with painless-DPN had significantly lower GABA:H2O compared to the other groups [Painless-DPN 1.47(0.23), Painful-DPN 1.61(0.33), HV 1.75(0.25) and T2DM with No-DPN 1.84(0.38); ANOVA  $p < 0.01$ ]. Post-hoc comparisons indicated significantly lower mean GABA/H2O in Painless-DPN compared to No-DPN ( $p < 0.005$ ) and significantly lower mean GABA/H2O in Painless-DPN compared with HV ( $p < 0.05$ ).

**Conclusion:** The thalamus is the sensory gateway to the cerebral cortex. The lower levels of GABA in this carefully characterised cohort and our previous finding of thalamic neuronal dysfunction in Painless-DPN may reflect reduced number of afferent pain impulses/central sensitisation. A further understanding of the cerebral neuronal excitatory/inhibitory balance inferred from H-MRS may help determine the mechanistic basis of pain perception in DPN.

## [O2] MAGNETIC RESONANCE DIFFUSION TENSOR IMAGING FOR EVALUATION OF DIABETIC POLYNEUROPATHY

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**Objective:** To evaluate the use of magnetic resonance (MR) diffusion-tensor-imaging (DTI) to demonstrate nerve lesions in patients with type-1 diabetes.

**Method:** Seven type-1 diabetic patients with polyneuropathy (+PNP), 7 type-1 diabetic patients without polyneuropathy (-PNP) and 8 healthy controls (HC) were included. Diffusion-tensor-images (1.4x1.4x3mm<sup>3</sup>; TR: 4200ms TE: 112ms; b0 = 0; b1 = 800) were acquired to evaluate the extent of focal lesions in the sciatic nerve using a 3 Tesla scanner (Magnetom-Skyra, Siemens AG). DTI fractional anisotropy (FA) (direction of molecule diffusion) and apparent diffusion coefficients (ADC) (molecule diffusion displacement) were calculated. The MR scans consisted of 16 axial slices of the sciatic nerve above the knee. The presence of PNP was determined based on nerve conduction studies, vibratory perception thresholds, a standardised clinical neurological examination and a symptom score.

**Results:** FA values of the sciatic nerve were significantly lower in diabetic patients with PNP compared to controls and diabetic patients without PNP, (+PNP: 0.39(0.21; 0.48), -PNP: 0.51(0.39; 0.60), HC: 0.51(0.41; 0.60)) (median, range) ( $p = 0.01$ ). Furthermore, there was a difference in the ADC between the groups, (+PNP: 0.42(0.32; 0.53), -PNP: 0.37(0.36; 0.39), HC: 0.36(0.31; 0.39)) ( $p < 0.05$ ).

**Conclusion:** Diffusion tensor imaging of the sciatic nerve showed lower FA values and higher ADC values in diabetic patients with PNP as compared to healthy controls and non-neuropathic patients. Lower FA values and higher ADC may reflect less constriction of low-grade protein flow along the nerve. The findings suggest that MR imaging can be used to diagnose PNP.

### [O3] CORNEAL CONFOCAL MICROSCOPY DETECTS EARLY SMALL NERVE FIBER REPAIR AFTER BARIATRIC SURGERY

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**Objective:** To establish if CCM can detect an early improvement in neuropathy after bariatric surgery.

**Method:** 32 morbidly obese subjects (non diabetic (n=17), T2DM (n=15)) underwent assessment of the neuropathy symptom profile (NSP), sural and peroneal nerve electrophysiology, Vibration Perception Threshold (VPT), cold (CT) and warm (WT) threshold, warm induced pain (WIP), corneal nerve fiber density (CNFD), branch density (CNBD) and fiber length (CNFL) at baseline, 6 (n=32) and 12 (n=16) months after bariatric surgery.

**Results:** 6 months after bariatric surgery there was a significant improvement in BMI (50.5±1.7 v 38.9±1.7, P<0.0001), HbA1c (52.4±4.6 v 37.9±1.4, P=0.01), systolic BP (132.9±4.0 v 123±3.1, P=0.002), NSP (5.0±1.01 v 2.7±0.9, P=0.05), WIP (47.4±0.4 v 48.3±0.4, P=0.027) and CNFL (14.06±0.5 v 14.8±0.7, P=0.006). 12 months after bariatric surgery there was a significant improvement in triglycerides (1.67±0.2 v 1.1±0.1, p=0.025), NSP (5.4±1.2 v 1.0±0.4, P=0.002), CNFD (22.4±1.6 v 29.1±1.6, P=0.004), CNFL (14.0±0.6 v 17.5±0.9, P=0.001) and CNBD (32.4±3.9 v 43.8±4.6, P= 0.019). Interestingly, at 6 months only subjects without T2DM (n=17) showed a significant improvement in CNFD (22.0±1.0 v 24.0±1.5, P=0.028), CNBD (25.3±2.6 v 29.4±4.0, P=0.039) and CNFL (13.6±0.5 v 14.4±0.8, P=0.016), whilst T2DM showed an improvement in CNFD (25.1±2.3 v 32.6±1.9, P=0.05) and CNFL (15.1±0.6 v 19.2±1.3, P=0.018) only at 12 months.

**Conclusion:** Bariatric surgery results in an improvement in weight, HbA1c, SBP and triglycerides, with an improvement in neuropathic symptoms and small fiber neuropathy (SFN) detected using CCM.

### [O4] IMPACT OF GLYCEMIC VARIABILITY ON NEUROSENSORY RETINA IN PATIENTS WITH TYPE 1 DIABETES MELLITUS

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**Objective:** Diabetic retinopathy (DR) has been considered primarily a retinal microvascular disorder. Nevertheless, recent studies have demonstrated that retinal neurodegeneration might develop early in the course of DR, even before the onset of microvascular changes. It is not yet known how hyperglycemia adversely affects the neurosensory retina.

The aim of our study was to evaluate the impact of overall glycemic load and glycemic variability (GV) on the different layers thickness of retinal nerve tissue in patients with type 1 diabetes mellitus (DM1) with no signs or mild non proliferative diabetic retinopathy, without peripheral neuropathy

**Method:** 29 consecutive subjects with DM1 and 13 healthy control subjects (C) were included. All subjects underwent a OCT Heidelberg Spectralis, with automatic segmentation of the retinal layers (RNFL, GCL, IPL, INL, ONL, OPL, EPR, Photoreceptors). All DM1 patients underwent a Continuous Glucose Monitoring (CGM), from which indexes of GV (SD, CONGA-1, CONGA-2, CONGA-4, J-index, LBGI, HBGI, MAGE, M-value) were calculated. Overall glycemic load was evaluated by HbA1c.

**Results:** RNFL thickness was significantly different between DM1 patients and C (14 µm ± 3.1 vs 12.5 µm ± 1.5, p<0.05). A positive correlation between RNFL and CONGA-1, M-value (p<0.05) and between INL and CONGA-1, CONGA-2, CONGA-4 (p<0.05) was found in DM1 patients. No significant correlation was found with HbA1c.

**Conclusion:** Retinal neurodegeneration is already present in DM1 patients with no or early signs of DR. GV, and not overall glycemic load, could play a pathogenic role in the structural damage of neurosensory retina in DM1 patients.

## [O5] VALIDATION OF THE COMPOSITE AUTONOMIC SYMPTOM SCORE 31 (COMPASS 31) FOR THE AUTONOMIC SYMPTOMS OF DIABETIC NEUROPATHY

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**Objective:** Composite Autonomic Symptom Score (COMPASS) 31 is a self-assessment questionnaire on autonomic symptoms developed from the Autonomic Symptom Profile and COMPASS, including 31 items with 6 domain weighted scores and a total weighted score. This study aimed to validate COMPASS 31, in its Italian version, for the diagnosis of diabetic cardiovascular autonomic neuropathy (CAN).

**Method:** Seventy-three diabetic patients (age 55±14 years, duration 12±10 years) fulfilled COMPASS 31 before undergoing CAN and diabetic polyneuropathy (DPN) assessment with cardiovascular reflex tests (CARTs), MNSI Questionnaire, MDNS, and vibration and thermal thresholds.

**Results:** COMPASS 31 total score differed between patients with and without CAN (29.9±19.5 Vs. 16.1±14.7, P=0.003) and with and without DPN (28.9±19.1 Vs. 12.7±11.3, P<0.0001). It was related to CARTs (autonomic score: r=0.31, P=0.009), and DPN measures (MNSI-Q: r=0.60, P<0.0001; MDNS: r=0.48, P<0.0001). ROC analysis demonstrated a fair diagnostic accuracy of total score for CAN (AUC: 0.748±0.068, 95% C.I. 0.599-0.861) and DPN (AUC: 0.742±0.061, 95% C.I. 0.611-0.845). The best cut-off values were 16 for early CAN [sensitivity: 75%; specificity: 65%; positive predictive value (PPV): 37%; negative predictive value (NPV): 90%], and 17 for both confirmed CAN and DPN (sensitivity: 70% and 65%; specificity: 67% and 79%; PPV: 25% and 68%; NPV: 93% and 78%, respectively). COMPASS 31 had a good internal consistency according to Cronbach's a coefficient of 0.73.

**Conclusion:** COMPASS 31 can represent a valid, reliable, easy to use, quantitative assessment tool for autonomic symptoms in diabetic neuropathy, with a fair diagnostic accuracy for both CAN and DPN.

## [O6] VITAMIN B12 DEFICIENCY IS ASSOCIATED WITH CARDIOVASCULAR AUTONOMIC NEUROPATHY IN PATIENTS WITH TYPE 2 DIABETES

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**Objective:** Cardiovascular autonomic neuropathy (CAN) is a severe diabetic complication associated with increased cardiovascular mortality. The risk of CAN in diabetes 2 patients could be increased by vitamin B12 deficiency as the case of peripheral neuropathy. This study investigates the association between serum levels of vitamin B12 and CAN in patients with type 2 diabetes.

**Method:** 469 ambulatory type 2 diabetes patients (mean diabetes duration 10.0 years, mean age 59.0 year, 63% men) had vitamin B12 measured and were screened for CAN using 3 standard cardiovascular reflex tests (CARTs): deep breathing test (E:I-ratio), lying-to-standing test (30/15) and the Valsalva maneuver. 5 minute resting heart rate (5min RHR) and heart rate variability indices (HRV) were also measured. CAN was diagnosed if at least 2 of 3 CARTs were abnormal. Associations were assessed by logistic and linear regression models adjusting for age, sex, diabetes duration and alcohol consumption.

**Results:** Serum levels of vitamin B12 were significantly lower in patients treated with metformin and/or proton pump inhibitors (PPIs) compare with patients not treated. A 25 pmol/l increase of vitamin B12 was associated with an odds ratio of CAN diagnosis of 0.94 (95%CI 0.88;1.00, P= 0.034) an increase of 0.21% in E:I-ratio (95%CI 0.01;0.43, P= 0.038) and a decrease in heart rate of 0.25 beats per minute (95%CI -0.47;-0.03, P= 0.025).

**Conclusion:** Serum vitamin B12 is negatively associated with CAN in patients with type 2 diabetes prompting the need for vitamin B12 screening in high risk patients e.g. those treated with metformin and/or PPIs.

## [O7] VITAMIN D LEVELS ARE REDUCED IN SUBJECTS WITH PAINFUL DIABETIC PERIPHERAL NEUROPATHY

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**Objective:** Reduced Vitamin D levels have been reported in diabetic peripheral neuropathy (DPN). However, the studies lacked adequate patient phenotyping and evaluation of potential confounding factors including assessment of sunlight exposure and daily activity. The aim of this study was to assess Vit-D levels in an appropriately designed study.

**Methods:** 45 type 2 diabetic (T2DM) Caucasian subjects (17 Painful-DPN, 14 Painless-DPN and 14 No-DPN) and 14 healthy volunteers (HV) had 25(OH)Vit-D measured between May and September. All subjects underwent neuropathy phenotyping with clinical, neurophysiological [NIS(LL)+7] and skin biopsy (IENFD and Sub epidermal NFD). They also had seasonal sunlight exposure and daily activity measured.

**Results:** Painful-DPN subjects were older and had higher body mass index (BMI). After adjusting for age, BMI and sunlight exposure, Vit-D levels (nmol/l) were significantly lower in Painful-DPN subjects [34.34(5.69), HV 64.95(6.85), No-DPN 50.00(6.1), Painless-DPN 53.22(6.1); ANCOVA  $p=0.01$ ]. Pairwise comparisons revealed main group difference between Painful-DPN vs Painless-DPN ( $p=0.02$ ) and Painful-DPN vs HV ( $p=0.002$ ). Sunlight exposure (ANOVA  $p=0.65$ ) and activity score (ANOVA  $P=0.46$ ) showed no significant difference among the groups. Vit-D and subepidermal NFD showed significant positive correlation ( $r=0.49$ ,  $p=0.008$ ) in subjects with DPN.

**Conclusions:** This study has demonstrated significant reduction of Vit-D in carefully phenotyped subjects with painful-DPN, independent of sunlight exposure. Patients with low Vit-D showed increased evidence of small fibre neuropathy. This novel finding suggests possible role of Vit-D in the pathogenesis of painful-DPN. Intervention trials with Vit-D in painful-DPN are now required to see if this might result in pain relief.

## [O8] CONGENITAL INSENSITIVITY TO PAIN EVIDENCES BY LACK OF C-NERVE FIBRES AT THE CORNEA

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**Objective:** The rare nerve growth factor beta (NGFB) mutation R221W causes a selective loss of thinly myelinated fibers, especially unmyelinated C-fibers. Carriers of this mutation show altered pain sensation. Here we have studied a large Swedish family with a mutation in the nerve growth factor beta (NGFB) gene causing insensitivity to deep pain without anhidrosis (hereditary sensory and autonomic neuropathy, type V; HSAN V). We investigated the relationship between peripheral afferent loss and pain evaluation by performing a careful quantification of C-fiber density in the cornea of the carriers, relating density to pain evaluation measures.

**Method:** Corneal confocal microscopy (CCM) was used to quantify C-fiber loss in 19 carriers (3 homozygous) and 19 age-matched controls. In addition, we collected pain evaluation data via the Situational Pain Questionnaire (SPQ), as well as neuropathy severity via the Neuropathy Deficit Score (NDS).

**Results:** Homozygotes, heterozygotes and control groups differed significantly in corneal C-fiber density, with the homozygotes showing a drastic afferent reduction. Importantly, peripheral C-afferent density correlated negatively with pain evaluation, revealed by SPQ scores.

**Conclusion:** This study is the first to investigate the contribution of unmyelinated C afferent density to the perceptual evaluation of pain. It demonstrates that the lower the peripheral C density, the lower the degree of reported pain intensity, indicating a functional relationship between C afferent density and higher-level pain experience. These findings have clinical and preclinical relevance for the assessment of peripheral contributions to pain syndromes.

## [O9] CORNEAL CONFOCAL MICROSCOPY DETECTS EARLY SMALL FIBRE DAMAGE AND INCREASED LANGERHANS CELL DENSITY IN CHILDREN WITH TYPE 1 DM

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**Objective:** Children with T1DM have no overt evidence of neuropathy. First generation corneal confocal microscopy (CCM) has previously shown an increase in Langerhans cells (LCs) in early neuropathy in adults with diabetes. The purpose of this study was to evaluate the presence and density of LCs and corneal nerve morphology in children with Type 1 diabetes mellitus (T1DM) using corneal confocal microscopy.

**Method:** We have studied 84 children with T1DM (age-14.6±2.3, duration of diabetes- 8.7±2.6, HbA1c-8.9±1.8) and 52 age-matched healthy control subjects (age-13.3±2.9) using CCM. Corneal nerve morphology and the density of Langerhans cells (LCs) were quantified in images obtained from the sub-basal nerve plexus.

**Results:** Corneal nerve fibre length (CNFL) (mm/mm<sup>2</sup>) (22.7±4.8 vs. 25.0±6.1; P=0.01) and corneal nerve branch density (CNBD) (no./mm<sup>2</sup>) (69.6±29.9 vs. 87.8±39.1; P=0.005) were lower, whilst corneal nerve fibre density (CNFD)(no./mm<sup>2</sup>) (31.1±7.5 vs. 31.7±7.5; P=0.7) and corneal nerve fibre tortuosity (CNFT) (TC) (13.7±5.1 vs. 12.8±3, P=0.2) did not differ in T1DM compared to control subjects. LC density (no./mm<sup>2</sup>) for both immature (58.1 ± 84.2 vs. 17.2± 22.1, P=0.003) and mature (3.2±5.2 vs. 1.5±3.1, P=0.03) cells was significantly higher in T1DM compared to control subjects. There was no correlation between LC density with HbA1c, duration of diabetes or corneal nerve fibre morphology.

**Conclusion:** Children with T1DM demonstrate an early reduction in corneal nerve branch density and length with no impact on the more proximal nerve trunk and an increase in corneal LC density. This indicates early immune activation and nerve degeneration in children with T1DM.

## [O10] AGREEMENT BETWEEN AUTOMATED AND MANUAL QUANTIFICATION OF CORNEAL NERVE FIBER LENGTH: IMPLICATIONS FOR DIABETIC NEUROPATHY RESEARCH

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**Objective:** Quantification of corneal nerve fiber length (CNFL) by in vivo corneal confocal microscopy represents a promising diabetic neuropathy biomarker, but applicability is limited by resource-intensive image analysis. We evaluated agreement between the established manual analysis protocol and a novel automated protocol.

**Method:** Sixty-eight controls, 139 participants with type 1 diabetes, and 249 participants with type 2 diabetes underwent CNFL measurement (N=456). Neuropathy severity was determined by clinical and electrophysiological criteria. CNFL was determined by manual (CNFL<sub>Manual</sub>, reference standard) and automated (CNFL<sub>Auto</sub>) protocols, and results were compared for correlation and agreement using Spearman coefficients and the method of Bland and Altman. Associations with neuropathy severity were evaluated by analysis-of-variance.

**Results:** Participants demonstrated broad variability in clinical characteristics associated with neuropathy. The mean age, diabetes duration and HbA1C was 53.1 ± 17.6 years, 15.9 ± 12.6 years, and 7.4 ± 1.6%, respectively, and 218 (47%) individuals had neuropathy. Mean CNFL<sub>Manual</sub> was 15.1 ± 4.9 mm/mm<sup>2</sup>, and mean CNFL<sub>Auto</sub> was 10.5 ± 3.71 mm/mm<sup>2</sup> (CNFL<sub>Auto</sub> underestimation bias, 4.58 ± 2.65 mm/mm<sup>2</sup> corresponding to 36.6 ± 22.1%). Bias was similar across healthy volunteer, type 1, and type 2 diabetes subgroups. Levels of CNFL<sub>Auto</sub> and CNFL<sub>Manual</sub> were both associated with neuropathy severity (ANOVA p<0.0001 for each comparison).

**Conclusion:** Although CNFL<sub>Auto</sub> substantially underestimated CNFL<sub>Manual</sub>, its bias was non-differential between diverse patient groups and its relationship with neuropathy severity was preserved. Determination of diagnostic thresholds specific to CNFL<sub>Auto</sub> should be pursued in diagnostic studies of diabetic neuropathy.

## [O11] SMALL NERVE FIBER STRUCTURE AND FUNCTION IN PAINFUL DISTAL POLYNEUROPATHY

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**Objective:** The introduction of skin biopsies to examine small nerve fiber morphology together with functional measures such as quantitative sensory testing (QST) has led to an improvement in diagnosing patients with small fiber neuropathy (SFN). Quantification of intraepidermal nerve fiber density (IENFD) is a commonly used measure in SFN. However, the structural and functional fiber characteristics are still unclear. This study combined structural and functional measurements to determine whether patients and healthy controls have differential patterns of correlations between structural and functional nerve measurements.

**Method:** 17 patients incl 6 with type 2 diabetes with painful distal polyneuropathy (PN) and 19 controls underwent comprehensive small fiber assessments including QST, response to topical capsaicin and analysis of skin biopsy samples (IENFD, epidermal and dermal nerve fiber length densities (eNFLD, dNFLD) and swellings).

**Results:** PN patients had reduced sensitivity to cold and heat, diminished capsaicin response, and lower IENFD, eNFLD and dNFLD compared to healthy controls (all  $p < 0.0003$ ). In PN patients, heat pain threshold was inversely related to IENFD ( $r = 0.58$ ,  $p = 0.01$ ). However, other QST parameters such as cold detection and cold pain thresholds did not correlate with the morphological parameters in PN.

**Conclusion:** The lack of correlation between several functional parameters and structural nerve changes in this sample of painful SFN suggest that altered sensory function is not a simple result of lost small nerve fibers. Studies are ongoing to explore this issue further.

## [O12] FACTORS INFLUENCING DIABETES POLYNEUROPATHY – ASSESSMENT USING METHODS OF SMALL FIBRE FUNCTION AND STRUCTURE

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**Objective:** A number of factors influence the development of Diabetes polyneuropathy (DPN) including poor glycaemic control, body mass index (BMI) and triglycerides (TGs). In this study we examine the relationship between these factors and small fibre function using the laser Doppler imager (LDI)FLARE technique as well as small fibre structure using the corneal confocal microscopy (CCM).

**Method:** 162 diabetes (DM) and 80 healthy volunteers (HV) were studied. All participants underwent clinical evaluation and fasting biochemical testing. CCM was performed using previously described methods and corneal nerve fibre density (CNFD) was derived using ACCMetrics® software. Small fibre function was assessed using the modified LDI<sub>FLARE</sub> which measures the size of the axon mediated neurovascular response to foot-skin heating.

**Results:** Within the DM cohort, both LDI<sub>FLARE</sub> and CCM (CNFD) significantly correlated with BMI ( $p < 0.0001$  and  $p < 0.0001$  respectively), HbA1c ( $p = 0.029$  and  $p < 0.0001$ ) and TGs ( $p < 0.0001$  and  $p < 0.0001$ ). However, within the HV group, the correlations were only with BMI ( $p = 0.015$  and  $p = 0.005$ ) and TGs ( $p = 0.008$  and  $p = 0.004$ ) but not with HbA1c ( $p = 0.50$  and  $p = 0.112$ ). In both groups, no relationship was observed with total cholesterol and in the diabetic group with duration of diabetes.

**Conclusion:** Our study demonstrates that despite assessing different aspects of neural integrity and in different anatomical sites, the LDI<sub>FLARE</sub> and CCM methods demonstrate excellent correlations with the same factors influencing DPN. Although this suggests that they may be interchangeable, longitudinal studies are needed to determine whether short-term changes of these factors influence both techniques to the same degree.

## [O13] MODULATING MOLECULAR CHAPERONES IMPROVES MITOCHONDRIAL BIOENERGETICS AND DECREASES THE INFLAMMATORY TRANSCRIPTOME IN DIABETIC SENSORY NEURONS

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**Objective:** We have previously demonstrated that modulating molecular chaperones with KU-32, a novobiocin derivative, ameliorates physiologic and bioenergetic deficits of diabetic peripheral neuropathy (DPN). We have replaced the coumarin core of KU-32 with a meta-fluorinated biphenyl ring system to create a new family of neuroprotective molecules termed novologues (novobiocin analogues). KU-596 has emerged as the lead candidate and the current study sought to determine whether KU-596 offers similar therapeutic potential for treating DPN.

**Method:** Wild type (WT) and heat shock protein 70 knockout (Hsp70 KO) mice were made diabetic for 8-12 weeks and given 4-6 weekly oral doses of 2-20 mg/kg KU-596. Psychosensory and electrophysiologic measures were performed. Adult sensory neurons were isolated and used for bioenergetics assessments and to isolate mRNA to perform RNA Seq analysis.

**Results:** KU-596 dose-dependently improved diabetes-induced hypoalgesia, NCV and sensory neuron bioenergetic deficits in WT but not Hsp70 KO mice. Bioinformatic analysis of the differentially expressed genes identified by RNA Seq analysis of sensory neuron RNA indicated that diabetes strongly increased inflammatory pathways. KU-596 therapy effectively reversed these increases independent of Hsp70. In contrast, the effects of KU-596 on decreasing the expression of genes involved in the production of reactive oxygen species were Hsp70-dependent.

**Conclusion:** These data indicate that novologue therapy offers an effective approach towards correcting nerve dysfunction in DPN, but that normalization of inflammatory pathways alone by novologue therapy seems to be insufficient to reverse insensate DPN. KU-596 is now in preclinical development toward a Phase I trial.

## [O14] THE MACROPHAGE ACTIVATION MARKER SOLUBLE CD163 IS ASSOCIATED TO DIABETIC NEUROPATHY

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**Objective:** Chronic low-grade inflammation is believed to play a role in the pathogenesis of diabetic neuropathy (DN).

Chronic low-grade inflammation is characterized by increased circulating levels of several inflammatory biomarkers, including soluble CD163 (sCD163), derived from activated macrophages.

**Method:** In this cross-sectional analysis, we studied people with screen-detected type 2 diabetes from the five-year follow up in the ADDITION-Denmark study. 701 people were tested for cardiac autonomic neuropathy (CAN) using three standard tests and 371 people were tested for distal peripheral neuropathy (DPN) using CASE IV. Serum was analysed for sCD163 by ELISA. We studied the association between sCD163 (<sup>2</sup>log) and the presence of DN using logistic regression models.

**Results:** Mean age 65.0 (6.9), 61% men, mean BMI 30.7 (5.3) and median HbA1c (p25, p75) 6.4 (6.0;6.9). The age and sex adjusted odds ratio (OR) for DPN was 1.73 (1.14;2.61) per doubling of sCD163. Adjustment for age, sex, BMI and HbA1c attenuated the OR to 1.64 (1.07;2.52). The age and sex adjusted OR for CAN was 1.50 (1.10; 2.06) per doubling of sCD163. The association was no longer statistically significant after adjustment for age, sex, BMI and HbA1c with OR 1.32 (0.96;1.84).

**Conclusion:** This study shows an association between sCD163 and DN. The association appears stronger for DPN than for CAN, and in the case of DPN is not accounted for by age, sex, obesity or glycaemic control. Our findings indicate that macrophage – related low grade inflammation is involved in the pathophysiology of DN.

## [O15] BRAIN-DERIVED NEUROTROPHIC FACTOR IN THE CEREBROSPINAL FLUID IS RELATED TO PERIPHERAL NERVE FUNCTION IN TYPE 2 DIABETIC PATIENTS

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**Objective:** To determine the concentration of Brain-Derived Neurotrophic Factor (BDNF) in the cerebrospinal fluid in type 2 diabetic patients and, secondly, to relate the findings to peripheral nerve function.

**Method:** Twenty-three type 2 diabetic patients (nine with and fourteen without diabetic polyneuropathy (DPN)) and eleven non-diabetic controls were included. Neuropathic status was determined by clinical examination, nerve conduction studies and vibratory perception thresholds. Based on the findings a neuropathy rank sum score was calculated for each patient.

**Results:** Diabetic patients were older and had higher BMI than controls (64 (47-79) vs. 55 (42-69) years,  $p < 0.05$  and 29.3 (23.9-37.6) vs. 26.2 (22.3-29.1) kg/m<sup>2</sup>,  $p < 0.01$ ), (median, range). No difference in age or BMI was found comparing diabetic patients with and without DPN.

BDNF levels did not differ between diabetic patients and controls (277 (85-521) vs. 236.5 (145-463) pg/mL,  $p = 0.93$ ). There was a trend for lower BDNF levels in diabetic patients with DPN as compared to patients without DPN (198 (131-362) vs. 367 (85-521) pg/mL,  $p = 0.10$ ). Interestingly, BDNF levels correlated inversely to measures of peripheral nerve function (Neuropathy Symptom Score:  $r = -0.57$ ,  $p < 0.01$ , Neurological Impairment Score:  $r = -0.42$ ,  $p < 0.05$ , Neuropathy Rank Sum Score:  $r = -0.62$ ,  $p < 0.01$ ).

**Conclusion:** DNF levels were inversely related to measures of peripheral nerve function. The findings suggest that lack of BDNF may be involved in the development of DPN or that DPN leads to lower neurotrophic support in the central nervous system.

## [O16] ROLE OF MACROPHAGES IN THE PATHOGENESIS OF DIABETIC POLYNEUROPATHY

Hiroki Mizukami<sup>1</sup>, Saori Ogasawara<sup>2</sup>, Tomohiro Tago<sup>2</sup>, Emi Ishiyama<sup>2</sup>, Soroku Yagihashi<sup>2</sup>

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**Objective:** It is recently suggested that diabetic condition enhances macrophage infiltration into peripheral nerves. The aim of this study is to elucidate what roles macrophages play in the pathogenesis of diabetic polyneuropathy (DPN).

**Method:** Sciatic nerves (SN) of STZ induced diabetic mice with 9 wks duration were dissected after confirmation of the presence of nerve conduction delay. Nerve macrophages were quantitated on the sections immunostained with Iba-1 as pan-macrophage marker. mRNA expressions of iNOS and CD163 were evaluated by qPCR. For in vitro experiment, Schwann cell lines (IMS32) were co-cultured with RAW246 macrophage cells (R0) or pro-inflammatory type M1 macrophages (RM1) that were differentiated by 25ug/ml LPS at a ratio of 100:1 for 24 hours, Co-culture experiment in trans-well chamber to avoid direct contact was also conducted. At end, mRNA expressions of cytokines of IMS32 were evaluated.

**Results:** Iba-1 positive cells were significantly increased in diabetic SN compared to those in non-diabetic controls ( $p < 0.01$ ). mRNA expression of iNOS was increased 4 folds in diabetic SN compared to that in controls, whereas that of CD163 was comparable between diabetic and non-diabetic nerves. In vitro, IMS32 co-cultured with R0 exhibited 25 times greater expression of TNF- $\alpha$  than IMS32 alone. The expression of pro-inflammatory cytokines was further enhanced in IMS32 co-cultured with RM1. In similar manner, IMS32 co-cultured with RM1 in trans-well chamber exhibited enhanced expression of pro-inflammatory cytokines compared to the cells with R0.

**Conclusion:** Diabetic nerve is characterized by macrophages infiltration with augmented inflammatory reactions which may affect Schwann cells.

## [O17] NOCTURNAL ANTIHYPERTENSIVE TREATMENT RESTORES 24 HOUR BLOOD PRESSURE PROFILE IN TYPE 1 DIABETIC PATIENTS WITH AUTONOMIC NEUROPATHY

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**Objective:** Cardiac autonomic neuropathy (CAN) and elevated nocturnal blood pressure are independent risk factors for cardiovascular disease in patients with diabetes. The objective of the present study was to test the efficacy of bedtime dosing (BD) versus morning dosing (MD) of the ACE inhibitor enalapril on 24 h blood pressure profile in patients with type 1 diabetes.

**Method:** In a randomised, double-blind, two-way cross-over study, 24 normoalbuminuric patients with long-term type 1 diabetes with CAN were treated for 12 weeks with either MD or BD of 20 mg enalapril, followed for 12 weeks of switched treatment regimen. The mean age of the patients were 60 +/- 7 (SD) years, 40 % were males, and the diabetes duration was 36 +/- 11 years.

**Results:** Night time SBP dipping increased 3 % ( $p < 0.05$ ) with BD of enalapril compared with MD. Similarly, MAP was reduced 2 mmHg ( $p = 0.07$ ). Daytime SBP and DBP were not significantly different between the two treatment regimens. No significant difference was found on left ventricular mass or left ventricular volume between the two treatment regimens. No adverse events were registered during night time treatment of blood pressure and no drop outs occurred during the study.

**Conclusion:** This study demonstrates for the first time that high risk long-term type 1 diabetic patients with autonomic neuropathy favourably and without risk can be treated with an ACE inhibitor during night. The potentially beneficial effect on long-term cardiovascular risk remains to be determined.

## [O18] BARIATRIC SURGERY RESTORES AUTONOMIC NERVE FUNCTION TOWARDS NORMAL IN OBESE SUBJECTS WITH DIABETES

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**Objective:** The aim of this study was to evaluate the impact of bariatric surgery on cardiac and sudomotor autonomic C-fiber function in obese subjects with and without Type 2 diabetes (T2DM), using sudorimetry and heart rate variability (HRV) analysis.

**Method:** Patients were evaluated at baseline, 12 and 24 weeks after vertical sleeve gastrectomy or Roux-en-Y gastric bypass. All subjects were assessed using Sudoscan™ to measure electrochemical skin conductance (ESC) of hands and feet, time and frequency domain analysis of HRV, Neurologic Impairment Scores of lower legs (NIS-LL) and quantitative sensory tests (QST).

**Results:** Fifty-three subjects completed up to 24-weeks of follow-up (18 non-T2DM, 21 pre-DM and 14 T2DM). ESC of feet improved significantly (MANOVA) towards normal values in T2DM subjects by 12 and 24 weeks (Baseline=55.92±3.4 vs 12-weeks=64.31±3.5 vs 24-weeks=69.92±2.98,  $p < 0.001$ ). HRV improved significantly in T2DM subjects (Baseline sdNN=41.54±7.47 vs 12-weeks=59.39±6.06 vs 24-weeks=68.08±8.05,  $p < 0.001$  and baseline rmsSD=23.85±3.93 vs 12-weeks=37.54±6.74 vs 24-weeks=39.08±7.67,  $p < 0.01$ ). Weight, body mass index (BMI), percent body fat, triglycerides and HDL improved significantly in all groups. A1C, Insulin and HOMA2-IR levels improved significantly in pre-DM and T2DM subjects. Multiple linear regression analysis showed feet ESC improvement at 24 weeks was independently associated with baseline A1C, insulin and HOMA2-IR levels; but not with age, gender, ethnicity, weight, BMI, body fat, triglycerides, or HDL.

**Conclusion:** This is the first study to show that bariatric surgery can restore both cardiac and sudomotor autonomic C-fiber dysfunction in subjects with diabetes, potentially impacting morbidity and mortality.

## [O19] ROLE OF GLUCOSE VARIABILITY ON SYMPATHO-VAGAL BALANCE IN PATIENTS WITH METABOLIC SYNDROME AND DIABETES

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**Objective:** The relationship between autonomic nervous system and glucose fluctuations is still partially unknown as well as the chronological sequence of this association. We aimed to evaluate the relationship between glucose variability (GV) and sympatho-vagal balance, in patients with insulin resistance, before the onset of diabetes mellitus.

**Method:** Forty-four patients with metabolic syndrome (MS), 26 type 2 diabetes mellitus (T2DM), 30 type 1 diabetes (T1DM) and 15 controls (C) underwent continuous glucose monitoring, from which these GV indexes were calculated: SD, MAGE, CONGA-1, CONGA-2, CONGA-3, CONGA-4, J-index, HBGI. From 5-minute ECG monitoring, prevalent sympathetic (Low Frequency, LF) and parasympathetic (High Frequency, HF) component, and sympatho-vagal balance (LF/HF) were calculated.

**Results:** GV progressively increased from C to MS, T2DM and T1DM ( $p=0.000$ ). MS, T2DM and T1DM showed a significantly lower HF (C:  $29.6 \pm 3.3\%$ ; MS:  $21.1 \pm 2.4\%$ ; DM2:  $20.6 \pm 3.1\%$ ; DM1:  $23.6 \pm 3.1\%$ ) and higher LF/HF (C:  $1.1 \pm 0.1$ ; MS:  $1.7 \pm 0.3$ ; DM2:  $1.4 \pm 0.3$ ; DM1:  $2.1 \pm 0.4$ ) than C ( $p<0.05$ ). In MS, T2DM and T1DM, GV positively correlated with LH and LF/HF and negatively with HF ( $p<0.05$ ). GV remained independent predictor of sympatho-vagal balance after controlling for age, waist circumference, glycaemia, HbA1c, DM duration.

**Conclusion:** GV is already increased in subjects with insulin resistance, before the onset of diabetes, and it is associated with an increased sympatho-vagal balance, mainly due to a reduction in parasympathetic component. Interventional studies are needed, to demonstrate if the reduction of GV improves sympatho-vagal balance.

## [O20] CARDIAC AUTONOMIC NEUROPATHY PREDICTS THE OCCURRENCE OF HYPERTENSION IN TYPE 2 DIABETIC PATIENTS

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**Objective:** In a cross-sectional study we previously showed that the prevalence of hypertension in diabetic patients increased with the severity of cardiac autonomic neuropathy (CAN) and that the CAN/hypertension profile was associated with a higher prevalence of vascular complications. The aim of this prospective study was to evaluate the predictive value of CAN for incident hypertension and the potential role of CAN/hypertension profile for new cardio-vascular complications.

**Method:** CAN was assessed by analysing heart rate variations during three standard tests (deep breathing, lying-to-standing, Valsalva). At baseline among a population of 310 patients (age  $41.7 \pm 12.8$  yrs, mean diabetes duration  $8.4 \pm 6.8$  yrs) CAN was present in 123 patients (72 type 2, 51 type 1 diabetics), and 62 had hypertension. The CAN+ patients were invited to a new evaluation visit 10-12 years later.

**Results:** Among the 123 CAN+ patients, 25 were lost at follow-up. Among the 98 others, 30 had hypertension at baseline: 6 of them had died (20%), of cardio-vascular cause for 5 of them. Among the 68 other CAN+ patients, all normotensive at baseline, 10 had cardio-vascular events, 20 became hypertensive (29%). The percentage of patients with incident hypertension increased with the severity of CAN ( $p<0.01$ ): 12.5%, 35% and 56.2%, respectively in the patients with one, two or three abnormal CAN function tests.

**Conclusion:** The present data support in diabetic patients the role of a vagal defect in the occurrence of new hypertension and suggest a worse vascular prognosis in the patients with both CAN and hypertension.

## [O21] INTEGRATED CARDIOVASCULAR/RESPIRATORY CONTROL IN TYPE 1 DIABETES

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**Objective:** Diabetic autonomic dysfunction and ventilatory control abnormalities both increase cardiovascular risk. Cardiovascular (baroreflex) and respiratory (chemoreflex) control mechanisms were studied separately in diabetes, but their reciprocal interaction had never been assessed. We hypothesized that prevalent autonomic neuropathy would depress both chemoreflexes and the arterial baroreflex mechanisms, whereas prevalent autonomic imbalance through sympathetic activation would depress the baroreflex but enhance chemoreflex mechanisms.

**Method:** In 46 type-1 diabetic subjects and 103 age-matched controls we measured RR interval, continuous noninvasive blood pressure, minute ventilation, oxygen saturation (SaO<sub>2</sub>) and end-tidal carbon dioxide (CO<sub>2</sub>) at rest and during progressive normoxic hypercapnia and progressive isocapnic hypoxia. We estimated resting baroreflex sensitivity from RRinterval and blood pressure variability, and hypercapnic and hypoxic chemoreflex sensitivities by the slopes of the regressions linking minute ventilation to CO<sub>2</sub> increase and to SaO<sub>2</sub> decrease, respectively. Autonomic function was evaluated by a standard battery of cardiovascular tests.

**Results:** Mild signs of autonomic dysfunction were present in 26/46 diabetics (score 1.42±0.14, group N+), and absent in 20/46 patients. Baroreflex sensitivity was reduced in the entire diabetic group (p<0.01), and particularly in group N+ (p<0.01). The hypercapnic chemoreflex was significantly increased in the entire diabetic group (p<0.05), and particularly in N+ diabetics (p<0.05). Conversely, the hypoxic chemoreflex was slightly (p:ns) depressed in the entire diabetic group.

**Conclusion:** A reduced sensitivity to hypoxia seems a primary factor leading to reflex sympathetic activation (enhanced hypercapnic chemoreflex and depression of baroreflex), hence suggesting a functional origin of autonomic abnormalities in initial diabetes.

## [O22] CARDIOVASCULAR AUTONOMIC NEUROPATHY AND CORONARY ARTERY CALCIFICATIONS IN ASYMPTOMATIC PATIENTS WITH TYPE 2 DIABETES

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**Objective:** High coronary artery calcium scores (CACS) were shown to predict a higher likelihood of inducible myocardial ischemia and to be associated with a poor cardio-vascular prognosis. Cardiovascular autonomic neuropathy (CAN) also alters cardio-vascular prognosis. This cross-sectional study aimed to test whether in type 2 diabetes CAN is a risk factor of coronary calcification and may interact with CACS for the risk of SMI.

**Method:** CACS was measured by computed tomography in 253 type 2 diabetic patients, without cardiac history or symptom, with a normal resting ECG and ≥1 additional risk factors. SMI was assessed using stress myocardial scintigraphy and/or stress echocardiography. CAN was assessed in 102 of them using three standard tests (deep breathing, lying-to-standing, Valsalva).

**Results:** CACS was ≥100 Agatston units in 34% of the patients. SMI was detected in 33 patients (13%). A CACS ≥100 predicted the presence of SMI: 30.2% of patients had SMI vs 11.3% of those with CACS <100 (odds ratio 3.4 [1.4-8.0], p<0.01). CAN, as defined by ≥2 abnormal tests, affected 46% of tested patients and was not associated with CACS ≥100 (p=0.17). CAN was not associated with SMI and did not change the risk of SMI related to CACS.

**Conclusion:** These data suggest that in asymptomatic high risk type 2 diabetic patients high CACS and CAN are highly prevalent. The risk of SMI is 3.4-fold increased when CACS is ≥100 but not changed by CAN. CAN assessment does not help to detect patients with high CACS.

## [O23] COGNITIVE IMPAIRMENT IN SUBJECTS WITH IMPAIRED GLUCOSE TOLERANCE IMPROVES WITH A LIFESTYLE INTERVENTION

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**Objective:** Recently published data show evidence of a neurodegenerative process in LCR rats with impaired glucose tolerance (IGT) consistent with those seen in aged-related dementing illnesses such as AD in humans and the neuropathology is associated with mitochondrial dysfunction\*. The current study examined cognitive impairment in subjects with impaired glucose tolerance.

**Method:** Prospective, single blinded, randomized study of subjects with impaired glucose regulation divided into two groups (1) standard care (SC) or (2) tailored diet and physical activity (TDPA) intervention. The Montreal Cognitive Assessment (MoCA) was administered at baseline, after 6 months and 1 year of the intervention. All 3 versions of the MoCA were used to reduce significant practice effects.

**Results:** In subjects with only IGT, 21 out of 59 (36%) of subjects had a MoCA < 26/30 (abnormal) at baseline. The most severely affected domain was delayed recall, where only 32% of subjects had a perfect score of 5 and the rest had scores <5 (mean 2.75 + 0.17). In subjects with a MoCA < 26/30, the mean MoCA was 23.43 + 0.30. After 1 year with the TDPA intervention, there was improvement in the MoCA in subjects with a baseline MoCA < 26 (P=0.017).

**Conclusion:** (1) Cognitive impairment is increased in subjects with IGT even before they develop diabetes; (2) Similar to minimal cognitive impairment, delayed recall is primarily affected; and (3) There is improvement in subjects with a MoCA < 26 following the TDPA intervention.

\* (Choi J et al. Ann Clin Trans Neurol 1(8):589-604, 2014)

## [O24] EFFECTS OF LONG-ACTING C-PEPTIDE ON PERIPHERAL NEUROPATHY IN TYPE 1 DIABETES – CLINICAL TRIAL RESULTS

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**Objective:** Replacement of native C-peptide has been shown to exert a beneficial influence on peripheral nerve function in type 1 diabetes. This study evaluated the effect of a long-acting C-peptide on nerve function in type 1 diabetes patients with mild to moderate peripheral neuropathy.

**Method:** 250 patients with type 1 diabetes and clinical signs of peripheral neuropathy and sural nerve conduction velocity (SNCV) >2SD below normal were randomized to receive long-acting (pegylated) C-peptide in weekly doses of either 0.8 mg (n=71) or 2.4 mg (n=73) or placebo (n=106) for 52 weeks. Bilateral SNCV and vibration perception threshold (VPT, Vibratron II) at the big toe were measured on two occasions at each time point: baseline, after 26 weeks and after 52 weeks. mTCNS was used to grade the peripheral neuropathy.

**Results:** Plasma C-peptide rose during the study to 1.8-2.2nM (lower dose) and to 5.6-6.1 nM (higher dose). After 52 weeks SNCV had increased by 1.0±0.24 m/s (P<0.001 within group) in the patients receiving C-peptide, the corresponding value for the placebo group was 1.2±0.29 m/s. There was no significant difference between the dose groups. Compared to basal, VPT had improved by 25% after 52 weeks of C-peptide therapy (change in C-peptide groups: -4.9±1.1µm, placebo group: -0.2±1.0µm, P<0.002). mTCNS was unchanged during the study. There was no significant development of antibodies to pegylated C-peptide during the study.

**Conclusion:** Once weekly administration of long-acting C-peptide for 52 weeks results in marked improvement in VPT but not SNCV.

## [O25] IMPACT OF DIABETIC NEUROPATHY ON DIABETES DISTRESS AND DEPRESSION IN LONGSTANDING T1DM: RESULTS FROM THE CANADIAN STUDY OF LONGEVITY IN TYPE 1 DIABETES

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**Objective:** Older patients with longstanding type 1 diabetes (T1DM) are at risk of neurological and micro/macrovacular complications, which negatively impact mental health. We aimed to compare associations of various complications with depression and diabetes-related emotional distress.

**Method:** 309 Canadians with over 50 years of T1DM submitted a questionnaire and recent laboratory and retinopathy reports. Complications were determined using the Michigan Neuropathy Screening Instrument (score $\geq$ 3/15), ophthalmologist reports, laboratory glomerular filtration rate $<$ 60mL/min and albumin:creatinine $>$ 2mg/mmol, and self-reported cardiovascular disease (CVD). Depression and distress were measured using the Geriatric Depression Scale (GDS) and Problem Areas in Diabetes Scale (PAID), respectively. Factors independently associated with depression and distress were analyzed by multiple linear regression.

**Results:** Among 309 participants, 130(42.3%) had neuropathy, 193(71.5%) had retinopathy, 110(38.6%) had nephropathy, and 105(34.0%) reported CVD. In univariate analysis, presence of neuropathy was associated with increased PAID ( $p<0.001$ ) and GDS scores ( $p<0.001$ ), while nephropathy was associated exclusively with increased PAID ( $p=0.025$ ), CVD was associated with GDS ( $p=0.035$ ), and retinopathy was not associated with either score. In multiple linear regression adjusting for complications, age, sex, and A1C, we found that i) only neuropathy ( $B=4.5$ ,  $p=0.002$ ), nephropathy ( $B=3.2$ ,  $p=0.029$ ), and lower age ( $B=-0.20$ ,  $p=0.020$ ) were associated with higher PAID score; ii) only neuropathy was associated with higher GDS score ( $B=1.4$ ,  $p<0.001$ ).

**Conclusion:** In longstanding T1DM, presence of neuropathy was independently and consistently associated with emotional distress and depression. Future research must explore the directionality of this association and determine potential interventions.

## [O26] PROGRESSIVE DECLINE OF COMPOUND MUSCLE ACTION POTENTIALS IN MOTOR NERVE CONDUCTION STUDIES IN JAPANESE TYPE 2 DIABETIC PATIENTS-FOUR YEAR FOLLOW-UP STUDY

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**Objective:** Despite an early and common complication of diabetes, the mode and pattern of clinical development of diabetic neuropathy are not well known. In this study, we examined the sequential changes of nerve conduction studies for 4 years to characterize the way how neuropathic changes will develop in type 2 diabetic patients.

**Method:** Among 2,310 type 2 diabetic patients who visited the Naka Memorial Clinic, 158 patients who underwent serial 4 year nerve conduction studies (NCS) were selected. Clinical profile and recordings of NCS of median and tibial nerves were retrospectively examined as to the changes of motor nerve conduction velocities (mNCVs)(m/s), amplitudes (CMAPs)(mV), F-wave latencies (s), and F-wave NCVs (m/s). Risk factors for the progression were analyzed by multiple regression analysis.

**Results:** At baseline, prevalence of neuropathy in 2,310 diabetic patients was 27% with a significant risk of HbA1c, hypertension, and duration of diabetes. The prevalence of clinical neuropathy in 158 cases was 30% at baseline and 29% at end of 4 year-follow up with significant improvement of HbA1c (8.6 to 6.9%). Over 4-year period, mNCVs of median and tibial nerves were slightly improved or consistent (+1.5%,  $p<0.05$ ; +0.8%, NS). In contrast, CMAPs of both nerves were decreased (-11.6%,  $p<0.01$ ;-3.7%,  $p<0.05$ ). Clinical profile of ankle jerk, vibration threshold, sensory tests were unaltered. For the decrease in CMAPs, no specific risk factors were identified.

**Conclusion:** This study demonstrated progressive decline of CMAPs over 4 year period despite improved blood glucose control in type 2 diabetic patients.

## [O27] MUSCARINIC TOXIN 7 ENHANCES SENSORY NERVE GROWTH IN VITRO AND IN VIVO IN NORMAL AND DIABETIC RODENTS

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**Objective:** Our recent work shows that inhibiting muscarinic receptors of sensory neurons induces AMP-activated protein kinase (AMPK) activity, nerve sprouting and regeneration in rodent models of diabetes. We hypothesized that muscarinic toxin 7 (MT7), a specific antagonist of the muscarinic acetylcholine type 1 receptor (M1R), would enhance AMPK, mitochondrial function and nerve growth in vitro and in vivo.

**Method:** Dorsal root ganglia (DRG) neurons from age-matched control and streptozotocin (STZ)-induced diabetic rats were cultured. Cellular bioenergetic status was assessed using a Seahorse Biosciences XF-24 Analyzer. Corneal nerve density was analyzed by corneal confocal microscopy in mice before, and at assorted time after, onset of STZ-induced diabetes.

**Results:** DRG neurons treated with MT7 (30-100nM) for 24h showed increased neurite outgrowth while topical delivery of MT7 to the eye of mice for 11 days significantly ( $p < 0.05$ ) increased corneal nerve density. MT7 enhanced AMPK phosphorylation 4-6 fold in cultured neurons. Mitochondrial basal respiration, coupling efficiency, respiratory control ratio, maximal respiration, and spare respiratory capacity were not changed by 1 or 2h treatment of cultures with MT7. However, maximal respiration and spare respiratory capacity were significantly elevated after 3h ( $p < 0.05$ ). Diabetes induced a significant ( $p < 0.05$ ) decrease in corneal nerve density compared to pre-diabetic values and topical delivery of MT7 to the eye of these diabetic mice for 2 weeks returned corneal nerve density to pre-diabetic values.

**Conclusion:** Our results reveal an entirely novel M1R-modulated pathway in sensory neurons that represents a potential therapeutic target to regulate mitochondrial function and nerve fiber growth in diabetes.

## [O28] CLINICAL NEUROPATHY PHENOTYPING AND ASSESSMENT OF BIOMARKERS IN PAINFUL DIABETIC PERIPHERAL NEUROPATHY

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**Objective:** Underlying mechanisms of Painful diabetic peripheral neuropathy (painful-DPN) remain uncertain. A recent study reported relatively preserved nerve regeneration and axonal swellings in distal leg intraepidermal nerve fibres (IENF) in painful DPN.

**Method:** 61 T2DM subjects and 19 healthy volunteers (HV) underwent detailed clinical and neurophysiological assessments and were subsequently divided into three groups based on the neuropathy composite score of the lower limbs [NIS(LL)] plus 7 tests (23 Painful-DPN, 19 Painless-DPN and 19 Type2 Diabetes with no neuropathy [No-DPN]). All subjects underwent punch skin biopsy 10 cm above the ankle and immunohistochemistry used to quantify total IENF with protein gene product 9.5 (PGP9.5), growth-associated protein 43 (GAP43) for regenerating IENF, and calcitonin gene related peptide (CGRP).

**Results:** DPN subjects were marginally older but statistically not significant [age, years: HV 55.1(10.6), No-DPN 58.3(8.6), Painless-DPN 60.8(10.03), Painful-DPN 60.17(9.7); ANOVA  $p = 0.28$ ]; had advanced neuropathy [NIS(LL)+7 score, No-DPN 1.4(1.2), Painless-DPN 19.6(7.6), Painful-DPN 28.9(16.4)]. IENF density was severely depleted ( $p < 0.001$ ) in both DPN groups [PGP9.5 IENFD/mm, HV 5.6(1.3), No-DPN 5.3(3.1), Painless-DPN 0.6(1.4), Painful-DPN 0.8(1.7)], with no differences between the latter two groups for PGP9.5, GAP43, CGRP, or GAP43/PGP9.5 ratio

**Conclusion:** While distal leg IENF density is recommended as “gold standard” for the diagnosis of small fibre neuropathy, in this study of patients with advanced neuropathy we found that these nerve markers may not differentiate between chronic painful-DPN and painless-DPN. Studies of molecular markers particularly in sub-epidermal nerve fibres, and mechanisms up-stream might be more relevant especially in advanced neuropathy subjects.

## [O29] HIGH GLUCOSE CONCENTRATION DOWN-REGULATES SIRT2 EXPRESSION IN SENSORY NEURONS VIA A SORBITOL DEHYDROGENASE-DEPENDENT PATHWAY

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**Objective:** Neuronal mitochondrial function is impaired in diabetes and Sirtuin 2 (SIRT2) is a key sensor of redox and metabolic state that regulates cellular bioenergetics. Our previous work shows that SIRT2 signalling within cultured adult sensory neurons drives axon regeneration and under diabetic conditions this pathway was impaired. We tested the hypothesis that high glucose concentration depleted SIRT2 expression via enhancement of polyol pathway activity.

**Method:** Type 1 diabetes was induced in rodents by streptozotocin (STZ). DRG sensory neurons derived from control and STZ-diabetic rats, or wild-type and SIRT2 knockout (KO) mice, were analyzed for gene expression or cultured in defined media with varying concentrations of D-glucose. Seahorse XF24 analyser measured mitochondrial function of cultured neurons.

**Results:** SIRT2 protein isoforms 2.1 and 2.2 were reduced by 20-30% in DRG of diabetic mice ( $p < 0.05$ ). After 72hrs exposed to high D-glucose (25mM vs 5mM) cultured sensory neurons showed a significant 2-fold ( $p < 0.05$ ) decrease in SIRT2 expression and respiratory capacity that was prevented by SDI-158 (inhibitor of polyol pathway enzyme sorbitol dehydrogenase). In cultures derived from diabetic rats expression of SIRT2 and electron transport chain components were significantly increased ( $p < 0.05$ ) by SDI-158. Intact DRG isolated from SIRT2 KO mice exhibited reduced expression of ATP synthase and Complex III components compared with wild type. This was associated with impaired mitochondrial bioenergetics in cultures of SIRT KO neurons.

**Conclusion:** The SIRT2 pathway drives axon regeneration and this signalling axis is impaired in diabetic sensory neuropathy due to enhanced polyol pathway activity caused by hyperglycaemia.

## [O30] SYSTEMIC EXTRACELLULAR SUPEROXIDE DISMUTASE (SOD3) LEVELS IN RELATION TO NERVE CONDUCTION OVER TWO YEARS IN RECENTLY DIAGNOSED TYPE 1 AND TYPE 2 DIABETES

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**Objective:** Oxidative stress is thought to play a key role in the pathogenesis of diabetic neuropathy. We determined the course of extracellular superoxide dismutase (SOD3) concentrations in relation to nerve conduction in recently diagnosed diabetic subjects over 2 years.

**Method:** We prospectively assessed serum concentrations of SOD3 and nerve conduction attributes over 2 years in 40 type 1 diabetes (T1D) and 88 type 2 diabetes (T2D) subjects of the German Diabetes Study (GDS). Baseline characteristics [T1D/T2D] - age: 35.0±12.0/54.2±9.7 [SD] years; male: 55/73%; BMI: 24.8±4.0/31.3±5.8 kg/m<sup>2</sup>, diabetes duration: 5.4±3.7/5.0±3.7 months; HbA1c: 7.0±1.6/6.5±1.0% (53.5±17.5/47.0±10.8 mmol/mol). Two-year follow-up [T1D/T2D] - BMI: 26.2±3.8/31.5±5.5 kg/m<sup>2</sup>, HbA1c: 7.0±1.2/6.6±1.1% (53.0±13.4/46.6±12.0 mmol/mol).

**Results:** SOD3 concentrations at baseline (T1D: 51.5±30.7 ng/ml; T2D 54.8±32.5 ng/ml) and two years follow-up (T1D: 35.5±16.1 ng/ml; T2D 33.1±15.4 ng/ml) were similar between the groups. However, compared to baseline, SOD3 levels declined in both groups ( $P < 0.0001$ ). Linear regression analyses (adjusted for sex, age, and BMI) revealed that at baseline in patients with T2D low SOD3 concentrations were associated with reduced peroneal ( $\beta = 0.412/P < 0.0001$ ), median ( $\beta = 0.257/P < 0.05$ ), and ulnar ( $\beta = 0.407/P < 0.0001$ ) nerve conduction velocity (NCV) and sural ( $\beta = 0.407/P = 0.001$ ) sensory NCV, and reduced median ( $\beta = 0.326/P = 0.008$ ), ulnar ( $\beta = 0.364/P = 0.001$ ), and sural ( $\beta = 0.373/P = 0.001$ ) sensory nerve action potential (SNAP). Low baseline SOD3 concentrations predicted the decline of ulnar motor NCV over 2 years ( $\beta = 0.372/P = 0.001$ ).

**Conclusion:** In conclusion, in patients with recently diagnosed T2D, low SOD3 serum concentrations were associated with nerve conduction slowing, declined over 2 years despite good glycemic control, and predicted the progression of ulnar motor NCV deficits.

## [O31] INVOLVEMENT OF INSULIN AND RHOA IN THE NEUROPROTECTIVE ACTIVITIES OF EXENDIN-4 IN VITRO

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**Objective:** Exendin-4 (Ex-4), a synthetic GLP-1 receptor agonist, has been shown to preserve neurons following axonal injury and neurodegenerative disorders; however, the underlying mechanisms remain unclear. We investigated the efficacy of Ex-4 on neurite outgrowth and neuronal survival in vitro.

**Method:** Neurite outgrowth and neuronal survival assays were performed on DRG neurons from 8-week-old Wistar rats in the presence or absence of insulin with different concentrations of Ex-4 (0, 1, 10, or 100 nM). RhoA activity in PC12 cells was determined by the G-LISA system.

**Results:** Ex-4 dose-dependently (1 nM ≤ 10 nM ≤ 100 nM) promoted neurite outgrowth and neuronal survival at two and seven days in culture, respectively. Insulin removal decreased the ratios of neurite-bearing cells from 38.6% to 27.5% and those of cell survival from 70.5% to 55.6% under Ex-4-free conditions; treatment with 100 nM Ex-4 in the absence of insulin increased the ratios from 27.5% to 41.2% and from 55.7% to 68.2%, respectively. These increased levels were equivalent to those in the control in the presence of insulin. Treatment with 100 nM Ex-4 suppressed the activity of RhoA, an inhibitory regulator for neurite outgrowth, in PC12 cells. Furthermore, these effects were attenuated by co-treatment with PI3 kinase inhibitor, LY294002.

**Conclusion:** These findings imply that Ex-4 enhances neurite outgrowth and neuronal survival through the activation of PI3 kinase signaling pathway, which negatively regulates RhoA activity. Ex-4 may compensate for the reduced insulin effects on neurons, thereby being beneficial for the treatment of diabetic neuropathy.

## [O32] OXIDATIVE AND CARBONYL STRESS IN RELATION TO POLYNEUROPATHY IN SUBJECTS WITH RECENTLY DIAGNOSED TYPE 1 AND TYPE 2 DIABETES

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**Objective:** We sought to determine whether biomarkers of systemic oxidative and carbonyl stress are altered in relation to diabetic sensorimotor polyneuropathy (DSPN) in recently diagnosed diabetes.

**Method:** We assessed serum concentrations of thiobarbituric acid reactive substances (TBARS), extracellular superoxide dismutase (SOD3), reduced glutathione (GSH), and methylglyoxal (MG) in 111 type 1 diabetes (T1D) and 223 type 2 diabetes (T2D) subjects of the German Diabetes Study (GDS) (T1D/T2D: age: 34.3±13.0/52.8±11.0 [SD] years; male: 57/65%; BMI: 24.6±4.1/31.7±6.0 kg/m<sup>2</sup>, diabetes duration: 7.2±3.2/6.1±3.0 months; HbA1c: 50.5±15.2/47.3±10.4 mmol/mol) and 38 healthy controls (age: 40.4±14.8 years; male: 55%; BMI: 25.4±4.0 kg/m<sup>2</sup>).

**Results:** TBARS levels were higher in T1D(3.1±2.0 μM) and T2D(3.2±1.8 μM) than in controls (0.9±0.3 μM) as was methylglyoxal (T1D:404±150, T2D:412±160, controls:154±69 nM, while SOD3 concentrations were reduced in T1D(38.9±14.9 ng/ml) and T2D(32.7±16.3 ng/ml) compared to controls (52.4±16.6 ng/ml) as was GSH(T1D: 1.6±0.6, T2D:1.7±0.8, controls: 2.7±1.2 μM)(all P<0.0001). Confirmed subclinical and clinical DSPN (Toronto Consensus) were present in 21% of T1D subjects and 29% of those with T2D. Multiple linear regression analysis revealed that low SOD3 levels were associated with the presence of DSPN in both T1D subjects (β=-0.319,P=0.002) and those with T2D (β=-0.151,P=0.030), while low methylglyoxal concentrations were associated with DSPN in T2D subjects (β=-0.153,P<0.022). No association with DSPN was noted for TBARS and GSH.

**Conclusion:** Patients with recently diagnosed T1D and T2D show systemic oxidative and carbonyl stress despite good glycaemic control, but only lower SOD3 concentrations in both T1D and T2D and lower methylglyoxal levels in T2D were linked to prevalent polyneuropathy.

## [O33] NEUROPATHY PREVALENCE COMPARED TO OTHER COMPLICATIONS IN LONGSTANDING T1DM: PRELIMINARY ANALYSIS OF THE CANADIAN STUDY OF LONGEVITY IN DIABETES COHORT

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**Objective:** Type 1 diabetes (T1DM) subjects can survive for extreme duration without retinopathy or nephropathy whereas estimates of neuropathy are uncertain. In a cohort with  $\geq 50$  years of T1DM, we aimed to assess the prevalence of microvascular complications and other indicator variables.

**Method:** 309 participants were recruited (2013-2014) across Canada by public advertisement and mailings to health professionals. Participants answered a comprehensive questionnaire and provided laboratory results. We assessed complications by eye-specialist fundus examinations, Michigan Neuropathy Screening Instrument  $\geq 3/15$ , eGFR  $< 60$  mL/min and albumin:creatinine  $> 2$  mg/mmol, and self-report of coronary artery disease (CAD), gastroparesis and peripheral vascular disease (PVD).

**Results:** In preliminary analysis, 309 participants (55% female) were  $66 \pm 8.5$  years of age, had mean diabetes duration of  $55 \pm 6.5$  years, BMI  $25 (23-28.2)$  kg/m<sup>2</sup>, and A1c  $7.5 \pm 1.1\%$ . Retinopathy was most prevalent at 78% compared to neuropathy (42%), nephropathy (48%), CAD (34%), gastroparesis (15%) and PVD (10%). 37 (12%) lacked evidence of any complication. In a Poisson regression generalized estimating equation (GEE) model, greater number of complications was independently associated with higher HbA1c (RR 1.05; 1.01-1.09), older age (RR 1.10; 1.06-1.13) and greater diabetes-specific emotional distress (RR 1.10; 1.08-1.13). In a logistic regression GEE model, male sex (OR 2.06; 1.16-3.62) and greater diabetes-specific emotional distress (OR 1.03; 1.00-1.06) were associated with greater odds of neuropathy.

**Conclusion:** Despite presence of salutary factors of diabetes management, only a small proportion of patients were resistant to all complications. Retinopathy – and not symptomatic neuropathy – was the dominant complication, indicating a need to better understand mechanisms that could promote resistance to specific complications.

## [O34] A MULTI NATIONAL NORMATIVE DATASET FOR CORNEAL NERVE MORPHOLOGY ASSESSED USING CORNEAL CONFOCAL MICROSCOPY

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**Objective:** To enable clinical translation and wider use of the technique of Corneal confocal microscopy, normative reference values need to be defined. We have therefore undertaken a multicenter collaboration to provide worldwide age adjusted normative values of corneal nerve fibre parameters.

**Method:** 1965 corneal nerve images from 343 healthy volunteers were pooled from six clinical academic centers across the world (Manchester, Brisbane, Calgary, Düsseldorf, Utah and Toronto). All subjects underwent examination with the HRT III. Images of the sub-basal nerve plexus were acquired by each centre using a standard protocol and analyzed by manually with using Semi-automated software and also by automated software. Age-trends were established using simple linear regression, and normative corneal nerve fiber density (CNFD), corneal nerve fiber branch density (CNBD), corneal nerve fiber length (CNFL) reference values were calculated using quantile regression analysis for each method of measurements.

**Results:** There was a significant linear age-dependent decrease in CNFD ( $-0.164$  no/mm<sup>2</sup> per year for men,  $P < 0.01$  and  $-0.161$  no/mm<sup>2</sup> per year for women,  $P < 0.01$ ) that determined with both analysing systems. There was no change with age in CNBD ( $+0.192$  no/mm<sup>2</sup> per year for men,  $P = 0.26$  and  $-0.050$  no/mm<sup>2</sup> per year for women;  $P = 0.78$ ). CNFL decreased in men ( $-0.045$  mm/mm<sup>2</sup> per year,  $P = 0.07$ ) and women ( $-0.060$  mm/mm<sup>2</sup> per year,  $P = 0.02$ ). Height, weight and BMI did not influence the 5th percentile normative values for any corneal nerve parameter.

**Conclusion:** This study provides robust worldwide normative reference values for corneal nerve parameters to be used in research and clinical practice in the study of diabetic and other peripheral neuropathies.

## [O35] THE PREVALENCE OF DIABETES MELLITUS (DM) IS INCREASED IN OLDER SUBJECTS WITH CHRONIC INFLAMMATORY DEMYELINATING POLYNEUROPATHY (CIDP)

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**Objective:** To examine the prevalence and diagnosis of CIDP in DM.

**Method:** Retrospective cohort study of patients with  $\geq 2$  claims for CIDP (confirmed CIDP; cCIDP) from the 2009–2013 PharMetrics Plus Database.

**Results:** From the total database population (N=101,321,694), the prevalence of patients with cCIDP (n=8173) was 8.07 per 100,000 persons, similar to the calculated prevalence for CIDP in previous studies. A total of 3399 patients had cCIDP with  $\geq 12$  months pre and post-index period. Within the cCIDP group, 1019 patients had  $\geq 2$  claims for confirmed DM (cDM) and 2380 patients had cCIDP without cDM. The median (SD) age for cCIDP without cDM and cCIDP with cDM was 55.8(15.2) and 61.5(11.7) years, respectively. cCIDP with cDM was far more common in males (60.5%) compared with cCIDP without cDM (53.6%). The peak prevalence for both cCIDP with or without cDM occurred in the age group 51–60 years. Within this group, 29.0% of patients had cCIDP without cDM versus 30.5% with cCIDP and cDM ( $p=0.36$ ). However, there was a significantly higher percentage of cCIDP with cDM patients than cCIDP without cDM, by decade, >60 years (each group  $p=0.01$ ). In contrast, cCIDP without cDM was more common by decade in the age groups 11–50 years (each group  $p=0.01$ ).

**Conclusion:** (1) 30% of all subjects with cCIDP also had cDM; (2) >60, the prevalence of cCIDP and cDM is increased; and (3) the presence of DM in older subjects, may result in failure to diagnose and treat concomitant CIDP.

## [O36] DIABETIC NEPHROPATHY LESIONS ASSOCIATE WITH CARDIOVASCULAR AUTONOMIC NEUROPATHY (CAN) IN PIMA INDIANS WITH TYPE 2 DIABETES

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**Objective:** To identify renal lesions that associate with CAN in Pima Indians with type 2 diabetes (T2D).

**Method:** Masked unbiased random sampling morphometric methods were used to measure renal structural parameters of diabetic kidney disease (DKD) in 63 Pima Indians (27% men) with T2D who underwent kidney biopsy. Glomerular filtration rate (GFR; iothalamate), urinary albumin/creatinine ratio (ACR), and other clinical variables were measured within a median 46 days of the biopsy. CAN was assessed a mean  $9.4 \pm 1.4$  years later by deep-breathing test and heart rate variability studies. Associations of CAN [E/I ratio, standard deviation of the normal R-R intervals (sdNN)] with structural variables were assessed by Spearman's correlations and by multiple linear regression after adjusting for age, sex, diabetes duration, HbA1c, ACR and GFR.

**Results:** Mean age was  $46 \pm 9$  years, diabetes duration  $16 \pm 6$  years, HbA1c  $9.1 \pm 1.9\%$ , GFR  $156 \pm 57$  ml/min, and median ACR  $25$  mg/g (IQR=9-68 mg/g). E/I correlated positively with percentage fenestrated endothelium (FE;  $r=0.26$ ,  $p=0.040$ ) and negatively with mesangial fractional volume (VvMes;  $r=-0.39$ ,  $p=0.002$ ) and glomerular basement membrane (GBM) width ( $r=-0.40$ ,  $p=0.001$ ). sdNN correlated negatively with VvMes ( $r=-0.34$ ,  $p=0.007$ ) and GBM width ( $r=-0.42$ ,  $p=0.001$ ). Neither E/I nor sdNN correlated with ACR or GFR. In multiple linear regression analyses, E/I and sdNN were positively associated with FE ( $p=0.011$ ,  $p=0.019$  respectively) and negatively associated with VvMes ( $p=0.018$ ,  $p=0.035$ ) and GBM width ( $p=0.034$ ,  $p=0.001$ ).

**Conclusion:** Pima Indians with T2D and DKD have a high prevalence of CAN, which is more severe in those with more severe renal structural damage.

POSTER ABSTRACTS



## [P1] LONGITUDINAL CHANGES OF SUDOMOTOR FUNCTION IN TYPE 1 DIABETES (T1D)

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**Objective:** To evaluate longitudinal changes in sudomotor function and associations with measures of cardiovascular autonomic neuropathy (CAN) in T1D.

**Method:** Sudomotor function was assessed by measuring electrochemical skin conductance (ESC) of hands and feet with SUDOSCAN (Impeto Medical) at baseline, 12 and 24 month in 36 subjects with T1D (mean age 39 ±13 years, mean diabetes duration 15 ±7 years, mean HbA1c 8.03 ±1.08%, no known complications), and 10 age-and-sex-matched healthy control (HC) subjects. CAN was assessed with cardiovascular reflex tests, heart rate variability (HRV) studies and positron emission tomography (PET) scans with [<sup>11</sup>C] meta-hydroxy ephedrine (HED), analyzed as left ventricle retention index (LVRI). Changes in ESC in T1D were analyzed using paired t-test. Correlation between mean hands and feet ESC and the log-transformed measures of HRV were estimated using Pearson correlation.

**Results:** At baseline, there were no differences between T1D and HC in the mean hands (68±16 vs 71±11µS; P=0.55) or mean feet ESC (79±7 vs. 79±1µS; P=0.87) respectively. There was a significant decline of hands ESC from 12 month to 24 month (mean change 10.4±12.7, P=0.002), and of feet ESC from baseline to 24 month (mean change 6.0±7.4, P=0.015). Both mean hands and feet ESC were positively significantly correlated with E/I ratio and measures of HRV during deep breathing. Hands ESC was also significantly correlated with the LVRI.

**Conclusion:** These data suggested that assessment of sudomotor function with SUDOSCAN (Impeto Medical) may be a promising diagnostic test to assess longitudinal changes in small fibers function in T1D.

## [P2] CARDIOVASCULAR AUTONOMIC NEUROPATHY PREDICTS DEVELOPMENT OF DIABETIC FOOT ULCER IN PATIENTS WITH TYPE 2 DIABETES MELLITUS

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**Objective:** We investigated factors that might influence the development of diabetic foot ulcers in patients with type 2 diabetes.

**Method:** From January 2003 to December 2004, a total of 1,534 patients with type 2 diabetes were consecutively enrolled. Significant diabetic foot ulcer was defined as a full thickness break in the epithelium with a minimum width of 5 mm. A cardiovascular autonomic function test (AFT) was performed to diagnose cardiovascular autonomic neuropathy (CAN) using heart rate variability parameters.

**Results:** The median follow-up time was 9.7 years. The mean age was 55.6 ± 10.8 years, and the duration of diabetes was 8.3 ± 7.0 years. At the follow-up, 135 patients (8.8%) developed new ulcers, and 26 patients (1.7%) underwent the amputation. The patients in the diabetic foot ulcer group had a longer duration of diabetes (p < 0.001), higher baseline HbA1c levels (p < 0.001), higher rates of smoking (P = 0.001), albuminuria (p < 0.001), retinopathy (p < 0.001), and received more insulin treatment (p < 0.001). A Cox hazard regression analysis revealed that the development of diabetic foot ulcer was significantly associated with the presence of cardiovascular autonomic dysfunction (normal vs. early CAN, HR 2.06, 95% CI 0.95-4.45; p = 0.066; normal vs. definite CAN, HR 2.50, 95% CI 1.18-5.26; p = 0.010) after adjusting for sex, age, diabetic duration, mean HbA1c, albuminuria, retinopathy, and treatment of insulin.

**Conclusion:** The development of diabetic foot ulcers was independently associated with cardiovascular autonomic dysfunction in patients with type 2 diabetes.

### [P3] VALIDATION OF COOLING DETECTION THRESHOLD AS A MARKER OF SENSORIMOTOR POLYNEUROPATHY IN TYPE 2 DIABETES

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**Objective:** The measurement of cooling detection thresholds (CDT) has been established in previous cross-sectional studies as a valid test for diabetic sensorimotor polyneuropathy (DSP) in type 1 diabetes. We aimed to validate its diagnostic performance in type 2 diabetes (T2D).

**Method:** 220 T2D subjects from a larger cohort underwent clinical and electrophysiological examinations including 3 small-fiber function tests: CDT, heart rate variability (HRV) and laser Doppler imaging of axon-mediated neurogenic flare responses to cutaneous heating ( $LDI_{FLARE}$ ), along with the Toronto Clinical Neuropathy Score (TCNS). Clinical DSP was defined by consensus criteria whereas preclinical DSP was defined by at least one electrophysiological abnormality. Area under the curve (AUC) and optimal thresholds were determined by receiver operating characteristic (ROC) curves.

**Results:** Subjects were aged  $63 \pm 11$  years with mean HbA1c of  $7.5 \pm 1.6\%$ . The 139(63%) clinical DSP cases had mean CDT value  $18.3 \pm 8.9^\circ\text{C}$ ; the 52(24%) preclinical DSP had  $25.3 \pm 3.5^\circ\text{C}$ ; and the 29(13%) controls had  $27.1 \pm 3.8^\circ\text{C}$ ; ( $p$ -value  $< 0.02$  for all three comparisons). For identification of clinical DSP  $AUC_{CDT}$  was 0.79, which exceeded  $AUC_{HRV}$  (0.60,  $p < 0.0001$ ),  $AUC_{LDI_{FLARE}}$  (0.69,  $p = 0.0003$ ) and  $AUC_{TCNS}$  (0.73,  $p = 0.03$ ). Optimal threshold for clinical DSP identification was  $< 22.8^\circ\text{C}$  (64% sensitivity and 83% specificity). For Preclinical DSP,  $AUC_{CDT}$  was 0.80, and the optimal threshold was  $\leq 27.5^\circ\text{C}$  (83% sensitivity and 72% specificity).

**Conclusion:** Akin to studies of T1D, CDT has acceptable diagnostic performance for the identification of both clinical and preclinical neuropathy in patients with T2D. Application of CDT as a non-invasive tool for systematic screening of early neuropathy in diabetes clinics should be considered.

### [P4] NONDIPPING IS A MAJOR PREDICTOR OF OBSTRUCTIVE SLEEP APNOEA SYNDROME IN DIABETES

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**Objective:** To determine the predictors of OSAS in diabetic patients with well-defined cardiometabolic risk, cardiac autonomic neuropathy (CAN), and diabetic polyneuropathy (DPN).

**Method:** In 177 patients (age  $59 \pm 11$ , duration  $15 \pm 12$  years, 36 with type 1), cardiometabolic risk, high risk for OSAS, sleep, CAN, DPN and 24h blood pressure (BP) were assessed using Lipid Accumulation Product (LAP) and Visceral Adiposity Index (VAI) (based on waist, triglycerides and HDL), the Berlin Questionnaire, the MOS Sleep Scale (MOS-SS), cardiovascular reflex tests (CARTs), MNSI Questionnaire, MDNS, vibration and thermal thresholds, and ambulatory BP monitoring.

**Results:** High risk for OSAS (2 categories among snoring behaviour, daytime sleepiness, hypertension and/or obesity) was found in 41% and associated with type 2 diabetes ( $\text{Chi}^2 = 10.8$ ,  $P = 0.001$ ), higher age ( $62 \pm 9$  Vs.  $57 \pm 12$  years,  $P = 0.004$ ), BMI ( $31 \pm 4$  Vs.  $28 \pm 4$   $\text{Kg/m}^2$ ,  $P < 0.0001$ ), LAP ( $65 \pm 38$  Vs.  $47 \pm 33$ ,  $P = 0.002$ ), VAI ( $2.1 \pm 1.3$  Vs.  $1.7 \pm 0.9$ ,  $P = 0.015$ ), and office systolic BP ( $140 \pm 18$  Vs.  $129 \pm 17$  mmHg,  $P < 0.0001$ ), lower % day-night change (D) in systolic BP ( $5.6 \pm 6.4$  Vs.  $9.0 \pm 6.2$  %,  $P = 0.0005$ ), worse sleep quality (SPI-9:  $37 \pm 21$  Vs.  $22 \pm 18$ ,  $P < 0.0001$ ), and lower E/I ratio ( $1.2 \pm 0.1$  Vs.  $1.3 \pm 0.2$ ,  $P = 0.023$ ) and Valsalva ratio ( $1.4 \pm 0.2$  Vs.  $1.5 \pm 0.3$ ,  $P = 0.002$ ), not with DPN measures. In a logistic regression analysis, independent predictors of high risk for OSAS were D systolic BP (OR=0.92, C.I. 0.86-0.98,  $P = 0.016$ ) and SPI-9 (OR=1.02, C.I. 1.01-1.05,  $P = 0.039$ ) ( $r^2 = 0.26$ ).

**Conclusion:** The major predictive role of nondipping, together with the weaker association with CARTs, supports a reciprocal interaction between OSAS and diabetes, mediated by autonomic dysfunction and resulting in an accumulative adverse cardiovascular impact.

## [P5] ASSOCIATION BETWEEN RISK FACTORS AND COGNITIVE IMPAIRMENT IN PATIENTS WITH TYPE 2 DIABETES MELLITUS

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**Objective:** The aim of this study was to investigate the association between diabetes-related risk factors and cognitive impairments assessed by different scales in patients with type 2 diabetes mellitus.

**Methods:** We enrolled 101 patients with type 2 diabetes mellitus mean age 62.2±5.61 years, (data are presented as mean±SD). BMI was 32.6±10.08 kg/m<sup>2</sup>, diabetes duration was 9.7±6.73 years, HbA1c— 8.1±1.36%. All subjects studied did not have any history of cerebrovascular accidents or depressive episodes. It has been assessed memory, speed, executive function. The statistical analysis was performed using SPSS-15.

**Results:** We revealed some association between diabetes-related risk factors and cognitive impairments in patients with type 2 diabetes mellitus. It was the negative correlation between duration of diabetes and executive functioning impairments revealed by SCWT,  $r=-0.22$ ,  $p<0.05$ . Also, executive functioning was inversely affected by higher HbA1c levels,  $r=-0.23$ ,  $p<0.05$ . Higher systolic blood pressure was associated with worsening of cognitive functioning by RAVLT, it was significant negative correlation between blood pressure and immediate memory ( $r=-0.29$ ,  $p<0.01$ ) and delayed memory ( $r=-0.23$ ,  $p<0.05$ ). The negative association between systolic blood pressure and working memory assessed by DSFB was revealed ( $r=-0.20$ ,  $p<0.05$ ).

**Conclusion:** There is a correlation between impairments of cognitive functioning and diabetes-related risk factors in patients with type 2 diabetes mellitus.

## [P6] CHANGES IN LEFT VENTRICLE CONTRACTILITY IN OBESE PATIENTS WITH IMPAIRED GLUCOSE TOLERANCE. ROLE OF AUTONOMIC FUNCTION

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**Objective:** Cardiac autonomic function is often altered in obese patients with glucose intolerance (IGT). This study examined the influence of autonomic function on left ventricle contractility in obese IGT patients.

**Method:** We included 66 non diabetic obese patients with normal blood pressure (BP) and without cardio-vascular history, 38 NGTs and 28 IGTs. BP was measured by applanation tonometry, cardiac vagal and sympathetic control (HF-HR, LF-HR) by spectral analysis (Task Force Monitor<sup>®</sup> finger plethysmography). Cardiac index (CI), stroke volume (SV) and thoracic fluid content (TFC) were measured in 39 patients by thoracic impedance. Total arterial compliance (TAC=SV/pulse pressure ratio) was calculated.

**Results:** IGTs had similar sex-ratio, age, BMI but higher CI, SV, TFC, TAC, and lower total peripheral resistance index ( $p<0.04$  to  $<0.0001$ ) than NGTs. IGTs (G1 and G2) and NGTs (G3 and G4) were separated into 4 groups according to HF-HR peak: below in G1 and G3 and over the median level in G2 and G4. G2 and G4 (35.5±9.4 and 38.4±6.6yrs) were younger than G1 and G3 (48±12 and 44±12yrs). The hemodynamic parameters were close in G1, G3 and G4. In G2, CI, SV, TFC, TAC were higher, particularly versus G1 ( $p<0.01$  to  $p<0.0001$ ) with higher LF-HR peak ( $p<0.01$ ) and G4 ( $p<0.04$  to  $p<0.01$ ) without difference for LF-HR (same results after age adjustment).

**Conclusion:** Among obese patients, IGTs exhibit higher left ventricle contractility than NGTs. This hyperkinetic profile is more marked in those with better autonomic function and consistent with an effect of mild hyperglycemia on enhanced catecholamine sensitivity.

## [P7] LEFT VENTRICLE HYPERKINESIA IN OBESE PATIENTS WITH IMPAIRED GLUCOSE TOLERANCE. RELATIONS WITH GLUCOSE VARIABILITY AND THE AUTONOMIC NERVOUS SYSTEM FUNCTION

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**Objective:** Glucose variability (GV) may play a role in diabetic complications. We recently showed that GV was greater in non diabetic obese patients with slightly elevated HbA1c levels. The aim was to examine the relationship between GV and left ventricle contractility and the autonomic function in obese patients with impaired glucose tolerance (IGT).

**Method:** We included 19 obese patients with IGT, normal blood pressure and without cardiovascular history. Cardiac vagal and sympathetic activity (HF-HR, LF-HR) were assessed by spectral analysis of heart rate variations, and mean systolic ejection rate (MSER) was measured (Task Force Monitor<sup>®</sup> finger plethysmography) at controlled breathing rate. Cardiac index (CI) and stroke volume (SV) were measured by thoracic impedance. GV was evaluated by calculating CONGA and J index from 24-hours continuous glucose monitoring.

**Results:** CONGA correlated with CI, SV and MSER ( $p < 0.05$  for all). Patients were separated into 2 groups: below in G1 and over the median level of HF-HR peak in G2. G2 patients were significantly younger than G1 patients ( $35.5 \pm 9.4$  vs  $48 \pm 12.6$  yrs). In G2, CI, SV and MSER were higher than in G1 ( $p < 0.0001$  for all) with higher LF-HR peak ( $p < 0.01$ ), even after age adjustment. Mean 24-h glucose, CONGA and J index were also higher ( $p = 0.03$  to  $0.002$ ).

**Conclusion:** Among obese IGT patients, those with preserved cardiac autonomic function exhibit higher left ventricle contractility, higher glucose and greater glucose variability. In these patients, cardiac hyperkinesia and more marked glucose disorders are likely to result from higher sympathetic activity.

## [P8] THE DIAGNOSTIC VALIDITY OF NERVECHECK: FROM FUNCTIONAL AND STRUCTURAL DAMAGE OF SMALL AND LARGE NERVE FIBRES TO NEUROPATHIC PAIN

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**Objective:** Quantitative sensory testing (QST) to assess thresholds for vibration and thermal sensation can quantify nerve dysfunction and may have relevance to painful symptoms and foot ulceration in diabetic patients. However, current QST devices are expensive and can be complex to use. NerveCheck is a new device (cost \$700) for QST assessment. We have assessed its reproducibility and diagnostic validity against established QST devices and its diagnostic ability to detect large (LFN) and small fibre neuropathy (SFN) as well neuropathic pain symptoms.

**Method:** 143 subjects (18 with painful, 55 with painless diabetic neuropathy and 70 controls) underwent QST assessment with NerveCheck; vibration perception threshold (VPT), Sural Sensory Nerve Action Potential (SNAP), cold (CPT) and warm (WPT) perception thresholds, IENFD and McGill pain questionnaire.

**Results:** NerveCheck's intra correlation coefficient was: VPT 0.79 (-4.2 to 6.6); CPT 0.86 (-1.38 to 2.7); WPT 0.71 (-2.36 to 3.83). NerveCheck showed a diagnostic efficiency of 86%, 79% and 71.5% for VPT, CPT and WPT, respectively for VPT (Neurothesiometer) and thermal thresholds (TSA-II). The AUC of VPT for SNAP (82.2%) was significantly higher than for IENFD (60.5%,  $P = 0.028$ ). There was a significantly greater nerve dysfunction in subjects with painful compared to painless neuropathy (VPT:  $2.51$  v  $5.01$ ,  $P = 0.006$ , CPT:  $3.17$  v  $4.72$ ,  $P = 0.005$  and WPT:  $3.61$  v  $4.78$ ,  $P = 0.001$ ).

**Conclusion:** NerveCheck is a new inexpensive QST device has comparable diagnostic ability to established QST equipment, detects damage to the correct fibre subtype and differentiates patients with and without neuropathic pain.

## [P9] CORNEAL CONFOCAL MICROSCOPY DEMONSTRATES SEVERE SMALL FIBRE NEUROPATHY IN DIABETIC PATIENTS WITH CHARCOT FOOT IN QATAR

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**Objective:** The pathogenesis of the Charcot foot in diabetes remains unclear. All patients diagnosed with the condition have evidence of a significant peripheral neuropathy with loss of sensation and elevated vibration perception (VPT). Small fibres play an important role in blood flow and inflammation and therefore may play an important role in Charcot. We have undertaken corneal confocal microscopy (CCM) in patients with clinical and radiological diagnosis of Charcot foot.

**Method:** 10 T2DM patients with a chronic Charcot foot (Charcot +), 10 age and diabetes duration-matched patients with T2DM without Charcot (Charcot -) and 10 age-matched control subjects underwent CCM to quantify corneal nerve fibre density (CNFD), branch density (CNBD) and fibre length (CNFL), VPT and metabolic testing.

**Results:** In Charcot + vs Charcot - vs Controls there was a significant stepwise reduction in CNFD ( $14.7 \pm 6.5$  v  $28.0 \pm 9.0$  v  $36.4 \pm 5.7$  no./mm<sup>2</sup>,  $P=0.0001$ ), CNBD ( $25.6 \pm 22.1$  v  $111.1 \pm 63.6$  v  $79.3 \pm 29.4$  no./mm<sup>2</sup>,  $P=0.01$ ), CNFL ( $11.4 \pm 6.1$  v  $26.2 \pm 10.5$  v  $25.4 \pm 3.1$  no./mm<sup>2</sup>,  $P=0.001$ ) and a significant increase in VPT ( $46.6 \pm 4.8$  v  $12.0 \pm 6.2$  v  $10.3 \pm 8.1$  V,  $P=0.0001$ ). Furthermore, in Charcot + vs Charcot - vs Controls, there was a significant reduction in HDLC ( $1.1 \pm 0.36$  v  $1.1 \pm 0.38$  v  $1.7 \pm 0.37$  mmol/mol,  $P=0.01$ ), and a significant increase in triglycerides ( $2.2 \pm 0.8$  v  $1.1 \pm 0.4$  v  $1.8 \pm 0.8$  mmol/mol,  $P=0.01$ ) and HbA1c ( $80.4 \pm 22.2$  v  $55.9 \pm 10.6$  v  $38.3 \pm 2.3$ ,  $P=0.001$ ).

**Conclusion:** These data suggest that small fibre neuropathy mediated by poorer glycemic control and deranged lipids may play a key role in the pathogenesis of Charcot neuroarthropathy.

## [P10] PHARMACOLOGICAL MODULATION OF AMPK IN EXPERIMENTAL DIABETIC PERIPHERAL NEUROPATHY

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**Objective:** We aim to investigate the effect of natural and small molecule activators of AMPK on various functional, neuro chemical and molecular alterations associated with DN.

**Method:** We assessed the pharmacological effect of berberine and A769662 in Streptozotocin (STZ) induced DN in rodents and Hyperglycaemia (100 mM) insulted neuro2a (N2A) cells. Nerve functional evaluation, oxidative, inflammatory bio marker identification in the STZ induced rats and nerve growth analysis and protein expression analysis in N2A cells were carried out to examine the pharmacological efficacy of AMPK activators.

**Results:** AMPK activators attenuated nerve conduction velocity and nerve blood flow deficits linked to DN ( $p<0.001$ ). AMPK activation hampered oxidative damage in sciatic nerve homogenates as well as N2A cells as evident by reduction in malondialdehyde (MDA), nitric oxide (NO) and improvement in glutathione (GSH). A reduction in the level of proinflammatory mediator profile such as interleukin-6 (IL-6) and tumor necrosis factor- $\alpha$  (TNF- $\alpha$ ) when compared to diabetic animals were also observed in the sciatic nerve lysates of rats treated with berberine and A769662 ( $p<0.001$ ). Neurite outgrowth analysis has pointed out that cellular AMPK activation ameliorated neurotropic impairment lent by hyperglycaemia in N2A cells. Western blotting analysis has shown that interventions could abrogate the aberrant NF- $\kappa$ B signalling and enhanced AMPK activity ( $p<0.01$ ) in N2A cells under high glucose conditions.

**Conclusion:** From these evidences we suggest that AMPK activation acts upstream of NF- $\kappa$ B signalling and the cross talk between the two might be one of the critical aspects responsible for neuroprotective potential of AMPK activators.

## [P11] THE DIAGNOSTIC PERFORMANCE OF NEUROPAD AGAINST DIFFERENT COMPOSITE TESTS OF DIABETIC NEUROPATHY

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**Objective:** The ability of Neuropad to diagnose diabetic peripheral neuropathy (DPN) has been questioned due to its good sensitivity but low specificity. We believe this is not a reflection of the poor diagnostic ability of Neuropad, but the large fibre weighted measures for defining DPN. We have therefore compared the diagnostic performance of Neuropad against 3 composite tests: Toronto criteria (symptoms - Neuropathy symptom profile (NSP)  $\geq 1$  or signs - Neuropathy Disability Score (NDS)  $\geq 3$  & peroneal motor nerve conduction velocity (PMNCV)  $\leq 42$ ); Doha criteria (symptoms or signs & abnormality in PMNCV or deep breathing heart rate variability (DB-HRV)  $\leq 15$  beats/min, or warm perception threshold (WPT)  $\geq 42$  °C); 3S criteria (abnormal symptoms or signs & abnormality in DB-HRV or WPT).

**Method:** 111 subjects with T1DM underwent evaluation with Neuropad and the 3 neuropathy composite tests.

**Results:** The number of subjects diagnosed with DPN was 41, 53 and 42 by the Toronto, Doha and 3S criteria, respectively. The AUC for abnormal Neuropad was: Toronto criteria- 77% (95% CI = 0.67 - 0.87); Doha criteria- 80% (95% CI = 0.71 - 0.88) and 3S criteria- 83% (95% CI = 0.75 - 0.91). The sensitivity and specificity progressively improved from the Toronto (77%, 68%) to Doha (83%, 64%) to 3S (84%, 73%) criteria, respectively.

**Conclusion:** This study emphasizes the need to include small fibre assessments in the diagnosis of DPN when validating the diagnostic performance of a small fibre test such as Neuropad.

## [P12] CHOLECYSTOKININ AS A MARKER OF MOTOR-EVACUATION FUNCTION OF ASSESSMENT OF THE STOMACH IN PATIENTS WITH DIABETES

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**Objective:** Nowadays the majority of etiopathogenetical factors of gastric dysfunction is unclear due to autonomic neuropathy in patients with diabetes. Many hormones are involved in the autonomic nervous system regulating gastrointestinal (GI) tract. The aim of this study is to examine the concentrations of cholecystokinin (CCK) in patients with and without dysfunction in GI motility.

**Method:** We studied 25 subjects with diabetes with duration of 13.5 $\pm$ 4.7 years, mean value of HbA1C was 8.6 $\pm$ 1.4% divided into 2 groups: diabetic without symptoms of dysfunction in GI motility (consisted of 15 participants, mean age was 44.8 $\pm$ 9.4 years) and patients confirmed of diabetic gastroparesis (DG) (10 patients, mean age was 46.7 $\pm$ 8.3 years) and 10 healthy volunteers (mean age was 45.4 $\pm$ 9.6 years) as control group. The plasma concentrations of CCK were measured by immunoassay. No subjects studied had signs of other disorders of dysfunction in GI motility.

**Results:** We have found out that plasma levels of CCK are significantly higher in patients with DG (8.14  $\pm$  0.24 ng/ml) compared to subjects of first and control groups (3.09  $\pm$  0.51ng/ml),  $p < 0.05$ . Low gastric motility has been diagnosed in 8 (80%) of second group with help of 13 C-octanoic breast test (13C-OBT): T 1/2- 93.5 $\pm$ 15.5 min, but in first and control groups that result is T 1/2- 77.4 $\pm$ 9.2 min. The method of rank correlation has proved correlation ( $r = 0.82$ ,  $p < 0.01$ ) between results of 13C-OBT and level of CCK.

**Conclusion:** This scientific result can suggest the occurrence of hypercholecystokininemia as a cluster of progression of DG.

## [P13] CORNEAL CONFOCAL MICROSCOPY – A RELIABLE METHOD TO ASSESS DIABETIC PERIPHERAL NEUROPATHY

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**Objective:** This article aims to compare corneal confocal microscopy (CCM) with acknowledged tests of diabetic peripheral neuropathy (DPN), to assess corneal nerve morphology using CCM in diabetic patients, and to underline possible correlations between biological parameters, diabetes duration and DPN severity.

**Method:** A total of 90 patients with type 2 diabetes were included in the study for whom we measured anthropometric parameters and we performed laboratory measurements (tests). The patients were assessed for diabetic peripheral neuropathy using Semmes-Weinstein Monofilament Testing (SWMT), Rapid-Current Perception Threshold (R-CPT) measurements using the Neurometer® and CCM. We stratified the patients according to DPN severity, based on four parameters extracted after image analysis.

**Results:** A higher percentage of patients were diagnosed with DPN using CCM (88.8%), compared with SWMT and R-CPT measurement (17.8% and 40% respectively). The incidence of DPN detected with CCM was considerable in patients with normal protective sensation and with normal R-CPT values. The incidence of DPN detected by CCM showed an ascending trend with increasing duration of diabetes and an important percentage of patients with a diabetes duration of less than five years, was found with severe neuropathy.

**Conclusion:** Our study showed that CCM is a useful noninvasive method for diabetic neuropathy assessment in early stages. It was proven to directly quantify small fiber pathology, and to stratify neuropathic severity, and therefore can be used as a new, reliable tool in the diagnosis, clinical evaluation, and follow-up of DPN.

## [P14] PERIPHERAL NEUROPATHY AND WERNICKE'S ENCEPHALOPATHY AFTER BARIATRIC RESTRICTIVE SURGERY

[Sarah Bathaei](#)<sup>1</sup>, Sabrina Chiheb<sup>1</sup>, Camille Pillegand<sup>1</sup>, Isabella Banu<sup>1</sup>, Christophe Barrat<sup>2</sup>, Paul Valensi<sup>1</sup>

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**Objective:** Symptomatic thiamin deficiency is an uncommon but serious complication of malabsorptive bariatric surgeries. It can cause severe peripheral neuropathy or Wernicke's encephalopathy which may be irreversible.

**Method:** We report 5 patients who developed peripheral neuropathy, one of them with encephalopathy, due to thiamin deficiency after bariatric restrictive surgery.

**Results:** Four patients presented central or peripheral neuropathy after sleeve gastrectomy and one after adjustable gastric band. The patients were aged between 20 and 47 years. They developed symptoms between 1 and 3 months after sleeve gastrectomy and 7 years after the gastric band. There was no vitamin deficiency particularly in vitamin B1 before surgery. Patients did not receive pre or post-operative vitamin supplementation. Before the onset of deficiency symptoms they complained of vomiting or gastroesophageal reflux impeding oral feeding. All showed sensory and/or motor axonal neuropathy and one also developed Wernicke's encephalopathy. The symptoms were significantly improved in the majority of patients after intravenous thiamine administration for several days associated with other vitamins (B6, PP, multivitamins, trace elements). No other etiology was found, in particular no diabetes and no excessive alcohol consumption.

**Conclusion:** Despite an exhaustive preoperative assessment including vitamin status, peripheral neuropathy and Wernicke's encephalopathy may occur after bariatric restrictive surgery. Such complications seem to affect only patients who present with vomiting or gastroesophageal reflux. These uncommon but severe complications are reversible if diagnosed and treated early by vitamin supplementation. This supplementation should be started as soon as possible in patients with vomiting or gastroesophageal reflux.

## [P15] CHANGES IN HEART RATE AND CARDIAC TIME INTERVALS IN OBESE PATIENTS WITH IMPAIRED GLUCOSE TOLERANCE. ROLE OF AUTONOMIC FUNCTION

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**Objective:** Alterations of cardiac autonomic function often affect patients with impaired glucose intolerance (IGT). This study aimed to examine the influence of autonomic function on heart rate (HR) and cardiac time intervals in obese patients with normoglycemia (NGT) or IGT.

**Method:** We included 66 non diabetic obese patients, with normal blood pressure (BP) and no cardio-vascular history, 38 NGTs and 28 IGTs. Left ventricular ejection duration (LVED) was assessed by applanation tonometry (SphygmoCor<sup>®</sup>), cardiac vagal (HF-HR) and sympathetic control (LF-HR) by spectral analysis. Pre-ejection period (PEP), mean systolic ejection rate (MSER) and rapid ejection period (REP) were measured by finger plethysmography (Task Force Monitor<sup>®</sup> finger plethysmography).

**Results:** Compared with NGTs, IGTs had similar sex-ratio, age, BMI, BP and HR, higher LVED, PEP, REP and MSER ( $p < 0.05$  to  $< 0.001$ ). In the overall population, fasting and 2-hours plasma glucose (OGTT) correlated with LF/HF-HR ( $p = 0.02$  and  $0.03$ ), even after age and BMI adjustment. Only in patients with HF-HR > median value, LF-HR correlated negatively with HR ( $r = -0.4$ ,  $p = 0.03$ ) and PEP ( $r = -0.35$ ,  $p = 0.04$ ); these patients were younger, had lower HR, higher MSER and LF-HR ( $p < 0.005$  for all) than those with HF < median, even after adjusting for age. In patients with HF-HR > median, IGTs had same age, BMI, HR, spectral peaks, but longer REP ( $p < 0.001$ ), MSER ( $p < 0.04$ ) and PEP ( $p < 0.06$ ) than NGTs.

**Conclusion:** In obese patients, vagal control is a stronger determinant for HR than sympathetic control. IGTs, with a good vagal control, have longer ejection times than NGTs which might suggest an effect of mild hyperglycemia on catecholamines sensitivity.

## [P16] THE CHARACTERISTICS OF COMPLETE BLOOD COUNT IN THE TYPE 2 DIABETIC PATIENTS WITH PERIPHERAL POLYNEUROPATHY

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**Objective:** Diabetic neuropathy is a common complication of type 2 diabetes mellitus. Increased spontaneous blood platelet aggregation has been reported in diabetes mellitus with microvascular complication. High level of blood platelet as well as platelet dysfunction could be harmful to the microcirculation and lead to microvascular complication. In this study, we examined the association between complete blood count and peripheral polyneuropathy (PPN) in type 2 diabetes patients.

**Method:** A total of 815 type 2 diabetes patients were included in the present study. Diabetic peripheral polyneuropathy was diagnosed in cases with typical neurological symptoms. Symptoms include a sensation of numbness, tingling, sharpness, or burning that begins in the both feet and spreads proximally and is usually present at rest, and worsens at night. Biochemical markers including complete blood count were assessed concurrently.

**Results:** The mean age of total subjects was  $57.44 \pm 13.86$ . 391 patients were male. In univariate analysis, The levels of white blood cell and red blood cell were not associated with peripheral polyneuropathy ( $P = 0.519$  and  $P = 0.971$ , respectively). Platelet and hemoglobin A1c levels were higher in patients with peripheral polyneuropathy compared with in patients without peripheral polyneuropathy ( $P = 0.011$  and  $P = 0.010$ , respectively). Multiple logistic regression analysis revealed platelet level as an independent risk factor for peripheral polyneuropathy in type 2 diabetic patients (odds ratio, 1.003; 95% confidence interval, 1.001-1.004;  $p = 0.002$ ).

**Conclusion:** In the present study, we found that raised platelet levels are more common in type 2 diabetic patients with peripheral polyneuropathy.

## [P17] INFLUENCE OF CHANGES IN VAGO-SYMPATHETIC ACTIVITY ON HEART RATE AND INSULIN RESPONSE TO ORAL GLUCOSE LOAD

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**Objective:** We showed that cardiac parasympathetic activity is often altered in non diabetic obese patients and similarly in metabolically healthy obese (MHO) patients. This study aimed to examine the influence of the changes in vago-sympathetic activity on heart rate (HR) and insulin response to OGTT in MHO patients.

**Method:** We recruited 24 patients, 34±13 years, BMI 42.2±6.9 kg/m<sup>2</sup>, with only one criterion of the metabolic syndrome (hyperglycemia in only one patient) in addition to large waist circumference. An OGTT was performed. Composite indexes of insulin secretion (insulinogenic index=IGI=Δinsulinemia(T0-T30)/Δglycemia(T0-T30), and oral disposition index=ODI=IGI/insulinemia) were calculated. Cardiac parasympathetic activity (HF-HR) and sympatho-vagal balance (LF/HF-HR) were evaluated by spectral analysis of HR variations (Finapres®), and plasma epinephrine and norepinephrine levels were measured during OGTT.

**Results:** Patients were separated in two groups according to parasympathetic activity at fasting: high or low (HF-HR > or < median value). The patients with high HF-HR at fasting maintained higher HF-HR during OGTT (p<0.001). They had lower LF/HF-HR at fasting and during OGTT (p=0.019). Epinephrine and norepinephrine response did not differ between the two groups. HR accelerated during OGTT in both groups (p=0.002) but was lower at fasting and during OGTT in the patients with high HF-HR (p=0.03). High HF-HR was associated with higher ODI (p=0.035).

**Conclusion:** Among MHO patients those with higher parasympathetic activity keep higher parasympathetic activity after glucose intake. This profile accounts for lower HR at fasting and after glucose load and seems to contribute to a greater insulin secretion.

## [P18] ELECTRONEUROMYOGRAPHICAL MONITORING CHILDREN WITH IDDM WHO APPLY INSULIN PUMP

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**Objective:** Electroneuromyographical monitoring children with IDDM who apply insulin pump

**Method:** 103 children with IDDM: average age - 10,41±1,85, boys - 46,6% 48, girls - 53,4%. The average duration IDDM - 5,29±0,32, A1c - 7,46±0,13, duration of applying IP - 2,32±0,18. All the children have passed electroneuromyography (ENMG) on on VikingSelect (Nicolet, USA). Motor and sensory nerve were studied over. Conduction velocity (CV) and Latent time (LT) were measured.

**Results:** There was no substantial difference between indicators of ENMG before and after IP conduction. Thus, the CV of motor nerves in 1<sup>st</sup> group 56,4% (A1c 6,60±0,07) was 48,77±0,44 m/s, LT - 3,15±0,08 msec, CV of sensory fibers - 36,90±1,01 m/s. Upon the use of IP we received following results: motor CV - 47,20±0,88 m/s, LT - 4,14±0,85 msec, sensory CV - 38,23±1,27 m/s (p>0,01).

In the 2<sup>nd</sup> group 33,9% (A1c 8,01±0,06) motor CV before IP was 47,77±0,74 m/s, LT - 3,24±0,11msec and after IP: 47,20±0,61 m/s, LT - 3,28±0,10 msec; CV of sensory fibers - 34,73±1,11 m/s and 37,08±1,41 m/s (p>0,01).

In the 3<sup>rd</sup> group 9,7% (A1c 10,51±0,45) – before IP motor CV 45,10±2,34 m/s, LT - 3,45±0,18msec, sensory CV - 33,70±2,51 m/s. After IP the results were: motor CV - 45,60±1,95 m/s, LT - 3,78±0,20msec, sensory CV - 35,50±2,12 m/s (p>0,01).

**Conclusion:** Existence of IP did not resulted in substantial effects on ENMG indicators among children with IDDM.

## [P19] RELATIONSHIP BETWEEN GLUCOSE VARIABILITY AND PERIPHERAL NERVES PARAMETERS IN PATIENTS WITH TYPE 1 DIABETES

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**Objective:** The impact of glycemic variability (GV) on peripheral neuropathy is still under debate. The aim of the present study was to investigate the relationship between PN and glucose variability, in patients with type 1 diabetes mellitus (T1DM).

**Method:** We consecutively recruited 47 T1DM patients, 25 treated with continuous subcutaneous insulin infusion (CSII) and 22 with multiple daily insulin injections (MDI). Patients with poor glycemic control ( $HbA_{1c} > 8\%$ ) were excluded. All patients underwent an electroneurography (ENG) with the evaluation of conduction velocity (CV), nerve wave amplitude and latency, at the level of both sensitive and motor fibers and a Continuous Glucose Monitoring (CGM), from which the following indexes of GV were calculated: SD, CONGA-1, CONGA-2, CONGA-4, J-index, LBG, HBG, MAGE, M-value and MAG.

**Results:** Glycemic control was similar ( $HbA_{1c} = 7.6 \pm 0.2\%$ , in both groups). GV and ENG parameters were not different between CSII and MDI. We found a negative correlation between motor CV and SD, CONGA-1, CONGA-2, CONGA-4, LI, J-index, HBG, MAGE, M-value and MAG ( $p < 0.01$ ) and between sensitive CV and CONGA-1 and J-index ( $p = 0.02$ ). There was also a positive correlation between both sensitive and motor wave latency and GV indexes ( $p < 0.05$ ). All the correlations were confirmed, after correcting for  $HbA_{1c}$  and diabetes duration.

**Conclusion:** Our study suggests a relationship between GV and the degree of peripheral nerve abnormalities in T1DM, both in patients with MDI and CSII therapy, which seems independent by overall glucose control.

## [P20] REACTIVE HYPOGLYCEMIA AND COUNTERREGULATORY RESPONSE AFTER BARIATRIC SURGERY

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**Objective:** Reactive hypoglycemia may occur after bariatric surgery due to still unclear mechanisms. We aimed to describe the changes in glucose tolerance after bariatric surgery in morbidly obese non diabetic patients and investigate counterregulatory hormones in those with reactive hypoglycemia.

**Method:** We included 45 patients, aged  $39 \pm 9$  years, BMI before surgery  $43.6 \pm 5.1$  kg/m<sup>2</sup>, 36 operated by sleeve gastrectomy and 9 by gastric by-pass. OGTT (75g) was performed before surgery and after  $>10\%$  weight loss. Plasma glucose, insulin, epinephrine and norepinephrine were measured at fasting and 2 hours after OGTT, and plasma cortisol on the same day at 8am and 4pm.

**Results:** Before surgery, 14 patients had IGT, 4 had IFG. After  $11 \pm 7$  months weight loss was 13-50%, BMI  $31.4 \pm 4.4$  kg/m<sup>2</sup>. After surgery all but one of these dysglycemic patients normalised OGTT, glucose and insulin at fasting and after glucose and HOMA-IR decreased ( $p < 0.001$  to  $< 0.0001$ ), without difference according to surgical procedures. Reactive hypoglycemia (2-hours glucose  $3.1-2.3$  mmol/l) affected 9 patients. These patients did not differ from the others for catecholamine and cortisol levels before surgery, were explored longer after surgery ( $p = 0.006$ ), and after surgery had higher 4pm cortisol levels ( $p = 0.01$ ), slightly lower 2-hours insulin ( $p = 0.08$ ) and norepinephrine ( $p = 0.06$ ), greater postoperative increase in 4pm cortisol ( $p = 0.03$ ) with a slightly greater increase in 2-hours norepinephrine ( $p = 0.08$ ).

**Conclusion:** One year after surgery glycemic disorders resolved in all but one dysglycemic patients. Reactive hypoglycemia affected 20% of our patients. It occurred despite lower insulin levels and enhanced pituitary-adrenal axis activity but inappropriate sympathetic response.

## [P21] AUTONOMIC TESTING: A STUDY ON THE DIAGNOSTIC VALUE OF EACH TEST IN REAL WORLD

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**Objective:** To verify the role in clinical practice of a single test (Deep Breathing DB) as screening of autonomic impairment with respect to the widely used Ewing's battery.

**Method:** 4100 patients with diabetes underwent DB. 355 were excluded (8.8%). On 334 of 902 with DB < 10%-percentile, we evaluated "DB confirmation" (i.e. DB performed on another day together with the three other tests of Ewing's battery). Statistical analysis on continuous variables was performed with ANOVA and Student's t test. Frequency data were analysed with chi-square test in a contingency table.

**Results:** In 3866 patients (Mean age  $\pm$  SD: 59.7 $\pm$ 10.8 years) the average value of DB was 1.27 $\pm$ 0.1. Subdividing patients into 4 age groups, significant differences among DB were detected (ANOVA, F ratio=179, p<0.0001, followed by post-hoc comparisons, all significant).

By dividing patients into two main age groups ( $\leq$ 55 y or >55y), the percentage of patients with values of DB < 10%-percentile was similar in the two age groups: 23.06% (age  $\leq$ 55 y) vs. 23.44% (age > 55 y), OR 1.02 (lower-upper 95%: 0.8-1.20).

The specificity and sensitivity of a pathological DB with impairment of 1, 2 or 3 tests were: 51% and 86% with 1 positive test, 35% and 92% with 2, 25% and 100% with 3.

**Conclusion:** DB seems to be the most sensitive test but little specific. Moreover diabetic patients seem to lose the age factor in their cardiovascular autonomic control. There is a major effect in younger patients according to previous data shown by the Addition study.

## [P22] ASSOCIATIONS WITH CARDIOVASCULAR AUTONOMIC NEUROPATHY AND ARTERIAL OXYGEN SATURATION DURING SLEEP IN PATIENTS WITH TYPE 2 DIABETES

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**Objective:** To evaluate the hypothesis that sudden death also may be due to respiratory dysfunction in diabetics, we analyzed associations with nocturnal hypoxemia during sleep (NHS) and cardiovascular autonomic neuropathy (CAN) in 80 patients with type 2 diabetes (T2D).

**Method:** The sample group consisted of 38 males and 42 females with average ages of 58 years. The severity of CAN was classified by Ewing & Clarke's classical cardiovascular autonomic tests (CAN score 0, 1, 2, >3). We used a pulse oximeter to monitor arterial oxygen saturation (SaO<sub>2</sub>) during sleep. Definite NHS was diagnosed when the total time at an SaO<sub>2</sub> < 85% was more than one minute in a single night (<N=8, 10%, Group III), and questionable NHS when the total time was from 15 seconds to one minute (N=18, 22% Group II). The remainder of the patients were considered to be normal (N=54, 68%, Group I).

**Results:** There was a significant correlation between the CAN score and the QTc interval (p<0.01). In comparing of the normoxemic Group I and the hypoxemic Group III, the duration of diabetes and HbA1c showed a significant difference (p<0.05). Nocturnal hypoxemic diabetes (Group III) showed a significant prolongation of QTc interval (p<0.05) and significant increase of CAN score (p<0.01).

**Conclusion:** The CAN score and QTc interval seem to be applicable to estimation of nocturnal hypoxemia in patients with T2D. However, we suggest that further study (the relationship between the sudden death of diabetics and the degree of arterial oxygen saturation during sleep) is required.

## [P23] THE HANDGRIP TEST IN THE ASSESSMENT OF CARDIOVASCULAR AUTONOMIC NEUROPATHY: TO USE OR NOT TO USE?

[Anna Korei](#)<sup>1</sup>, [Zsuzsanna Putz](#)<sup>2</sup>, [Ildikó Istenes](#)<sup>2</sup>, [Miklós Kempler](#)<sup>2</sup>, [Orsolya Vági](#)<sup>2</sup>, [Réka Nagy](#)<sup>3</sup>, [Katalin Keresztes](#)<sup>4</sup>, [Vincenza Spallone](#)<sup>5</sup>, [Péter Kempler](#)<sup>3</sup>

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**Objective:** The objective of our study was to assess the diagnostic value of handgrip test in detecting CAN as well as to identify the factors having impact on handgrip test results in diabetic patients.

**Method:** Our study involved 353 patients with diabetes (age: 60,2±7,4 years; diabetes duration: 15,6±9,9 years; HbA1c: 8,2±1,9%; with type 1 diabetes: 18,1%). CAN was assessed by five CARTs: the deep breathing test, Valsalva ratio, 30/15 ratio, handgrip and orthostatic hypotension (OHT) test.

**Results:** Results of the handgrip test did not show any association with results of the deep breathing test ( $p=0,897$ ), 30/15 ratio ( $p=0,357$ ) and Valsalva ratio ( $p=0,781$ ). An association between handgrip and OHT failed to be proven ( $p=0,833$ ). Sensitivity, specificity, positive and negative predictive value of the handgrip test versus definite diagnosis of CAN were 22,9%, 78,8%, 51% and 51,3%, respectively. The results of handgrip test showed a significant negative association with the presence of hypertension ( $\gamma=-0,315$ ,  $p=0,009$ ). The diastolic BP elevation during the manoeuvre was inversely related to the baseline diastolic BP ( $\rho=-0,283$ ,  $p=0,013$ ). In multivariate analysis, the significant inverse association between abnormality of the handgrip test and hypertension was independent of anthropometric parameters, diagnosis of CAN, sensory loss and medication.

**Conclusion:** Our data may provide evidence that the handgrip test should no longer be part of the cardiovascular autonomic testing being highly dependent of the hypertensive status and baseline blood pressure. The mechanism for the inverse association could be an increased sympathetic cardiovascular activation in response to sustained handgrip in patients with diabetes and hypertension.

## [P24] DAY AND NIGHT HEART RATE VARIABILITY FOR DETECTION OF CARDIAC AUTONOMIC NEUROPATHY

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**Objective:** Cardiac autonomic neuropathy (CAN) has been detected at time of diagnosis in patients with type 2 diabetes (T2DM). CAN presentation is not limited by patient age or duration of disease and can occur before DM is evident clinically. During CAN sub-clinical phase, heart rate variability (HRV) can help in its detection before the disease is symptomatic. Holter monitoring (HM) was recommended as an instrument for CAN precise diagnostics.

**Aim of study:** To compare twenty-four hours HRV parameters in patients with T2DM and without and with cardiovascular autonomic reflex tests (CARTs) in DM patients.

**Method:** In groups of 46 T2DM patients and 46 age and gender matched controls HRV computed from HM (5 Time, 4 Frequency Domain, 2 circadian indexes) was compared between groups and with 2 bedside CARTs (deep paced breathing, lying-to-standing tests). No patient had decompensated heart, kidney, endocrine or other disease which could affect HRV.

**Results:** Only 31 (67.4%) DM patient had one or both positive CARTs (CARTpos), whereas all patients had changed one and more 24-hour HRV parameter, changed 24hour HRV tests sum was higher in CARTpos patients (5[5] vs 3[2],  $p<.01$ ) and in T2DM patients (4[4.5] vs 1[2],  $p<.001$ ). ROC curve showed fair diagnostic effectiveness of HM based HRV for CAN detection (AUC=.74 (.583;.899), cut-off point - 4 positive tests (sensitivity 74%, specificity 62%,  $p=.015$ ).

**Conclusion:** Inclusion of 24-hours HRV in DM patient evaluation could improve CAN detection at early subclinical stages. 24-hour HRV can be discussed for DM patients with negative bedside CARTs.

## [P25] BLOOD PRESSURE VARIABILITY IN SUBJECTS WITH TYPE 1 DIABETES

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**Objective:** To assess the prevalence and risk factors for non-dipping of systolic and diastolic blood pressure (BP) as a maker of cardiovascular autonomic neuropathy (CAN) among subjects with type 1 diabetes (T1D).

**Method:** Forty-one subjects with T1D (25 females, age 34±13 years, duration 13±6 years, HbA1c 8±1.2%) without cardiovascular disease, dyslipidemia, or hypertension at baseline were enrolled in 3-year observational cohort study. Subjects were phenotyped for CAN with heart rate variability and cardiovascular reflex tests. Indices of glucose variability (mean amplitude of glycemic excursions, low- and high-blood glucose index), derived from 7-day continuous glucose monitoring (iPro, Medtronic), and serum inflammatory biomarkers were measured in all subjects. 24-hour BP profiles were obtained with a portable oscillometric recorder (Spacelabs90207, Redmond, WA). Non-dipping was defined as nocturnal systolic and/or diastolic BP fall off < 10%. Differences between dippers and non-dippers were evaluated using the t-test and Wilcoxon rank sum test.

**Results:** At baseline 29% T1D subjects were non-dippers, prevalence that remained unchanged at 1 and 2 year follow-up. Age, diabetes duration, glycemic control, lipid profile and glycemic variability indices were not different between dippers and non-dippers. However, non-dippers had significantly higher levels of inflammatory makers including C-reactive protein as compared to non-dippers [median (IQ range): 4.1(0.3, 7.2) vs. 0.70(0.1,1.9), P= 0.042].

**Conclusion:** These preliminary data suggest that non-dipping is prevalent in patients with T1D and subclinical CAN and may be mediated by chronic inflammation. Ongoing follow-up and analyses in this cohort are further evaluating this relationship and other risk factors.

## [P26] CHARACTERISTICS OF CARDIOVASCULAR AUTONOMIC AND CENTRAL AFFERENT FUNCTION IN PATIENTS WITH RECENTLY DIAGNOSED TYPE 1 OR TYPE 2 DIABETES

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**Objective:** The shortest period of diabetic exposure leading to different neuronal dysfunctions is poorly documented. The aim was to characterize the autonomic (AN) and central nerve function in patients with recently diagnosed type 1 or type 2 diabetes (DM).

**Method:** 40 patients with type 1 or type 2 DM were involved (type 1: n=21, age: 28.82 years, duration of DM: 2.1±0.5 months; type 2 DM: n=19, age: 48.4±3.9 years, duration of DM: 3.3±0.8 months; mean±SE). Cardiovascular reflex tests (CRT) and four waves (I-IV/V) of brainstem auditory-evoked potentials (BAEP) were analyzed.

**Results:** The CRT-s and the latencies of BAEP did not differ from controls among type 1 DM patients. The AN score was higher in type 2 DM (AN score: 2.16±0.5 vs 0.33±0.1, p<0.01; diabetic vs control). The heart rate response to breathing was lower in type 2 DM patients than in controls (17±2.1 vs 23.1±2.3 min., p<0.05) and a negative correlation was found between Valsalva ratio and wave V latency of BAEP (r=-0.61, p<0.01). There was a non-significant tendency of longer latencies of all BAEP waves in type 2 DM patients than in controls.

**Conclusion:** The autonomic and central function was intact in short type 1 diabetes. Moderate parasympathetic dysfunction was found in recently diagnosed type 2 diabetes. The abnormal values of a parasympathetic test correlated with the latency of the auditory-evoked potentials. Our data support that parasympathetic dysfunction rather than central afferent impairment should be considered as the early sign of neuropathy in recently diagnosed type 2 diabetes.

**[P27] HIGH FAT FED MOUSE MODELS OF NEUROPATHY**

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**Objective:** C57BL/6J mice fed a 60% high fat diet, from lard, develop pre-diabetes and a small and large fiber neuropathy. If low-dose streptozotocin (STZ) is added to this paradigm, animals become frankly diabetic. We compared the severity of neuropathy between pre-diabetes and diabetes.

**Method:** Mice were fed control (10% lard) or high fat (60% lard) chow from 4 to 36 weeks of age. One group of high fat fed mice received low-dose STZ at 12 weeks. Longitudinal changes in small and large nerve fiber function, glucose and insulin tolerance, fasting blood glucose and body weight were assessed over time.

**Results:** Mice with pre-diabetes developed neuropathy characterized by prolonged hindpaw withdrawal latencies, slowed sural and sciatic nerve conduction velocities (NCVs) and decreased intraepidermal nerve fiber densities (IENF). Unexpectedly this neuropathy was of equal severity to that of mice with frank diabetes despite differences in fasting glucose (high fat fed 233.5±12.17 mg/dL compared to high fat fed with STZ 426.6±36.63 mg/dL).

**Conclusion:** Severity of neuropathy in high fat fed C57BL/6J mice is equal in pre-diabetes and diabetes, supporting the growing body of evidence that glucose alone is not the primary driver of neuropathy.

**[P28] CABENOXOLONE PREVENTS ER STRESS INDUCED HYPOTHALAMIC NEURONAL APOPTOSIS**

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**Objective:** Hypothalamus has been appreciated to be the headmaster to regulate energy balance by coordinating peripheral homeostatic activities including nutrient sensing, appetite control, energy expenditure, and carbohydrate and lipid metabolism. Hypothalamic endoplasmic reticulum (ER) stress is known to be increased in obesity. Induction of ER stress on hypothalamic neurons has been reported to cause hypothalamic neuronal apoptosis and malfunction of energy balance eventually resulting in obesity. Cabenoxolone is a nonselective gap junction decoupler and 11 $\beta$ -hydroxysteroid dehydrogenase type 1 (11 $\beta$ -HSD1) inhibitor. 11 $\beta$ -HSD1 converts inactive glucocorticoid to an active form. Cabenoxolone has shown an anti-apoptotic effect in several studies. In this study, the effect of cabenoxolone on ER stress in hypothalamic neurons was investigated.

**Method:** Primary fetal hypothalamic neurons dissected from time-pregnant rats (Sprague-Dawley) were cultured with cabenoxolone. ER stress was induced by treating tunicamycin in hypothalamic cells. Cell viability was quantified by the 3-(4,5-Dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide (MTT) assay and ER stress markers such as ATF6, ATF4, XBP1s or CHOP were examined with western blot and immunocytochemistry. Cleaved Caspase3 and Cleaved PARP were examined. ROS was measured with DCF-DA assay

**Results:** Tunicamycin induced ER stress increased apoptosis and ROS on mice hypothalamic neuron. Cabenoxolone was shown to decrease tunicamycin induced ATF6 and CHOP expression. Cabenoxolone also decreased ROS and apoptosis of hypothalamic neuron.

**Conclusion:** The result of this study suggests that cabenoxolone has a preventive effect against ER stress induced apoptosis on hypothalamic neuron. Further study is warranted to clarify the effect of cabenoxolone on hypothalamic regulatory functioning of energy balance.

## [P29] DIETARY REVERSAL IMPROVES PERIPHERAL NERVE FUNCTION IN PRE-DIABETIC C57BL/6J MICE

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**Objective:** C57BL/6J male mice on a high fat diet (HFD) develop pre-diabetes, and metabolic and peripheral nerve deficits. We investigated whether dietary reversal can halt or reverse the progression of HFD-induced peripheral neuropathy.

**Method:** 3 cohorts of male mice were placed on varying diets. Control and HFD mice were fed control (10% kcal lard; Ctrl) or high fat diet (54% kcal lard; HFD) chow, respectively, from 4-24 weeks of age. A third cohort of mice was fed HFD from 4-20 weeks of age, and control diet from 20-24 weeks of age (dietary reversal; DR).

**Results:** HFD mice displayed increased body weight (BW), fasting glucose (FG) and insulin, impaired glucose tolerance (IGT) and reduced motor (MNCV) and sensory nerve conduction velocities (SNCV). DR mice exhibited improved BW, FG, insulin, and glucose sensitivity compared with HFD mice. Electrophysiological assessment of DR mice showed a significant improvement in both MNCV and SNCV at 24 weeks.

**Conclusion:** Metabolic and electrophysiology parameters of HFD-fed mice are improved by only 4 weeks of DR.

## [P30] TARGETING PAINFUL DIABETIC NEUROPATHY IN A RAT MODEL OF TYPE 1 DIABETES: THERAPEUTIC EFFICACY OF NOVEL MESENCHYMAL STEM CELL POPULATIONS

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**Objective:** Diabetic neuropathy (DN) is one the most common complications of diabetes. Moreover, a third of the patients with DN develop painful symptoms. We aimed at investigating the therapeutic potential of novel bone marrow-derived mesenchymal stem cell (MSC) populations in the streptozotocin (STZ)-induced Wistar rat model of painful DN. These MSC populations result from the development of a new platform technology for MSC based on the Orbsen Therapeutics Ltd. discovery of a novel MSC marker, CD362 (<http://www.reddstar.eu/>).

**Method:** Human heterogeneous plastic adherent (PA)-MSCs, CD362<sup>+</sup> MSCs, CD362<sup>-</sup> MSCs, or vehicle were intravenously injected in STZ rats 1 week post-STZ injection. The efficacy of the different MSC populations in preventing the development of behavioural signs of painful DN was evaluated for 9 weeks. The Randall-Selitto paw-pressure test and the Hargreaves test were used to evaluate mechanical and thermal sensitivities, respectively. Body weights, blood glucose levels, and blood glycated haemoglobin A1C (Hb<sub>A1C</sub>) levels were also monitored.

**Results:** Treatment of STZ rats with CD362<sup>+</sup> MSCs significantly improved mechanical hyperalgesia and prevented the development of thermal hypoalgesia as compared to non-treated STZ rats. Metabolic parameters typical of this disease model (impaired weight gain, hyperglycaemia, and elevated Hb<sub>A1C</sub> levels) were not affected by MSC treatment.

**Conclusion:** Our data strongly suggest that administration of the most efficacious MSC population—CD362<sup>+</sup> MSC—may be a useful strategy to manage painful DN symptoms. We are currently evaluating the mechanisms underlying the effects of these MSCs.

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## [P31] IVIG THERAPY MARKEDLY AMELIORATES SMALL FIBER FUNCTION IN DIABETIC PAINFUL NEUROPATHY

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**Objective:** Conventional nerve conduction studies only detect large fibre neuropathy and not useful in evaluating the impairment of small fibres such as A-delta and C fibers. In this study, we tried to evaluate the effect of IVIg in painful diabetic neuropathy, using intra epidermal electrical stimulation, which can selectively activate A-delta nociceptors.

**Method:** We examined 12 patients affected by painful distal symmetrical sensory neuropathy associated with diabetes. All patients were treated with IVIg (0.4g/kg/day for 5 days). Pain ratings were assessed by the Visual Analogue Scale. A-delta fibre pain threshold value on foot was measured using intra epidermal electrical stimulation. Large fibre function was assessed by conventional nerve conduction studies.

**Results:** 11 of 12 patients showed a remarkable improvement in neuropathic pain following IVIg therapy. Pain assessed by the determination of mean VAS score was reduced 8.1 to 3.2 from days 7-28 following treatment. Before IVIg treatment, A-delta fibre pain threshold mean values were high in people with diabetes compared with control subjects (0.425mA vs. 0.030mA,  $P<0.001$ ). After treatment, A-delta fibre pain threshold values were decreased significantly (0.225mA,  $P<0.01$ ). Mean reduction rates was higher in 6 patients who showed normal sural nerve CSAP ( $> 5\mu V$ ). Pain threshold reduction rate was correlated with symptomatic pain duration but not diabetic duration or HbA1C levels.

**Conclusion:** Our study suggests that intra-epidermal electrical stimulation, a non-invasive and easy measurement of small fibre pain threshold values, is useful to evaluate the effect of IVIg. IVIg might be a promising therapy for diabetic pain.

## [P32] REDUCED LOWER LIMB MUSCLE STRENGTH AND VOLUME IN PATIENTS WITH TYPE 2 DIABETES: RELATIONSHIP TO NEUROPATHY, INTRAMUSCULAR FAT AND VITAMIN D LEVELS

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**Objective:** Patients with diabetes may develop lower limb weakness and muscle atrophy and are at increased risk of falling. Aim: To explore the underlying basis for this abnormality.

**Method:** 20 patients with T2DM and 20 healthy control subjects underwent assessment of strength and size of knee extensor, flexor and ankle plantar and dorsiflexor muscles in relation to the presence of diabetic polyneuropathy (DPN), intramuscular non-contractile tissue (IMNCT) and serum 25OHD levels.

**Results:** Patients with T2DM had significantly lower knee extensor ( $P=0.003$ ) strength and muscle volume of knee extensors ( $P=0.045$ ) and flexors ( $P=0.019$ ). Ankle plantar flexor strength ( $P=0.001$ ) was also significantly reduced without a reduction in ankle plantar flexor ( $P=0.23$ ) or dorsiflexor ( $P=0.45$ ) muscle volumes, but with increased ankle plantar ( $P=0.006$ ) and dorsiflexor ( $P=0.005$ ) IMNCT in T2DM patients. Patients with DPN had significantly lower knee extensor strength compared to non-DPN ( $P=0.02$ ), with no difference in knee extensor volume ( $P=0.38$ ) or ankle plantar flexor strength or volume ( $P=0.21$  and  $P=0.96$  respectively). There was no significant difference for the strength and volume of knee extensors ( $P=0.32$  and  $P=0.18$ ) or ankle plantar flexors ( $P=0.58$  and  $P=0.12$ ) between T2DM patients with a 25OHD  $<25\text{nmol/L}$  vs  $>25\text{nmol/L}$ .

**Conclusion:** Patients with T2DM have a significant reduction in proximal and distal leg muscle strength, which is related to proximal but not distal reduction in muscle volume, due to greater intramuscular fat accumulation in distal muscles. Proximal but not distal muscle strength was related to DPN but not with IMNCT or the level of 25OHD.

### [P33] GLUCOSAMINE INDUCED NEUROPATHY AND ITS ASSOCIATION WITH NERVE INSULIN RESISTANCE

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**Objective:** We previously reported that glucosamine (GlcN) caused Schwann cell death in vitro and peripheral neuropathy in mouse accompanied by ATP depletion. Since ATP is indispensable to phosphorylation of signaling molecules, the shortage of ATP may impair the phosphorylation of insulin signaling molecules, which may contribute to the development of diabetic polyneuropathy (DPN). It is yet to be known, however, whether GlcN per se elicits insulin resistance in the peripheral nerve. In this study, we examined molecular alterations of insulin signaling and its association with neuropathy in GlcN-injected mice with or without insulin treatment.

**Method:** C57Bl/6 mice were administered (i.p.) with 2 g/kg GlcN. Groups of animals were injected with insulin (5U, i.v.) to augment phosphorylated signaling after GlcN administration or saline alone for comparison. After GlcN injection, perception threshold by tail flick test, motor nerve conduction velocity (MNCV) were sequentially monitored. Western blots for phosphorylation of Akt were conducted on the sciatic nerve extirpated 20 minutes after insulin injection.

**Results:** We found significant reduction of perception 5 minutes after GlcN and significant decrease of MNCV. While Akt was markedly phosphorylated after insulin injection in control mice, it was much suppressed in mice injected with GlcN. In contrast, the effects of GlcN injection on Akt expression were not influenced 60 minutes before insulin injection.

**Conclusion:** Our results indicate that GlcN-induced neuropathic changes and nerve insulin resistance, which also occur in experimental animal models of diabetes.

### [P34] THE EFFECTS OF ANGIOTENSIN II RECEPTOR BLOCKER (ARB) ON NEUROPATHY IN SPONTANEOUSLY HYPERTENSIVE RATS (SHR)

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**Objective:** Neuropathy has been documented in SHR. However, its underlying mechanism is still unknown. We have studied the effects of ARB on SHR neuropathy.

**Method:** Male SHR (n=13) and Wistar Kyoto rats (WKY, n=14) have been used. At age of 16 weeks, oral azilsartan (1 mg/kg/day) treatment started. Blood pressure, motor nerve conduction velocity (MCV) of sciatic-tibial nerves, plantar sensory examination using von Frey, have been monitored after 4 to 26 weeks of treatment. At the end of experiment, Laser Doppler flux and thermographic studies of the hind paw, and pathological investigation of DRGs and sciatic-tibial and sural nerves were assessed.

**Results:** At the beginning of treatment, 1) blood pressure was significantly higher in SHR than WKY; 2) MCV was significantly slower in SHR when compared with WKY;  $51.1 \pm 0.8$  and  $55.1 \pm 0.8$  m/s respectively  $p < 0.001$ ; and 3) the threshold of von Frey sensory tests was significantly increased in SHR. After 26 weeks of treatment in SHR, blood pressure was significantly lower when compared with those of pretreatment in SHR, but delayed MCV in SHR was not significantly improved;  $57.7 \pm 1.5$  in treated SHR,  $57.1 \pm 1.3$  in non-treated SHR,  $65.1 \pm 0.9$  in treated WKY,  $65.0 \pm 1.1$  m/s in non-treated WKY. Impaired von Frey test in plantar was not significantly altered by 26-week ARB treatment.

**Conclusion:** Delayed MCV and sensory abnormalities in SHR were not affected significantly by ARB treatment. Neuropathic process in SHR may not be caused by hypertension per se.

## [P35] MITOCHONDRIAL TRANSCRIPTION FACTOR A REGULATION OF MITOCHONDRIAL DEGENERATION IN EXPERIMENTAL DIABETIC NEUROPATHY

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**Objective:** Mitochondrial transcription factor A (TFAM) wraps MITOCHONDRIAL dna (mtDNA) and promotes mtDNA replication and transcription. We studied whether over expression of TFAM prevents experimental peripheral diabetic neuropathy using TFAM transgenic mice (TFAM Tg) that express human TFAM (hTFAM).

**Method:** Wild Type (WT) and TFAM Tg mice were made diabetic by the administration of streptozotocin. Neuropathy endpoints were motor and sensory nerve conduction velocities, mechanical allodynia, thermal nociception, and intraepidermal nerve fiber density (IENFD). In the Dorsal Root Ganglion (DRG) neurons, mtDNA copy number and damage to mtDNA were quantified by qPCR and TFAM levels were measured by Western blot.

**Results:** Levels of mouse mtDNA and the total TFAM (mouse TFAM + hTFAM) in the DRG increased by ~2-fold in the TFAM Tg mice compared to WT mice. Mice with 16-wk duration of diabetes developed motor and sensory nerve conduction deficits, behavioral deficits, and intraepidermal nerve fiber loss. All these changes were mostly prevented in diabetic TFAM Tg mice and were independent of changes in blood parameters. Mice with 16-weeks of diabetes had a 40% decrease in mtDNA copy number compared to non-diabetic mice ( $p < 0.01$ ). Importantly the mtDNA copy number in diabetic TFAM Tg mice reached the same level as that of WT non-diabetic mice.

**Conclusion:** There was upregulation of mtDNA and TFAM in 6-week diabetic mice, suggesting that TFAM activation could be a therapeutic strategy to treat peripheral neuropathy.

## [P36] REDUCED INDUCTION OF GP130 CYTOKINES AND NEUROPEPTIDES IN AXOTOMIZED SYMPATHETIC AND SEN-SORY NEURONS IN A MOUSE MODEL OF TYPE 1 DIABETES

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**Objective:** Neuropathy is a major diabetic complication. While the mechanism of this neuropathy is not well-understood, it is believed to result in part from deficient nerve regeneration. Work from our laboratory established that gp130 family of cytokines are induced in animals after axonal injury and are involved in the induction of regeneration-associated genes (RAGs) and in the conditioning lesion response (Zigmond, 2012). Here, we examine whether a reduction of cytokine signalling occurs in diabetes.

**Method:** Streptozotocin (STZ) was used to destroy pancreatic  $\beta$  cells, leading to chronic hyperglycemia. Mice were injected with either low doses of STZ (5x 60mg/kg) or a single high dose (1x 200mg/kg) and examined after two or one month, respectively. At these times, unilateral surgeries were performed on diabetic and vehicle-treated animals. Neurons in both superior cervical ganglia and 5<sup>th</sup> lumbar dorsal root ganglia were axotomized.

**Results:** Significantly reduced induction of two gp130 cytokines, leukemia inhibitory factor and interleukin-6, occurred in diabetic animals in both ganglia 6 and 24 h after injury. The induction of IL-11 was unaffected. These effects were accompanied by reduced phosphorylation of signal transducer and activator of transcription 3 (STAT3), a downstream effector of the gp130 signalling pathway. We also found decreased induction of several gp130-dependent RAGs, including galanin and vasoactive intestinal peptide. We currently are exploring whether these biochemical changes lead to deficits in neurite outgrowth of SCG and DRG neurons.

**Conclusion:** Together, these data suggest a novel mechanism for the decreased response of diabetic sympathetic and sensory neurons to injury.

## [P37] THE IDENTIFICATION OF THE TISSUE-SPECIFIC GENE EXPRESSION SIGNATURES OF PIOGLITAZONE TREATMENT IN A MURINE MODEL OF TYPE 2 DIABETES

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**Objective:** Diabetic nephropathy (DN) and diabetic peripheral neuropathy (DPN) are the most common complications of diabetes. Even though pioglitazone is frequently used to treat Type 2 Diabetes (T2D), its effect on diabetic complications at the transcriptomic level is not well established. In this study, we aim to elucidate the underlying mechanisms of differential gene regulation patterns that are associated with pioglitazone treatment in kidney (glomeruli and cortex) and nerve [dorsal root ganglia (DRG) and sciatic nerve (SCN)] tissues from db/db mice, a murine model of T2D.

**Method:** Differential analysis between db/db and pioglitazone treated db/db using RNA-Seq was performed to identify significantly dysregulated genes for all tissues. In addition, we applied Self Organizing Maps, an unbiased clustering method, in order to identify coherent expression patterns for all genes between SCN and glomeruli. Functional enrichment and pathway analyses were performed to find key dysregulated genes and pathways.

**Results:** Differential analysis demonstrated that pioglitazone regulated the expression of a large number of genes in SCN and glomeruli, but not in DRG and cortex. In addition, the differentially expressed genes related to the regulation of inflammatory response and programmed cell death, were reversed in glomeruli; however, they were exacerbated in SCN. The SOM analysis revealed that genes overrepresented in the calcium signaling and mitochondrial dysfunction pathways were reversed in kidney but not in nerve.

**Conclusion:** Our results identified the tissue-specific gene expression signatures of pioglitazone treatment in T2D. These data suggest potential pharmaceutical targets to tailor different diabetic complications.

## [P38] IS IGT-ASSOCIATED SENSORY NEUROPATHY DRIVEN ONLY BY GLYCEMIA?

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**Objective:** Traditional cardiovascular risk factors play an important role in the development of neuropathy in diabetes. In the present study, we aimed to investigate risk factors of sensory neuropathy in patients with impaired glucose tolerance (IGT) and healthy volunteers

**Method:** Seventy-five people with impaired glucose tolerance and 40 age and gender matched healthy volunteers underwent a detailed clinical examination and neurological assessment. Sensory nerve function was assessed by using Neurometer (current perception threshold [CPT]) and Medoc devices. Autonomic neuropathy was detected by the five standard cardiovascular autonomic tests. Mean 24-h systolic and diastolic blood pressures were assessed by 24-hour ambulatory blood pressure monitoring.

**Results:** The prevalence of sensory neuropathy was 58% in subjects with impaired glucose tolerance. The Odds ratio (OR) was 11.23 (CI: 3.57-35.35). This association was independent from the presence of autonomic neuropathy or the measure of BMI, HbA1c, blood pressure and heart rate. However, adjustment for fasting plasma glucose attenuated the association notably (OR: 6.75; CI: 1.33-34.27), and the significance was lost after adjustment for 120 min glucose level (OR: 3.76; CI: 0.26-54.10). Sensory neuropathy in patients with IGT showed a strong association with 120 min glucose level (OR: 1.78; CI: 1.20-2.63) in the entire population studied.

**Conclusion:** Our data suggest that postprandial glycemia (120 min glucose level) is a risk factor for sensory neuropathy in subjects with IGT which is independent of all other known cardiovascular risk factors. This new observation may be important to the development of risk reduction strategies.

## [P39] ROLE OF TRANSIENT RECEPTOR POTENTIAL CHANNELS TRPV1 AND TRPM8 IN DIABETIC PERIPHERAL NEUROPATHY

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**Objective:** TRPV1 and TRPM8 are heat and cold sensing non-selective cation channels, respectively. We sought to determine whether modulation of TRPV1 and TRPM8 might contribute to altered thermal sensitivity in DPN.

**Method:** STZ-and a transgene-induced diabetic animals were used and thermal (heat and cold) sensitivities were determined. Membrane currents were recorded using patch-clamp technique.

**Results:** An enhanced TRPV1-mediated currents in dorsal root ganglion (DRG) neurons, with a corresponding elevation in TRPV1 protein expression were observed in paw skin, DRG and spinal cord tissues collected from hyperalgesic diabetic mice. Next, we tested cold sensitivity to implicate a possible role of TRPM8 in DPN. Acetone-induced cold sensitivity was enhanced in diabetic mice as compared to non-diabetic mice. DRG neurons dissociated from diabetic hyperalgesic mice exhibited a decrease in TRPM8-mediated currents as compared to non-diabetic mice. In diabetic mice, intraplantar injection of capsaicin, a TRPV1 agonist induced painful behavior but the severity was significantly reduced when co-administered with menthol, a TRPM8 agonist. Then, we determined the modulation of TRPV1- and TRPM8-mediated currents by activation of PKA and PKC. Both, forskolin, a PKA activator and PDBu, a PKC activator upregulated TRPV1-mediated currents, in contrast, TRPM8-mediated currents were downregulated.

**Conclusion:** These findings suggest that diabetic thermal hyperalgesia mediated by up regulation of TRPV1 function may be further aggravated by the down regulation of TRPM8 function.

## [P40] N-3 POLYUNSATURATED FATTY ACIDS PROTECT OXIDATIVE STRESS-INDUCED CYTOTOXICITY BY INDUCTION OF ANTIOXIDANT ENZYMES IN IMMORTALIZED ADULT MOUSE SCHWANN (IMS-32) CELLS

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**Objective:** N-3 polyunsaturated fatty acids (n-3 PUFAs) such as docosahexaenoic acids (DHA) and eicosapentaenoic acids (EPA) were proposed to have direct antioxidant effects on vascular tissues. Furthermore, n-3 PUFAs display a variety of bioactive actions including anti-inflammatory and antioxidant effects. In this study, we investigated whether n-3 PUFAs have protective actions against oxidative stress on neural cells.

**Method:** 1) IMS-32 cells were pretreated with DHA or EPA, and stimulated by tert-butyl hydroperoxide (tBHP). 2) Cell viability was measured by the MTT assay. 3) mRNA and protein expressions of the antioxidative enzymes, heme oxygenase-1 (HO-1) or NAD(P)H quinone oxidoreductase 1 (NQO1) were determined by quantitative RT-PCR and immunoblotting. 4) The nuclear fraction was assessed for the binding activity to Nrf2 of antioxidant response element (ARE).

**Results:** 1) Decreased cell viability by tBHP was ameliorated by DHA or EPA. 2) DHA or EPA increased mRNA and protein levels of HO-1 or NQO1. 3) The binding activity to Nrf2 of ARE was elevated by DHA or EPA.

**Conclusion:** These findings suggest that n-3 PUFAs induce antioxidative enzymes through Nrf2 and would protect neural cells from the hyperglycemia-induced oxidative stress in diabetic neuropathy.

## [P41] TREATMENT RESPONSIVENESS IN CIDP PATIENTS WITH DIABETES IS ASSOCIATED WITH HIGHER DEGREES OF DEMYELINATION

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**Objective:** To explore the association between the degree of demyelination in CIDP, and treatment responsiveness.

**Method:** A retrospective chart review of CIDP subjects assessed between 1997 and 2013 was performed to compare treatment responsiveness using different sets of criteria.

**Results:** 99 CIDP patients were included, 34 with diabetes mellitus (DM). Treatment responsiveness was higher in CIDP-DM fulfilling 1 or more EFNS/PNS criteria, (63% vs. 31%,  $p=0.03$ ), and in CIDP+DM fulfilling 2 or more criteria (89% vs. 36%,  $p=0.01$ ). Nonetheless, treatment responsiveness in CIDP+DM had the highest odds ratio (3.73,  $p=0.01$ ). Similar results were also shown in simplified uniform study criteria, with 10% cut off values for CIDP-DM, compared to 30% for CIDP+DM.

**Conclusion:** In CIDP+DM, higher degrees of demyelination are associated with treatment responsiveness, implying the need for to adjust current criteria in these patients.

## [P42] GLYCEMIA IMPACTS SURVIVAL OF GLIOBLASTOMA PATIENTS TREATED WITH RADIATION AND TEMOZOLOMIDE

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**Objective:** Evidence suggests hyperglycemia is associated with worse outcomes in glioblastoma (GB). This study aims to confirm the association between glycemia during radiotherapy (RT) and temozolomide (TMZ) treatment and overall survival (OS) in patients with newly diagnosed GB.

**Method:** This retrospective study included GB patients treated with RT and TMZ from 2004-2011, randomly divided into independent derivation and validation datasets. Time-weighted mean (TWM) glucose and dexamethasone dose were collected from start of RT to 4 weeks after RT. Univariate (UVA) and multivariable (MVA) analyses investigated the association of TWM glucose and other prognostic factors with overall survival (OS).

**Results:** In total, 393 patients with median follow-up of 14 months were analyzed. In the derivation set ( $n=196$ ) the median OS was 15 months and median TWM glucose was 6.3 mmol/L. For patients with a TWM glucose  $\leq 6.3$  mmol/L and  $> 6.3$  mmol/L, median OS was 16 months and 13 months, respectively ( $p=0.03$ ). On UVA, TWM glucose, TWM dexamethasone, age, extent of surgery and performance status were associated with OS. On MVA, TWM glucose remained an independent predictor of OS ( $p=0.03$ ) along with TWM dexamethasone, age, and surgery. The validation set ( $n=197$ ), with similar baseline characteristics, confirmed that TWM glucose  $\leq 6.3$  mmol/L was independently associated with longer OS ( $p=0.005$ ).

**Conclusion:** This study demonstrates and validates that glycemia is an independent predictor for survival in GB patients treated with RT and TMZ.

### [P43] EARLY LOWER LIMB MUSCLE ABNORMALITIES IN SUBJECTS WITH IMPAIRED GLUCOSE TOLERANCE IN RELATION TO INTRAMUSCULAR FAT AND VITAMIN D LEVELS

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**Objective:** To quantify muscle strength and size in subjects with impaired glucose tolerance (IGT) in relation to intramuscular non-contractile tissue (IMNCT) and vitamin D deficiency.

**Method:** 20 patients with IGT and 20 healthy control subjects underwent assessment of strength and size of knee extensor, flexor and ankle plantar and dorsiflexor muscles in relation to the amount of IMNCT and serum 25OHD levels.

**Results:** In subjects with IGT knee extensor strength ( $P=0.17$ ) and volume ( $P=0.77$ ) and knee flexor volume ( $P=0.97$ ) did not differ from control subjects. However, ankle plantar flexor strength was reduced ( $P=0.04$ ) with no difference in ankle dorsiflexors ( $P=0.07$ ) or ankle plantar flexor ( $P=1.00$ ) volume. IMNCT was significantly increased in the ankle plantar flexors and dorsiflexors ( $P=0.02$ ). There was a significant reduction in ankle plantar flexor strength ( $P=0.02$ ) but not volume ( $P=0.81$ ) in subjects with IGT with a 25 hydroxyvitamin D (25OHD)  $<25\text{nmol/L}$  vs  $>25\text{nmol/L}$ .

**Conclusion:** Patients with IGT have a significant reduction in distal but not proximal leg muscle strength which was related to vitamin D deficiency and greater intramuscular non contractile tissues accumulation in the distal muscles. Proximal and distal muscle volumes were normal in IGT compared to controls. These data suggest that distal motor abnormalities may occur early in relation to T2DM and may also be amenable to therapy with vitamin D.

### [P44] PERIPHERAL NEUROPATHY IS RELATED TO REDUCED SUDOMOTOR FUNCTION IN ADULT PATIENTS WITH TYPE 1 DIABETES

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**Objective:** The aim of this study was to evaluate the sudomotor function with SUDOSCAN+ in patients with type 1 diabetes (DM1).

**Method:** The study included 404 adult DM1 patients (194 women) aged 41 (IQR:32-51) years, disease duration 23 (18-30) years. The study group was subdivided into two groups depending on the presence of peripheral neuropathy. We measured electrochemical skin conductance (ESC) with SUDOSCAN+ on feet (Feet ESC) and hands (Hands ESC). We evaluated glycaemic control of diabetes using HbA1c value and skin autofluorescence (AF) measured with AGE-Reader.

**Results:** Peripheral neuropathy was diagnosed in 44% of patients. Patients with peripheral neuropathy, compared to those without it, had lower Feet and Hands ESC [69 (46-81) vs 83 (76-87) $\mu\text{S}$ ;  $p<0.001$ ; 56 (39-69) vs 69 (60-78) $\mu\text{S}$ ,  $p<0.001$ ]. We found a negative correlation between Feet and Hands ESC and patients' age ( $R_s=-0.41$ ,  $p<0.001$ ;  $R_s=-0.40$ ,  $p<0.001$ ), duration of diabetes ( $R_s=-0.33$ ,  $p<0.001$ ,  $R_s=-0.30$ ,  $p<0.001$ ), HbA1c level ( $R_s=-0.13$ ,  $p=0.01$ ,  $R_s=-0.12$ ,  $p=0.02$ ), skin AF ( $R_s=-0.34$ ,  $p<0.001$ ,  $R_s=-0.30$ ,  $p<0.001$ ), and positive correlation with the eGFR ( $R_s=0.38$ ,  $p<0.001$ ,  $R_s=0.31$ ,  $p<0.001$ ). In a multivariate logistic regression model ESC was independently associated with the presence of peripheral neuropathy (Feet ESC OR 0.96; 95%CI:0.95-0.98,  $p<0.001$  and Hands ESC OR 0.97; 95%CI:0.95-0.98,  $p<0.001$ ). This association was independent from age, sex, duration of diabetes, HbA1c, skin AF and eGFR.

**Conclusion:** In adults with type 1 diabetes and peripheral neuropathy sudomotor function is markedly reduced. The longer duration of diabetes, worse glycaemic control or reduced renal function, the greater sudomotor dysfunction.

## [P45] CHANGES IN HYPODERMIC ADIPOSE TISSUE COULD AFFECT SKIN WOUND OCCURRENCE DURING OBESITY

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**Objective:** The role of obesity in the appearance of skin pressure ulcers remains controversial. In obesity, hypodermic adipose tissue grows at the expense of surrounding tissues. The aim of the present study was to evaluate blood perfusion and related lesions after skin compression in obese mice.

**Method:** C57BL6 male mice were randomly assigned to a control or hypercaloric diet (HCD) for 4 and 12 and 20 weeks. Nerve sensitivity (mechanical and thermal) was assessed in each group. Skin compression was induced by a magnetic force using 2 magnets. Skin perfusion was examined using laser Doppler imaging before skin compression, immediately after compression release, 24 h and 5 days later. Skin injuries were determined by photography. We studied the changes in mice adipose tissue weights in hypodermic and subcutaneous layers.

**Results:** The body weight and adiposity of obese mice increased with HCD duration. Peripheral nerve sensitivities to thermal and mechanical tests decreased with HCD duration. At 24-hour post-compression release the compressed area was less ischaemic in the HCD4 and HCD12 groups than in HCD20. Interestingly HCD4 and 12 exhibited less cutaneous lesions than in diet-matched control mice. Indeed, short-term obesity increased the cutaneous and sub-cutaneous adiposity that could protect against compression but long-term obesity with diabetes occurrence has an adverse effect on the skin and induced larger ischemia and necrosis.

**Conclusion:** During obesity several parameters can affect the development of skin lesions related to pressure loads, including increased skin adiposity, changes in pressure transmission and the severity of nerve alteration. Characterization of the hypodermic and subcutaneous adipose tissue should give more information on the inflammatory status and influence (On-going study).

## [P46] NATURAL HISTORY OF NEUROPATHY IN TYPE 2 DIABETIC PATIENTS WITH MILD NEUROPATHY: A 3 YEARS FOLLOW UP STUDY

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**Objective:** To investigate the natural history of neuropathy in patients with type 2 diabetes and mild neuropathy over the course of 3 years.

**Method:** 32 patients with T2DM (age:62±7 years; duration diabetes:11.5±8 years) with mild neuropathy studied at baseline and annually at 12, 24 and 36 months. Each patient underwent detailed assessments at each visit including neurological examinations, symptoms, signs, electrophysiology, quantitative sensory testing, corneal sensitivity and corneal confocal microscopy. 20 aged-matched healthy subjects underwent the same neurological examinations at baseline.

**Results:** Although clinically signs and symptoms of patients are still at normal range at baseline, there were significant differences between patients and controls for neurological parameters. Changes at 12, 24 months was not significant. Changes for main parameters per year have been established. Neuropathy deficit score did not change over this period of time. Neurological examinations showed slow deterioration assessed by vibration perception threshold, nerve conduction at peroneal and sural nerves and warm and cold sensation thresholds. Significant reduction in branch density, length of corneal nerve fibres were observed at 36 months.

**Conclusion:** This findings show a slow deterioration of nerve functions over 36 months period which suggest that in the absence of changes at main risk factors still the function of nerves deteriorate with increasing age and the duration of disease. Corneal nerve parameters showed the maximum changes over this period of time, which makes them an ideal marker for future longitudinal studies of diabetic neuropathy. Indeed longer period of follow-up at larger cohort of patients will be needed.

## [P47] COMPARISON OF QUALITY OF LIFE IN PAINFUL AND PAINLESS DIABETIC PERIPHERAL NEUROPATHY

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**Objective:** This study was performed to determine the comparison of quality of life and sleep impairment in painful and painless diabetic peripheral neuropathy (PDPN).

**Method:** The study pool consisted of 200 randomly selected peoples with type 2 diabetic peripheral neuropathy. PDPN was diagnosed over 4 pain score using visual analogue scales (VAS) and medical history. The patients were asked to answer the Brief Pain Inventory-Short Form (BPI-SF), Medical Outcomes Study Sleep (MOS-Sleep) Scale and estimate the quality of life in people with diabetic peripheral neuropathy.

**Results:** Among the patients with diabetic peripheral neuropathy (n=200), 82 (41%) were diagnosed with PDPN. All pain severity and interference measures were higher in patients with PDPN than those in patients with painless DPN. Peoples with PDPN had more sleep impairment than painless with DPN. MOS 6 items-sleep adequacy, respiratory problem during sleep, sleep initiation problem, sleep maintenance problem, and somnolence-sleep scale were lower in patient with painful DPN than painless DPN.

**Conclusion:** Patients with painful DPN have greater discomfort during daily activities and sleep, and reduced QoL compared to patients with painless DPN. We suggested that physicians should carefully consider pain symptoms in patients with diabetic peripheral neuropathy.

## [P48] SKIN AUTOFLUORESCENCE IS RELATED TO INTRAEPIDERMAL NERVE FIBER DENSITY IN TYPE 1 DIABETIC PATIENTS WITH LONG DISEASE DURATION

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**Objective:** The aim of the study was to assess the accumulation of advanced glycation end products (AGEs) in patients with long lasting type 1 diabetes (DM1) in relation to the presence of diabetic neuropathy.

**Method:** We evaluated 102 DM1 patients (58 men), aged 43 (IQR:34-54), disease duration 23 (18-30) years. Peripheral neuropathy was diagnosed in patients with two or more of the following five elements: The presence of symptoms, lack of ankle reflexes, impaired sensation of touch, temperature and/or vibration. We used AGE Reader device to measure skin autofluorescence (AF) phenomenon, which occurs because of fluorescent properties of AGEs. We assessed vibration perception threshold (VPT) with neurothesiometer. PGP 9.5-immunoreactive nerve fibers were counted to assess intraepidermal nerve fiber density (IENFD) in skin biopsy.

**Results:** We found peripheral neuropathy in 50% of DM1 patients. Patients with neuropathy as compared to subjects without neuropathy had higher skin AF [2.7 (2.3-3.2) vs 2.1 (1.8-2.5)AU; p<0.001] and lower IENFD [10 (7-13) vs 12 (8-15)/mm; p=0.005]. We found a positive correlation between skin AF and patients' age (Rs=0.49, p<0.001), diabetes duration (Rs=0.41, p<0.001), VPT (Rs=0.48, p<0.001) and negative correlation between skin AF and IENFD (Rs=-0.25, p=0.01) and HDL cholesterol level (Rs=-0.20, p=0.04). In multivariate logistic regression presence of neuropathy was independently associated with skin AF [OR 3.41, 95%CI: 1.17-9.91, p=0.02]. This association was independent from gender, diabetes duration, age, smoking and IENFD.

**Conclusion:** Presence of small and large fiber neuropathy in type 1 diabetic patients is associated with higher accumulation of AGEs in the skin.

## [P49] VALIDITY OF AN AUTOMATED PROTOCOL OF IN VIVO CORNEAL CONFOCAL MICROSCOPY FOR DIABETIC SENSORIMOTOR POLYNEUROPATHY DETECTION IN TYPE 1 DIABETES

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**Objective:** In vivo corneal confocal microscopy (IVCCM) has been validated as a diagnostic tool for diabetic sensorimotor polyneuropathy (DSP), with manual assessment of corneal nerve fibre length (CNFL) showing best operating characteristics. We aimed to determine and compare the diagnostic validity of CNFL when measured using an automated analysis protocol.

**Method:** IVCCM was performed on 89 type 1 diabetes participants and 71 healthy volunteers concurrent with clinical and electrophysiological examinations. Post-examination, CNFL was determined using both a manual and automated analysis protocol. CNFL from both methods was compared between healthy volunteers, DSP controls, and DSP cases using ANOVA. Receiver operating characteristic (ROC) curves for the identification of DSP were generated for both methods, and results were compared.

**Results:** Mean age of the 71 healthy volunteers, 50(56%) DSP controls, and 39(44%) DSP cases was 40±17, 34±15, and 49±14y respectively (p<0.0001). CNFL<sub>Manual</sub> was 18.6±4.5, 17.2±4.2, and 11.4±3.7 mm/mm<sup>2</sup> for the healthy volunteers, DSP controls, and DSP cases, respectively (p<0.0001), and CNFL<sub>Automated</sub> was 12.4±3.8, 11.8±3.2, and 8.3±2.8 mm/mm<sup>2</sup> (p<0.0001). Area under the ROC curve was 0.87 for CNFL<sub>Manual</sub> and 0.80 for CNFL<sub>Automated</sub> (p=0.0002). The optimal diagnostic threshold was 14.0 mm/mm<sup>2</sup> for CNFL<sub>Manual</sub> and 11.3 mm/mm<sup>2</sup> for CNFL<sub>Automated</sub>.

**Conclusion:** Though lower when compared to the manual method, CNFL measured by the automated protocol retains its diagnostic validity for identifying DSP in type 1 diabetes. This suggests that automating the image analysis process can improve efficiency and generalizability of IVCCM without sacrificing diagnostic capability. Further work must be done to validate diagnostic thresholds.

## [P50] SENSITIVE DIABETIC NEUROPATHY AND AN EARLY CLINICAL DIAGNOSTIC ACCURACY ARE ASSOCIATED WITH QUANTITATIVE DETECTION OF SUBTYPES NERVES FIBERS DYSFUNCTION IN DIABETES: ASSESSMENT OF A NEW DEVICE VS STANDARDIZED CLINICAL TOOLS

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**Objective:** Peripheral neuropathy (PN) is associated with increased rate of morbidity and mortality. Due to these reasons, it is important to detect PN as early as possible. Nerve dysfunction (NS) includes, vibration, thermal, and pain thresholds in diabetic patients. Our objective was to demonstrate the ability of a new inexpensive and handled Quantitative Sensory Testing device (QST) NerveCheck, to detect clinical and subclinical neuropathic dysfunctions in type 1 and type 2 diabetic patients (DM 1-2,) in a latin-european population. We compare NerveCheck vs standardized clinical tools.

**Method:** 198 DM 1-2; underwent NerveCheck, vibration perception threshold (VPT), cold (CPT), warm (WPT) Heat pain test (HPT) in comparison with clinical tools : McGill Questionnaire (PQ), the Total symptom score (TSS) Neuropathic disability score(NDS). Neuropathy diagnostic (Neurodiab consensus) Statistical Methods: Pearson chi<sup>2</sup> (chi<sup>2</sup>); Kappa concordance agreement (KCA).

**Results:** NerveCheck complet Test (NCK.CT) vs. global clinical tools=TTS+PQ+NDS (GCT), Pchi<sup>2</sup>=26.1054, Pr=0.0001, KCA=64,25%, Prob>Z=0.0001. GCT detected PN 65.05% of 100% NCK.CT. and 35.7% (+) TSS of 100% detected PN by NerveCheck, Pchi<sup>2</sup>=5.2578, Pr=0.022, KCA 60.31%, Prob>Z=0.001. VPT NS in 64% of 100% NCK.CT, Pchi<sup>2</sup>=17.1333, Pr=0.0001, KCA=64.82%, Prob>Z=0.00001. CPT 30.68% NS in 100% of abnormal NDS, Pchi<sup>2</sup>=208476, Pr=0.00001. HPT 43.75% NS in 100% of normal NDS subjects, Pchi<sup>2</sup>=13.7586, Pr=0.00001, KCA=63.82, Prob>Z=0.00001. There was a significantly greater NS detected in subjects with NCK.CT compared GCT.

**Conclusion:** NerveCheck is a new inexpensive QST device, that allows an accuracy diagnostic ability to detect nerves fibers subtype damage in patients with clinical or subclinical PN stages.

## [P51] MIBG IMAGING AND LEFT VENTRICULAR DYSFUNCTION PATIENTS WITH DIABETES MELLITUS TYPE 1

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**Objective:** To investigate if there is an association between cardiac sympathetic activity assessed with 123I metaiodobenzylguanidine (MIBG) imaging and Left Ventricular Dysfunction (LVD) in patients with Diabetes Mellitus type 1 (DMT1).

**Method:** Twenty seven patients (13 female), aged 37.6±10 years, with a duration of DMT1 20.3±8.9 years. Participants were evaluated for autonomic dysfunction with Autonomic Function Tests (AFT) [mean circular resultant (MCR), Valsalva maneuver (Vals), postural index (PI), orthostatic hypotension (OH)] and cardiac MIBG [with the ratio of the heart to upper mediastinum count density (H/M) at 15 minutes and 4 hours post-injection]. Within one month patients underwent evaluation of systolic and diastolic left ventricular function with Tissue Doppler Imaging. The following indices measured: Ejection fraction, Sm, E/A ratio, Em/Am and E/Em.

**Results:** One patient had two abnormal AFTs, 5 had one and all remaining patients had normal AFT tests. In contrast, only 3 patients had normal MIBG measurements (H/M 15min and 4h ≥ 1.80). Indices of MIBG correlated significantly with the duration of diabetes (H/M 4h:  $r=-0.470$ ,  $p=0.02$ ; H/M 15min:  $r=-0.439$ ,  $p=0.03$ ) and indices of diastolic LV function: E/Em (H/M 4h:  $r=-0.428$ ,  $p=0.03$ ; H/M 15min:  $r=-0.502$ ,  $p=0.01$ ), Em/Am (H/M 4h:  $r=0.490$ ;  $p=0.01$ , H/M 15min:  $r=0.655$ ,  $p=0.0005$ ). DM duration correlated significantly with all AFTs.

**Conclusion:** In DMT1 patients: (a) sympathetic dysfunction, as assessed with cardiac MIBG imaging, is associated with LVDD, (b) AFTs (predominantly addressing the parasympathetic system) are insensitive markers of early cardiovascular autonomic neuropathy. Hence, cardiac MIBG imaging can predict LV diastolic dysfunction early in the course of DMT1.

## [P52] THE QUANTITATIVE ASSESSMENT OF NERVE FIBERS IN INTERNAL ORGANS IN COMPARISON WITH CUTANEOUS SMALL NERVE FIBERS IN STZ INDUCED DIABETIC RATS

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**Objective:** Peripheral neuropathy can be occurred all of the nerve. However, exact relations of degree and severity in organ nerve damages are not clear. Therefore, we performed the quantitative comparison of peripheral nerve fibers (NF) of organs in the STZ induced diabetic rats.

**Method:** Animals were divided into 4 groups as follows: Normal (N), diabetes (DM), DM+insulin (DM+INS), and DM+alpha lipoic acid 100mg/kg (DM+ALA). Quantification of NFs in pancreas and kidney was performed using arbitrary unit of one hundred twenty fixed unit on the captured image. Gastric NFs were also assessed using arbitrary line in the gastric mucosa from gastric mucosal surface. Cutaneous NFs were quantified by intraepidermal NF density (IENFD).

**Results:** The number of arbitrary fixed unit including NFs in pancreas, gastric mucosa, and kidney was decreased in the diabetic rats and glucose control by insulin blunted this trend ( $P<0.05$ ). However, there were no significant differences between DM and DM+ALA groups in each comparison. IENFD change was correlated with peripheral nerve changes of each organs as follows:  $6.5\pm0.64$  vs  $4.6\pm0.37$ , vs  $6.1\pm0.6$ ,  $P<0.05$ , Normal, DM, and DM+INS respectively. However, there was a significant difference of IENFD between DM and DM+ALA, and ALA could not show the consistent effect on the peripheral nerves of each organ.

**Conclusion:** Peripheral NFs of internal organ can be damaged similarly in diabetic condition and these trends can be related with IENFD. However, therapeutic responses to drug without glucose control may be different according to the location or neuronal type.

## [P53] REPRODUCIBILITY OF IN VIVO CORNEAL CONFOCAL MICROSCOPY USING AN AUTOMATED ANALYSIS PROGRAM FOR DETECTION OF DIABETIC SENSORIMOTOR POLYNEUROPATHY

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**Objective:** In vivo Corneal Confocal Microscopy (IVCCM) is a validated, non-invasive test for diabetic sensorimotor polyneuropathy (DSP) detection, but its utility is limited by the image analysis time and expertise required. We aimed to determine the intra- and inter-observer reproducibility of a novel automated analysis program compared to manual analysis.

**Method:** In a cross-sectional diagnostic study, 20 non-diabetes controls (mean age 41.4±17.3y, A1c 5.5±0.4%) and 26 subjects with type 1 diabetes (42.8±16.9y, 8.0%±1.9%) underwent two separate IVCCM examinations by one observer and a third by an independent observer. Along with nerve density, branch density, and nerve tortuosity, corneal nerve fibre length (CNFL) was obtained by manual analysis (CNFL<sub>MANUAL</sub>), a protocol in which one image per eye was manually selected for automated analysis (CNFL<sub>SEMI-AUTOMATED</sub>), and one in which selection and analysis was performed electronically (CNFL<sub>FULLY-AUTOMATED</sub>).

**Results:** Mean CNFL<sub>MANUAL</sub> was 16.7±4.0, 13.9±4.2 mm/mm<sup>2</sup> for non-diabetes controls and diabetes subjects, while CNFL<sub>SEMI-AUTOMATED</sub> was 10.2±3.3, 8.6±3.0 mm/mm<sup>2</sup> and CNFL<sub>FULLY-AUTOMATED</sub> was 12.5±2.8, 10.9 ± 2.9 mm/mm<sup>2</sup>. Inter-observer intraclass correlation coefficient (ICC) and 95% confidence intervals were 0.73[0.56, 0.84], 0.75[0.59, 0.85], and 0.78[0.63, 0.87], respectively (p=NS for all comparisons). Intra-observer ICC were 0.72[0.55, 0.83], 0.74[0.57, 0.85], and 0.84[0.73, 0.91], respectively (p<0.05 for CNFL<sub>FULLY-AUTOMATED</sub> compared to others). The other IVCCM parameters had lower ICCs than CNFL.

**Conclusion:** Despite an apparent measurement (underestimation) bias in comparison to the manual strategy of image analysis, fully-automated analysis preserves the reproducibility of CNFL measurement. Future work must determine the diagnostic thresholds for fully-automated measures.

## [P54] ELEVATED PAIN THRESHOLD IN PAINFUL DIABETIC NEUROPATHY: A STUDY BY INTRAEPIDERMAL ELECTRICAL STIMULATION

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**Objective:** Painful diabetic neuropathy is a common complication of diabetes mellitus. Patients with painful neuropathy often describe hyperalgesia or allodynia evoked by light touch. It has been morphologically demonstrated that small nerve fibers such as A-delta and C fibers are predominantly affected in typical cases of painful neuropathy. Intra-epidermal electrical stimulation (IES) is a new technique which assesses function of A- delta fibers in the epidermis. The aim of this study was to investigate A-delta nerve fiber function in painful diabetic neuropathy.

**Method:** We recruited nine patients with painful diabetic neuropathy and ten healthy subjects served as controls. For nociceptive IES, we introduced a concentric bipolar needle electrode. This electrode selectively activated cutaneous A-delta fibers. We placed the IES electrode onto the skin of the dorsum of the foot and began stimulation with an intensity strong enough for the subject to feel a pricking sensation and reduced the current in steps of 0.01mA until no sensation was felt. We defined pain threshold as the minimum electrical intensity at which a subject felt a pricking sensation.

**Results:** Mean pain threshold values in the patient and control groups were 0.210±0.26mA and 0.028±0.08mA (p<0.05), respectively.

**Conclusion:** Our data indicated an elevated pain threshold in epidermis in painful diabetic neuropathy. In other words, we observed hypo-function in A-delta nerve fiber terminals in the epidermis even in a painful condition. The present study demonstrated that pain sensation of the epidermis is reduced in painful diabetic neuropathy.

## [P55] USEFULNESS OF MNSI TO SCREEN SYMPTOMATIC DIABETIC PERIPHERAL NEUROPATHY

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**Objective:** Michigan neuropathy screening instrument (MNSI) is one of non-invasive tests to screen symptomatic diabetic peripheral neuropathy (DPN). If MNSI score is more than 3 points, DPN may be suspected in patients with diabetes mellitus (DM). We studied the usefulness of MNSI to screen symptomatic DPN when using this criteria.

**Method:** We randomly selected 136 patients among the patients with DM, and examined the presence of DPN symptoms, age, sex, duration of DM, glycated hemoglobin, 10 g monofilament test, pinprick test, vibration test, Achilles reflex, MNSI, and total symptom score.

**Results:** The number of patients with symptomatic DPN was 48 (35.3%). When the criteria of MNSI score  $\geq 3$  points was met, the sensitivity and specificity for the screening of symptomatic DPN were 80.8% and 90.9%. The number of patients without symptomatic DPN and with more than 3 points of MNSI score was 8. In the questionnaires of numbness, burning pain, and dry skin of foot, more than half of cases showed abnormal responses. Based on the results of MNSI score in patients without symptomatic DPN, age had no statistical differences. When the MNSI score  $\geq 2$  points was met, the sensitivity and specificity for the screening of symptomatic DPN were 91.7% and 84.1% in receiver operating characteristic curve (AUC, 0.918; 95% confidence interval, 0.866-0.971;  $p < 0.05$ ).

**Conclusion:** In this study, altering the cut point from  $\geq 3$  points to  $\geq 2$  points improves the usefulness of screening for MNSI.

## [P56] ASSESSING CORNEAL NERVE MORPHOLOGY WITH VISUAL ANALYSIS

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**Objective:** Corneal confocal microscopy has enabled recent advances in the diagnosis of nerve damage for a range of peripheral neuropathies, in particular diabetic neuropathy. However, analyzing the multivariate microscopic values in association with other clinical and neurological data remains challenging. To this end, we propose a visual analysis approach to show the data in comprehensible manner and in this way, to support experts in understanding and assessing complex relationships.

**Method:** We demonstrate our approach with a normative data set from a multinational study, including four common attributes for judging corneal nerve morphology (fiber length (CNFL), tortuosity (CNFT), density (CNFD), branch density (CNBD)) from 343 healthy volunteers. We analyzed different aspects of the data set using four dedicated visualizations techniques. Coordinated interaction helped exploring correlations between patients' attributes and generate meaningful overviews. In addition, we applied automated computations to support the visual analysis with aggregations and quantitative assessments of the data.

**Results:** Visual analysis confirms recent findings such as age-dependent decrease in CNFL, which can be directly observed, but also reports several new patterns. Particularly, we identify deviations in the value distributions of the four corneal nerve attributes induced by different protocols used for the microscopic image acquisition in participating centers of the study.

**Conclusion:** Visual analysis supports experts in assessing multivariate corneal nerve morphology values obtained using corneal confocal microscopy and will facilitate to apply this technology at clinical settings in the study of diabetic and other peripheral neuropathies.

## [P57] STAGING SYSTEM OF DIABETIC NEUROPATHY BY NERVE CONDUCTION STUDY

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**Objective:** Nerve conduction study (NCS) serves as a golden standard in diagnosis of diabetic polyneuropathy (DPN); nevertheless, no staging system by NCS exists. We propose DPN staging system by NCS, consisting of five stages; NCS-0 (normal): no abnormal parameter, NCS-I (mildly abnormal): presence of any delay in distal latency of CMAP, MCV, SCV, or minimal F-wave latency, or presence of a-wave, NCS-II (moderately abnormal): decrease in sural SNAP < 5 $\mu$ V, NCS-III (severely abnormal): decrease in abductor hallucis (AH)-CMAP to 2-5mV, and NCS-IV (ultimately abnormal): AH-CMAP < 2mV or lost. The idea of this criterion is derived from the fact that the most sensitive parameter is minimal F-wave latency in early DPN, and that fall in compound potential starts from sural SNAP, and later followed by decrease in AH-CMAP in advanced patients. To validate this system we carried out NCS in 105 diabetic patients and 126 healthy volunteers.

**Method:** In addition to NCS, Michigan Neuropathy Diagnostic Instrument (MNDI) was evaluated. In some patients, IENFD was obtained from biopsied skin of the calf.

**Results:** MNDI scores and IENFD/mm were as follows respectively; NCS-I: 2.7, 7.9, NCS-II: 4.0, 4.5, NCS-III: 4.6, 2.9, NCS-IV: 5.1, 0.

**Conclusion:** The present NCS staging system for DPN seems to work well, particularly in those with asymptomatic, painless patients.

## [P58] SUDOSCAN AS A TOOL FOR EARLY SCREENING OF DIABETIC MICROVASCULAR COMPLICATIONS: EXPERIENCE OF A FRENCH HOSPITAL

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**Objective:** The screening of microvascular complications in patients with type 2 diabetes is not optimal, especially for neuropathy at early stage. Sweat glands are innervated by small autonomic C-fibers and measurement of sweat function has been proposed to evaluate peripheral small fiber neuropathy. This study aimed to evaluate SUDOSCAN, an easy, fast, non-invasive and quantitative measurement of sweat function for the screening of microvascular complications.

**Method:** 189 patients with type 2 diabetes had clinical examination including monofilament testing, blood tests including renal function, ophthalmologic examination (n=113), SUDOSCAN with hands and feet conductance measurements ( $\mu$ S) and global autonomic risk score. Results were expressed as mean $\pm$ SD and comparisons were made by a Student test.

**Results:** The mean age was 60 $\pm$ 16 years, 49% were men, HbA<sub>1c</sub> 9.0 $\pm$ 1.3%. Feet conductances of patients having Fasting blood glucose > 7.2 mmol/L or urinary albumin excretion (UAE)  $\geq$  15 mg/L were significantly lower (70 $\pm$ 15 vs 74 $\pm$ 16  $\mu$ S, p=0.03 and 69 $\pm$ 17 vs 75 $\pm$ 14  $\mu$ S, p=0.002 respectively). Patients with abnormalities to monofilament testing had also lower feet conductances (65 $\pm$ 20 vs 75 $\pm$ 11  $\mu$ S, p=0.003). Same tendency was observed in patients with retinopathy. Global autonomic risk score using 35 as threshold had a sensitivity of 78% and a specificity of 54% to detect at least one microvascular complication. No adverse event or discomfort has been reported during or following the SUDOSCAN recording.

**Conclusion:** These results indicate that SUDOSCAN could be used for early detection of microvascular complication and potentially for the patient follow-up as the result is quantitative.

## [P59] THE LARGEST STUDY ON THE IMPACT OF NEUROPATHY ON QUALITY OF LIFE (QOL) IN DIFFERENT AGE GROUPS OF ROMANIAN PATIENTS WITH SELF-REPORTED DIABETES

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**Objective:** Objective was to evaluate and compare quality of life (QOL) in different age groups of patients with self-reported diabetes, with and without neuropathy (DN), using scores for the Total and five subdomains of the Norfolk QOL-DN tool.

**Method:** In this cross-sectional survey, conducted between June and December 2012, 181 healthcare providers from 51 Romanian cities distributed the linguistically translated Romanian Norfolk QOL-DN questionnaire to their patients. 23,543 patients completed 35 questions related to their own health perception over the previous 4 weeks. We included patients between 20 and 89 years old, with complete demographic data resulting in 21,114 validated forms.

**Results:** This is the largest study on age group differences in perception of QOL in patients with self-reported diabetes with and without DN. The decline of Total QOL and all 5 subdomains scores (higher scores = worse) was linearly related to increasing age ( $p < 0.001$ ). Patients between 50-59 years old reported a Total QOL score 2.07 fold higher than scores of patients between 20-29 years old; and patients between 80-89 years old reported a score 3.27 fold higher compared to the 20-29 age group. Patients from all age categories had Total QOL and all 5 subdomains scores greater than normative data.

**Conclusion:** Diabetes has a greater impact on QOL and all its domains in older patients than in younger ones based on scores obtained with Norfolk QOL-DN questionnaire. Neuropathy impacted QOL negatively in patients with diabetes in all age groups.

## [P60] DIFFERENT IMPAIRMENT OF PERIPHERAL NERVOUS SYSTEM FIBERS: A CLINICAL STUDY IN TYPE 1 AND 2 DIABETES

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**Objective:** To verify if there is a different impairment of peripheral nervous system fibers in patients with type 1 and type 2 diabetes in clinical setting.

**Method:** 213 patients with diabetes (62 type 1 and 151 type 2) underwent clinical evaluation performed with TTS, MDNS and Medock device for studying warm sensibility (WS, C fibers 2-5 micron of diameter) cold sensibility (CS, A $\delta$  fibers 2-5 micron of diameter) and vibration perception threshold (VPT, large fibers 16 micron). Statistical analysis was performed with Student's t, ANOVA and ANCOVA.

**Results:** All the parameters were statistically different between the two groups (type 1 and type 2) and the influence of disease duration and type of diabetes were then evaluated with ANCOVA: VPT showed a significant relationship with duration of disease and with the type of diabetes whereas WS and CS weren't influenced by the duration of disease but only by the type of diabetes.

**Conclusion:** In patients with diabetes WS and CS impairment is strongly linked to the type of diabetes whereas VPT impairment is linked both to the type of diabetes and disease duration. We suggest a iatrogenic effect of insulin therapy in the first group (patients with type 1 diabetes) or a longer silent disease in the second group (patients with type 2).

## [P61] CHARACTERISTICS OF DIABETIC FOOT ULCERS BY ETIOLOGIC CLASSIFICATION IN HOSPITALIZED PATIENTS

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**Objective:** To identify differences in the characteristics of patients with DFUs according to their etiological classification and to find out risk factors for amputation.

**Method:** From January 2013 to March 2015, a total 98 hospitalized patients with DFUs in were retrospectively reviewed. DFUs were etiologically classified as being of neuropathic or neuro-ischemic origin. Descriptive analyses were performed to characterize study subjects, foot-related factors, and multivariate analysis was performed to assess risk factors for limb amputation.

**Results:** 38 (38.8%) of the patients had a peripheral neuropathy with PAD (Group 1), 52 (53.1%) of the patients had a neuropathy without PAD (Group 2) and 7 (7.1%) of the patients were not evaluated. Patients in the Group 1 significantly older and had a long duration of diabetes, had lower estimated glomerular filtration rate, and had high prevalence of other macrovascular complications compared to patients in the Group 2 ( $p<0.05$ ). Locations of DFUs were different between two groups: Plantar involvement was rare and frequently involve dorsal area and digits in Group 1. In contrast, both plantar and dorsal areas were common locations of DFUs in group 2. Amputation rates of each group were 18 (47.4%) in Group 1 and 19 (36.5%) in Group 2.

**Conclusion:** Further studies on DFUs addressing their etiology warranted for early identification of patients at risk of DFUs and minimize amputation risk.

## [P62] HEMORRHEOLOGICAL APPROACH FOR EARLY DETECTION OF DIABETIC MICROANGIOPATHY

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**Objective:** Hemorrheological parameters, such as erythrocyte deformability, erythrocyte aggregation are altered in patients with diabetes mellitus. These changes of erythrocyte in turn make whole blood more viscous and may play an important role on the pathogenesis of vascular complications of diabetes mellitus.

**Method:** 190 subjects were divided by five groups according to their past history and test results as follows: Healthy control (n=28), prediabetes (pre-DM, n=14), diabetes without vascular complications (DM-no Cx, n=89), diabetes with microvascular complications (DM-microCx, n=43), and diabetes with macrovascular complications (DM-macroCx, n=15).

**Results:** A significant reduction of erythrocyte deformability was observed in DM-no Cx and DM-microCx group compared with healthy control (0.318 & 0.314 vs. 0.347  $p<0.05$ ). Whereas, AI does not show significant tendency ( $p$ -value $<0.05$ ). And critical shear stress shows significant difference between DM-no Cx and DM-microCx group (273.41 vs 339.47  $p<0.05$ ).  $SS_{1/2}/Elmax$  shows significant reduction in DM-no Cx and DM-microCx group compared with healthy control (0.245 & 0.242 vs. 0.271  $p<0.05$ ).

**Conclusion:** EI is a sensitive parameter to detect impairment of erythrocyte in diabetic process. And critical shear stress is also a useful parameter to detect diabetic microangiopathic complications early. Through analyzing tendency of these hemorrheologic factors, discovering the new hemorrheologic parameter and making the equation or scoring system to detect diabetic microcomplications is very important task.

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**NEURODIAB 2015**

Annual Meeting

25th Annual Meeting of the  
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