9TH - 12TH SEPTEMBER 2016 / BUCHAREST, ROMANIA
RAMADA PARC / PLAZA HOTEL

NEURODIAB 2016
Annual Meeting

NEURODIAB
Society for
Diabetic
Neuropathy

26th Annual Meeting of the
Diabetic Neuropathy Study Group of the
European Association for the Study of Diabetes (EASD)

PROGRAM AND ABSTRACTS

INDEX

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 etc. In pursuit of this aim it will also encourage appropriate survey and clinical trials.

NEURODIAB celebrates its 26th anniversary at the 2016 Annual meeting in Bucharest, Romania.

UNIVERSITY SQUARE
BUCHAREST, ROMANIA

Simona Frontoni MD, PhD

Chairman, Neurodiab

Professor of Endocrinology, University of Rome Tor Vergata Rome, Italy

Chief, Endocrinology and Diabetes - San Giovanni Calibita Fatebenefratelli Hospital, Rome, Italy

Rodica Pop-Busui MD, PhD

Professor of Internal Medicine Metabolism, Endocrinology and Diabetes, University of Michigan, Ann Arbor, MI, USA

Co-Director, Neuropathy Center University of Michigan, USA

Elected Associate Chair for Clinical Research at the University of Michigan, USA

Honorary member of the Society for Diabetic Neuropathy

Dear Friends and Colleagues,

It is our great pleasure to welcome you to the 26th Annual Scientific Meeting of NEURODIAB at Complex Ramada Plaza and Ramada Parc Hotels, Bucharest, Romania.

The 2016 meeting will be an opportunity for all the clinicians and experimental investigators in the field of diabetic neuropathy from across the world to discuss their research work and to share the most updated data on pathogenesis, assessment and treatment of diabetic neuropathy. But it will also be a great opportunity for young researchers or newcomers in the field to meet and spend time with senior scientists for refining and exploiting their research ideas.

The meeting will include oral and poster sessions, keynote lectures and symposia, and the format is designed to favour a friendly and collaborative atmosphere, due to the relatively small number of attendees, and lots of scientific but also prearranged social sections.

We really hope you will enjoy the meeting!

Simona Frontoni and Rodica Pop-Busui,
on behalf of the Organizing Committee

PROGRAM OVERVIEW

FRIDAY 9 SEPTEMBER 2016

13.30 – 14.00 REGISTRATION & WELCOME COFFEE
14.00 – 14.30 WELCOME
14.30 – 15.15 GØRAN SUNDKVIST CLINICAL AWARD
15.15 – 15.45 KEYNOTE SESSION
AUTONOMIC NERVOUS SYSTEM FUNCTIONS AND DYSFUNCTIONS DURING SLEEP
15.45 – 17.45 ORAL SESSION
YOUNG INVESTIGATORS ORAL PRESENTATIONS
17.45 – 18.30 PRE-CLINICAL AWARD
19.30 DINNER

SATURDAY 10 SEPTEMBER 2016

08.00 – 08.30 KEYNOTE SESSION
DIABETIC RETINAL SENSORY NEUROPATHY
08.30 – 10.00 ORAL SESSION
SMALL FIBERS
10.00 – 10.15 COFFEE BREAK AND EXHIBITION
10.15 – 10.45 KEYNOTE SESSION
MECHANISMS OF HYPOXIA IN DIABETES
10.45 – 12.15 ORAL SESSION
AUTONOMIC NEUROPATHY
12.15 – 13.15 WÖRWAG PHARMA SYMPOSIUM
13.15 – 14.15 LUNCH BREAK
14.15 – 17.15 POSTER SESSION
YOUNG INVESTIGATORS PRESENTATIONS
17.15 – 17.30 COFFEE BREAK AND EXHIBITION
17.30 – 19.00 ORAL SESSION
EPIDEMIOLOGY
19.00 – 19.30 GENERAL ASSEMBLY
20.00 DINNER

SUNDAY 11 SEPTEMBER 2016

08.00 – 08.30 KEYNOTE SESSION
UROLOGIC COMPLICATIONS AND AUTONOMIC DYSFUNCTION IN DIABETES
08.30 – 10.00 ORAL SESSION
TREATMENT
10.00 – 10.30 COFFEE BREAK AND EXHIBITION
10.30 – 11.00 KEYNOTE SESSION
OVERCOMING BIOENERGETIC MALADAPTATIONS TO HYPERGLYCAEMIA
11.00 – 12.30 ORAL SESSION
PATHOGENESIS AND DIAGNOSIS
12.30 – 13.30 LUNCH BREAK
13.30 – 16.00 POSTER SESSION
- PATHOGENESIS AND TREATMENT
- AUTONOMIC AND EPIDEMIOLOGY
- DIAGNOSIS

16.00 – 16.30 COFFEE BREAK AND EXHIBITION
16.30 – 18.00 ORAL SESSION
PAIN
18.00 – 18.15 CLOSING REMARKS
19.30 DINNER

DAILY PROGRAM

FRIDAY 9 SEPTEMBER 2016

13.30 – 14.00		REGISTRATION & WELCOME COFFEE	
14.00 – 14.30		WELCOME Welcome by Professor Simona Frontoni, Italy, Chairman NEURODIAB Welcome Address by Professor Andrew Boulton, UK, Past President, European Association for the Study of Diabetes (EASD) Welcome by Professor Rodica Pop-Busui, USA, on behalf of the Organizing Committee	
14.30 – 15.15		GØRAN SUNDKVIST CLINICAL AWARD SANJEEV SHARMA Chairs: Simona Frontoni, Italy and Henning Andersen, Denmark	
15.15 – 15.45		KEYNOTE SESSION AUTONOMIC NERVOUS SYSTEM FUNCTIONS AND DYSFUNCTIONS DURING SLEEP Chairs: Simona Frontoni, Italy and Henning Andersen, Denmark	*Pietro Cortelli, Department of Biomedical and NeuroMotor Sciences (DIBINEM); Istituto delle Scienze Neurologiche di Bologna, Italy*
15.45 – 17.45		ORAL SESSION YOUNG INVESTIGATORS ORAL PRESENTATIONS Chairs: Simona Frontoni, Italy and Henning Andersen, Denmark	
	01	Abnormal brain white matter integrity in Diabetic Neuropathy	*Dinesh Selvarajah, UK*
	02	Enhanced dermal nerve regeneration despite pronounced epidermal nerve fibre loss in Type 2 Diabetes patients with painful and painless polyneuropathy	*Gidon Bönhof, Germany*
	03	Delivery of microRNA-146a alleviates peripheral nerve damage and suppresses proinflammatory genes in a mouse model of diabetes	*Xian Shuang Liu, USA*
	04	Can slow breathing reveal obstructive sleep apnoea in Type 2 Diabetes and obese patients?	*Lucio Bianchi, Italy*
	05	Association between early peripheral motor unit loss and neuroretinal dysfunction in patients with Type 1 Diabetes mellitus	*Fabiana Picconi, Italy*
	06	Hyperlipidemia alters endoplasmic reticulum-mitochondrial contact site formation and mitochondrial respiratory capacity in dorsal root ganglion sensory neurons	*Amy Rumora, USA*
	07	Dietary reversal improves peripheral neuropathy in a murine model of Type 2 Diabetes	*Phillipe O'Brien, USA*
	08	Sudomotor dysfunction as a measure of small fiber neuropathy in Type 1 Diabetes (T1D)	*Lynn Ang, USA*
17.45 – 18.30		PRE-CLINICAL AWARD ASHUTOSH KUMAR Chairs: Simona Frontoni, Italy and Henning Andersen, Denmark	
19.30		DINNER	

DAILY PROGRAM

SATURDAY 10 SEPTEMBER 2016

08.00 – 08.30		**KEYNOTE SESSION** DIABETIC RETINAL SENSORY NEUROPATHY Chairs: Rodica Pop-Busui, USA and Rayaz Malik, USA	*Thomas Gardner, Department of Ophtalmology, University of Michigan, USA*
08.30 – 10.00		**ORAL SESSION** SMALL FIBERS Chairs: Rodica Pop-Busui, USA and Rayaz Malik, USA	
	09	Corneal Confocal Microscopy is a rapid reproducible ophthalmic technique for quantifying corneal nerve abnormalities	*Alise Kalteniece, UK*
	010	Concurrent Diagnostic Validity of in vivo Corneal Confocal Microscopy (IVCCM) to identify Diabetic Polyneuropathy in Type 1 Diabetes: A Pooled Multicenter Analysis	*Bruce Perkins, Canada*
	011	Concurrent Diagnostic Validity of In Vivo Corneal Confocal Microscopy (IVCCM) to identify Diabetic Polyneuropathy in Type 2 Diabetes: A Pooled Multicenter Analysis	*Leif Erik Lovblom, Canada*
	012	Corneal confocal microscopy and optical coherence tomography detect axonal loss in multiple sclerosis despite normal glucose tolerance	*Ioannis Nikolaos Petropoulos, Qatar*
	013	Ethnic differences in small fiber function in subjects with T2DM	*Carolina Casellini, USA*
	014	Early detection of small fibre neuropathy by corneal confocal microscopy in newly diagnosed Type 2 Diabetes mellitus	*Mitra Tavakoli, UK*
10.00 – 10.15		**COFFEE BREAK AND EXHIBITION**	
10.15 – 10.45		**KEYNOTE SESSION** MECHANISMS OF HYPOXIA IN DIABETES Chairs: Luciano Bernardi, Finland and Dan Ziegler, Germany	*Sergiu-Bogdan Catrina, Department of Molecular Medicine and Surgery, Karolinska Institutet, Stockholm, Sweden*
10.45 – 12.15		**ORAL SESSION** AUTONOMIC NEUROPATHY Chairs: Luciano Bernardi, Finland and Dan Ziegler, Germany	
	015	Energy metabolism perturbations associate with measures of cardiovascular autonomic neuropathy (CAN) in Type 1 Diabetes (T1D) patients	*Rodica Pop-Busui, USA*
	016	Slow breathing acutely reduces reactive oxygen species and improves autonomic and vascular function in Type 2 Diabetes	*Luciano Bernardi, Finland*
	017	Differential association between impaired maximal aerobic capacity and cardiac autonomic dysfunction in recently diagnosed Type 1 and Type 2 Diabetes	*Dan Ziegler, Germany*
	018	Sequential compression/decompression by a pulsating suit increases cutaneous microcirculatory blood flow in patients with Type 2 Diabetes	*Amel Rezki, France*
	019	Role of glycemic variability in the changes in cutaneous microcirculatory blood flow in patients with impaired glucose tolerance or Type 2 Diabetes	*Amel Rezki, France*
	020	Cardiac autonomic neuropathy is strongly associated with abnormal cardiac repolarisation	*Solomon Tesfaye, UK*

12.15 – 13.15		**WÖRWAG PHARMA SYMPOSIUM**	
		Chair: Solomon Tesfaye, UK	
		Painful polyneuropathy is common but largely undiagnosed in subjects with and without diabetes participating in a nationwide educational initiative (PROTECT Study)	*Dan Ziegler, Germany*
		Pathogenetic therapy in diabetic neuropathy – "Quo vadis neuropathy?"	*Peter Kempler, Hungary*
13.15 – 14.15		**LUNCH BREAK**	
14.15 – 17.15		**POSTER SESSION**	
		YOUNG INVESTIGATORS PRESENTATIONS	
		Chairs: Vincenza Spallone, Italy and Tamás Várkonyi, Hungary	
	P1	Effects of acute glycemic stress on measures of cardiovascular autonomic neuropathy (CAN) in patients with Type 1 Diabetes (T1D)	*Lynn Ang, USA*
	P2	A prospective study assessing effects of short-term glycaemia on small fibre structure and function in newly diagnosed Type 1 Diabetes	*Sanjeev Sharma, UK*
	P3	One-year progression of retinal neurodegeneration in patients with Type 1 Diabetes mellitus not affected by Peripheral Neuropathy	*Sara Coluzzi, Italy*
	P4	Association between structural brain abnormalities and cognitive functioning in patients with Type 2 Diabetes mellitus	*Nadegda Zherdova, Ukraine*
	P5	High fat diet-fed female C57BL6/J mice develop early peripheral neuropathy in the absence of systemic insulin resistance	*Phillipe O'Brien, USA*
	P6	A 2-year prospective comparative study of changes in small fibre function and structure in subjects with diabetes and healthy controls using the LDI_{flare} technique and corneal confocal microscopy methods	*Sanjeev Sharma, UK*
	P7	Changes in sympathovagal activity and obstructive sleep apnea after bariatric surgery	*Jean-Louis Nguewa, France*
	P8	Accurate and early diagnosis of neuropathy in routine clinical practice using combined large and small fibre assessments	*Solomon Tesfaye, UK*
	P9	Niclosamide ethanolamine uncoupling treatment does not prevent the development of diabetes, peripheral neuropathy or sensory neuron metabolic reprogramming in BKS-DBDB mice	*Lucy M Hinder, USA*
	P10	Use of corneal nerve fibre length (CNFL) for diabetic neuropathy identification in older patients with longstanding Type 1 Diabetes	*Leif Erik Lovblom, Canada*
	P11	Metformin treatment may impair orthostatic blood pressure recovery	*Christian Stevns Hansen, Denmark*
	P12	Patients with extreme duration Type 1 Diabetes T1DM show protection from small fibre neuropathy (SFN) detected using corneal confocal microscopy (CCM) and skin biopsy	*Shazli Azmi, UK*
	P13	Withdrawn	
	P14	Corneal Confocal Microscopy (CCM) detects an improvement in small fibre neuropathy after bariatric surgery in obese subjects with Type 2 Diabetes mellitus (T2DM)	*Shazli Azmi, UK*
	P15	Investigating for inflammatory markers in corneal nerves of obese patients	*Mitra Tavakoli, UK*
	P16	Corneal Confocal Microscopy: A prognostic marker for stroke outcome	*Adnan Khan, Qatar*
	P17	Agreement between clinical scores of Diabetic Neuropathy and nerve conduction studies in elderly Type 2 Diabetic patients – A cross sectional study	*Signe Toft Andersen, Denmark*

	P18	Sensitivity of various diagnostic markers for early detection of Diabetic Neuropathy	*Mitra Tavakoli, UK*
	P19	Reduced cutaneous microvascular reponse to topical capsaicin evaluated by in vivo reflectance confocal microscopy as a potential marker for Diabetic Neuropathy	*Mihaela Adriana Ghita, Romania*
	P20	Prevalence of autonomic neuropathy in the metabolic syndrome compared to impaired glucose tolerance	*Lindsay Zilliox, USA*
	P21	Implementation of corneal confocal microscopy for screening diabetic neuropathy in primary care: A feasibility and acceptability study	*Mitra Tavakoli, UK*
	P22	The effect of Omega-3 supplementation on Diabetic Neuropathy: Results from a clinical pilot trial	*Evan Lewis, Canada*
	P23	Correlation between chronic inflammatory demielinating polyneuropathy and diabetes mellitus	*Vharoon Sharma Nunkoo, Romania*
	P24	Novel role for the Lipid-Sensor LXR (Liver X Receptor) in Peripheral Sensory Neurons	*Virginie Mansuy Aubert, USA*
17.15 – 17.30		COFFEE BREAK AND EXHIBITION	
17.30 – 19.00		ORAL SESSION EPIDEMIOLOGY Chairs: Peter Kempler, Hungary and Bruce Perkins, Canada	
	O21	Cardiovascular autonomic neuropathy and cardiovascular outcomes in the DCCT/EDIC study	*Rodica Pop-Busui, USA*
	O22	Progression or regression of clinical neuropathy in patients with Type 2 Diabetes over 5 year observation period	*Soroku Yagihashi, Japan*
	O23	Occurrence of diabetic foot by NCS-Severity of Diabetic Neuropathy: A 5-year prospective observation	*Masayuki Baba, Japan*
	O24	Withdrawn	
	O25	The prevalence of diabetic neuropathy and risk of foot ulceration in Qatar	*Georgios Ponirakis, Qatar*
	O26	Divergent course of sensorimotor and cardiac autonomic function over five years in recently diagnosed Type 1 and Type 2 Diabetes	*Alexander Strom, Germany*
19.00 – 19.30		GENERAL ASSEMBLY	
20.00		DINNER	

DAILY PROGRAM

SUNDAY 11 SEPTEMBER 2016

08.00 – 08.30		KEYNOTE SESSION UROLOGIC COMPLICATIONS AND AUTONOMIC DYSFUNCTION IN DIABETES Chairs: Eva Feldman, USA and Paul Valensi, France	*Aruna Sarma, Department of Urology, University of Michigan, Ann Arbor MI, USA*
08.30 – 10.00		ORAL SESSION TREATMENT Chairs: Eva Feldman, USA and Paul Valensi, France	
	027	Treatment of Type 2 Diabetic rats after chronic hyperglycemia with combination therapy consisting of enalapril, α-lipoic acid, and menhaden oil on Diabetic Neuropathy	*Mark Yorek, USA*
	028	Gabapentin topical: Efficiacy and safety evaluation in Diabetic Peripheral Neuropathy (GATESET)	*Navneet Wadhwa, India*
	029	Autonomic nervous system dysfunction ameliorates after kidney and kidney-pancreas transplantation	*Hanna Paajanen, Finland*
	030	Effects of benfotiamine in subjects with sensorimotor Diabetic Polyneuropathy: A double-blind, randomized, placebo-controlled, parallel group study over 12 months	*Alin Stirban, Germany*
	031	Bariatric surgery improves autonomic dysfunction and markers of inflammation in obese subjects with Type 2 Diabetes	*Carolina Casellini, USA*
	032	Resiniferatoxin for the treatment of Diabetic Peripheral Neuropathy	*Louis Premkumar, USA*
10.00 – 10.30		COFFEE BREAK AND EXHIBITION	
10.30 – 11.00		KEYNOTE SESSION OVERCOMING BIOENERGETIC MALADAPTATIONS TO HYPERGLYCAEMIA Chairs: Vera Bril, Canada and Bogdan Florea, Romania	*Paul Fernyhough, Division of Neurodegenerative Disorders, St. Boniface Research Center and Dept. of Pharmacology & Therapeutics, University of Manitoba, Canada*
11.00 – 12.30		ORAL SESSION PATHOGENESIS AND DIAGNOSIS Chairs: Vera Bril, Canada and Bogdan Florea, Romania	
	033	Role of proinflammatory reaction in Diabetic Polyneuripathy - impact of macrophage activation on the insulin resistance of schwann cells	*Hiroki Mizukami, Japan*
	034	Characterization of spontaneously immortalized Schwann cell lines from normal and aldose reductase-deficient C57BL/6 mice	*Kazunori Sango, Japan*
	035	Activation of GPR40 and GPR120 protects oxidative stress-induced cell death in immortalized adult mouse schwann cells	*Koichi Kato, Japan*
	036	Corneal Confocal Microscopy demonstrates immune activation and greater corneal nerve damage in patients with Type 1 compared to Type 2 Diabetes	*Maryam Ferdousi, UK*
	037	Combined retinal/Neuropathy/Renal screening service: An effective model for early detection of Diabetic Peripheral Neuropathy	*Solomon Tesfaye, UK*
	038	Diffusion-Tensor-Imaging MR-Neurography for the detection of Polyneuropathy in Type 1 Diabetes	*Henning Andersen, Denmark*
12.30 – 13.30		LUNCH BREAK	

13.30 – 16.00 POSTER SESSION

PATHOGENESIS AND TREATMENT

Chair: Mitra Tavakoli, UK

P25	Withdrawn	
P26	The relationship between indices of oxidative stress and the manifestations of Diabetic Distal Polyneuropathy in patients with Type 2 Diabetes and NAFLD	*Vadym Sinaiko, Ukraine*
P27	Insulin enhances ampk activity and mitochondrial function in DRG neurons	*Paul Fernyhough, Canada*
P28	Over-expression of muscarinic acetylcholine Type 1 receptor causes cytoskeletal abnormalities and defects in mitochondrial trafficking in adult sensory neurons	*Paul Fernyhough, Canada*
P29	Peripheral nerve distribution in pancreatic islet in experimental diabetic animal model	*Tae Sun Park, Korea*
P30	Neuronal over expression of SIRT1 protein treats Diabetic Neuropathy	*Krish Chandrasekaran, USA*
P31	Mechanisms underlying the neuroprotective actions of a novel mesenchymal stem cell population in a rat model of Type 1 Diabetes with Diabetic Neuropathy - Associated altered pain perception	*Isaura Tavares, Portugal*
P32	Obesity, in addition to hyperglycemia, is one of the main drivers of polyneuropathy	*Brian Callaghan, USA*
P33	Efficacy of acupuncture therapy of gastroparesis in patients with Type 2 Diabetes mellitus	*Iryna Kostitska, Ukraine*
P34	Treatment of C57BL/6J Type 1 Diabetic mice with salsalate, menhaden oil, the combination of salsalate and menhaden oil, or resolvin D1 on neuropathic endpoints	*Mark Yorek, USA*
P35	Effects of antioxidant alpha-lipoic acid on quality of life in Type 2 Diabetic patients with cardiac autonomic neuropathy	*Chong Hwa Kim, Korea*
P36	Effects of antioxidant alpha-lipoic acid on heart rate variability in Type 2 Diabetic patients with cardiac autonomic neuropathy	*Jae Hyuk Lee, Korea*
P37	Therapeutic efficacy of NSI-189 in diabetic mice	*Calcutt Nigel, USA*
P38	Nicotinamide riboside is a potential therapy for Diabetic Neuropathy	*Krish Chandrasekaran, USA*
P39	Polyneuropathy in severe obese patients: Effect of the Y-in-Roux gastric bypass	*Helena Schmid, Brazil*

POSTER SESSION

AUTONOMIC AND EPIDEMIOLOGY

Chair: Soruko Yagihashi, Japan

P40	Searching the optimal ways of screening for autonomic cardiovascular neuropathy in patients with Type 1 Diabetes mellitus	*Roksana Mukharyamova, Russia*
P41	Longitudinal changes in measures of cardiovascular autonomic neuropathy (CAN) in Type 1 Diabetes (T1D)	*Lynn Ang, USA*
P42	Characteristics of cardiovascular autonomic function in insulin pump-treated Type 1 Diabetic patients	*Tamás Várkonyi, Hungary*
P43	Influence of cardiac autonomic dysfunction and arterial stiffness on subendocardial myocardial viability in patients with Type 2 Diabetes	*Lucio Bianchi, Italy*
P44	Pupil dilatation with tropicamide does not affect indices of cardiaovascular autonomic neuropathy – The addition Denmark Study	*Marie Mathilde Bjerg Christensen, Denmark*

P45	Impaired cardiovascular autonomic function and diminished vibration perception are present among patients with high risk for the development of Type 2 Diabetes mellitus screened by the findrisc questionnaire	*Orsolya Erzsébet Vági, Hungary*
P46	Relation between autonomic activity and the post-prandial hemodynamic changes in healthy individuals	*Marinos Fysekidis, France*
P47	Relationship between cardiac autonomic dysfunction, high blood pressure and renal function	*Isabela Banu, France*
P48	Cardiovascular autonomic dysfunction predicts hemoglobin A1c variability in subjects with Type 2 Diabetes	*Yeoree Yang, Korea*
P49	Analysis of diurnal heart rate pattern in diabetic patients with permanent atrial fibrillation	*Aivars Lejnieks, Latvia*
P50	Prevalence of Diabetic Neuropathy among patients with Type 2 Diabetes mellitus in Uzbekistan	*Feruza Takhirova, Uzbekistan*
P51	The Association between Vitamin D status and Diabetic Retinopathy	*Eun Young Lee, Korea*
P52	The association between Metabolic Syndrome and Diabetic Retinopathy	*Eun Young Lee, Korea*
P53	Diabetic Peripheral Neuropathy and Sudomotor Dysfunction among Saudi patients with newly diagnosed Type 2 Diabetes mellitus	*Amal Madanat, Saudi Arabia*
P54	Exploring the association between Metabolic Syndrome components and polyneuropathy in an obese population	*Brian Callaghan, USA*
	POSTER SESSION DIAGNOSIS Chair: Dinesh Selvarajah, UK	
P55	Accuracy of electrochemical skin conductance measurement for the assessment of small fiber neuropathy	*Jean-Henri Calve, France*
P56	Is impaired olfactory function a clinical manifestation of neurovascular degeneration in Type 1 Diabetic patients?	*Aleksandra Araszkiewicz, Poland*
P57	Sleep disturbance and depression in patient's with painful neuropathy	*Leanne Hunt, UK*
P58	The effect of erectile dysfunction on quality of life (QOL) in a large study of Romanian men with self-reported Diabetic Neuropathy	*Bogdan Florea, Romania*
P59	Female sexual dysfunction with self-reported diabetes and neuropathy on quality of life (QOL): A large study on Romanian patients	*Cosmina Bondor, Romania*
P60	The impact of urinary incontinence and sexual dysfunction with self-reported diabetes and neuropathy on quality of life (QOL): A large study on Romanian patients	*Ioan A. Veresiu, Romania*
P61	Should we avoid the handgrip test in the assessment of cardiovascular autonomic neuropathy in diabetic patients? – Exploratory factor analysis	*Anna Körei, Hungary*
P62	Cluster analysis of symptoms, pain severity, qualrity of sleep and life in patients with Diabetic Peripheral Neuropathy identifies subgroups	*Jong Chul Won, Korea*
P63	Absent ankle reflexes - still a specific sign of Diabetic Polyneuropathy in the elderly - A cross sectional studie	*Signe Toft Andersen, Denmark*
P64	Neurological and electrodiagnostic evaluation in patients with Diabetic Neuropathy	*Tudor Lupescu, Romania*
P65	Nervecheck: for the assessment sensitization test in Diabetic Peripheral Neuropathy	*Ariel Odriozola, Spain*

	P66	The utility of point of care sural nerve conduction devise (DPN-check) for identification of Diabetic Neuropathy - A cross sectional study	*Mustafa Aykut Kural, Denmark*
	P67	Association between MIR499 gene polymorphism and diabetic neuropathy in Type 2 Diabetes	*Vincenza Spallone, Italy*
	P68	EEG aspects in renal hemodialysis: Comparison of Diabetic vs. Non-Diabetic patients	*Bogdan Florea, Romania*
16.00 – 16.30		COFFEE BREAK AND EXHIBITION	
16.30 – 18.00		ORAL SESSION PAIN Chairs: Solomon Tesfaye, UK and James Russel, USA	
	O39	Brain MRI abnormalities in patients with Type 2 Diabetes mellitus	*Boris Mankovsky, Ukraine*
	O40	The corellation between the Guillain-Barré syndrome and impaired glucose control	*Vitalie Lisnic, Moldova*
	O41	Mechanisms of diabetic neuropathic pain focussing on sodium channels	*Troels Staehelin Jensen, Denmark*
	O42	The relationship between Vitamin D and Thalamic Neurochemistry in painful Diabetic Neuropathy	*Solomon Tesfaye, UK*
	O43	The prevalence of painful Diabetic Neuropathy in Qatar and Vitamin D deficiency as a risk factor	*Georgios Ponirakis, Qatar*
	O44	Small but not large fibre neuropathy measures differentiate patients with painful from painless diabetic neuropathy	*Hassan Fadavi, UK*
18.00 – 18.15		CLOSING REMARKS	*Simona Frontoni, Italy*
19.30		DINNER	

[O1] ABNORMAL BRAIN WHITE MATTER INTEGRITY IN DIABETIC NEUROPATHY

S. Pallai[1,2], J. Harding[1,2], ID. Wilkinson[1,2], D. Selvarajah[1,2], S. Tesfaye[1,2]

[1]Department of Human Metabolism, University of Sheffield, UK
[2]Sheffield Teaching Hospitals NHS Foundation Trust, Sheffield, UK

Objective: We have previously demonstrated significant brain and spinal cord volume loss in diabetic distal symmetrical polyneuropathy (DSPN). Brain changes were localised to regions involved with somatosensory processing e.g. somatosensory cortex, cingulate cortex, insula with reduction in grey matter volume. This supports the hypothesis that changes seen in DSPN occur throughout the somatosensory pathway. What remains unknown is the integrity of the white matter tracks that connect different brain regions. Our previous anecdotal data have suggested differences in the integrity of the corticospinal tracts between the spinal cord and somatosensory cortex in DSPN. In this study, we examined this in greater detail using Magnetic Resonance (MR) Diffusion Tensor Imaging (DTI) to estimate cerebral water diffusion directionality and inferred intracranial axonal tract architecture integrity.

Methods: 16 healthy volunteers (8 males, mean age 56.1 ± 10.6 years), 16 type 2 diabetes patients without neuropathy (7 males, mean age 57.9 ± 6.8) and 15 type 2 diabetes patients with painless DSPN (10 males, mean age 59.5 ± 10.1) underwent DTI on MR at 3T (Achieva, Philips Healthcare) using a spin-echo, EPI-based 32-direction technique (b=0, 800s/mm^2, voxel size =2.5x2.5x2.5mm^3) and detailed clinical and neurophysiological assessments(NIS-LL+7 to quantify severity of DSPN). Group mean diffusivity (MD) maps were generated for each group using the FMRIB Software Library TBSS analysis program and compared using FSL view (results cluster corrected, $p<0.05$). MF is a measure of diffusivity in a brain region. Higher MD implies greater disruption of white matter tract integrity and vice-versa.

Results: Study groups were matched for age, gender and duration of diabetes. There were multiple brain regions, including the primary somatosensory cortex (right 30,-45,50; left -36,-30,50), thalamus (-23,-33,4), insular cortex (32,35,5) and cingulate gyri (8,7,34), where the MD was higher in the type 2 diabetes patients with painless DSPN than the health volunteer group($p<0.05$) and diabetic subjects with no neuropathy ($p=0.08$). There were no brain regions where MD was higher in the healthy volunteers/noneuropathy subjects compared to painless DSPN.

Conclusions: This study for the first time has shown alterations in white matter MD in patients with DSPN. Increased MD in the primary somatosensory cortex in patients with DSPN is suggestive of white matter microarchitecture degeneration and supports the evidence of neuronal loss in the somatosensory cortex in patients with DSPN. Furthermore, these results also support the previous evidence of thalamic neuronal dysfunction in DSPN on MR spectroscopy. Changes in the degree of white matter structure might provide a pathophysiological underpinning of spinal cord atrophy and brain volume reduction in DSPN.

[O2] ENHANCED DERMAL NERVE REGENERATION DESPITE PRONOUNCED EPIDERMAL NERVE FIBRE LOSS IN TYPE 2 DIABETES PATIENTS WITH PAINFUL AND PAINLESS POLYNEUROPATHY

G. Bönhof[1], A. Strom[1,3], S. Püttgen[1], B. Ringel[1], J. Brüggemann[1], K. Bódis[1,3], K. Müssig[1,2,3], J. Szendrödi[1,2,3], M. Roden[1,2,3], D. Ziegler[1,2,3], for the PROPANE and GDS study groups

[1]Institute for Clinical Diabetology, German Diabetes Center at Heinrich Heine University, Leibniz Center for Diabetes Research, Düsseldorf, Germany
[2]Department of Endocrinology and Diabetology, Medical Faculty, Heinrich-Heine-University, Düsseldorf, Germany
[3]German Center for Diabetes Research (DZD), Neuherberg, Germany

Aims: The determinants and mechanisms in the development of diabetic sensorimotor polyneuropathy (DSPN) and neuropathic pain remain unclear. We examined the degree of cutaneous nerve fibre loss and regeneration in patients with painful (DSPN+p) or painless DSPN (DSPN-p) entities.

Methods: Skin biopsies from the distal lateral calf were obtained from 32 type 2 diabetes patients with DSPN-p, 34 patients with DSPN+p (DSPN-p/DSPN+p: age [mean±SD]: 71.3±8.1/67.0±8.6 years; male: 90.6/76.5%; BMI: 28.9±4.1/31.0±4.4 kg/m²; diabetes duration: 15.2±10.7/15.5±9.9 years) and 27 control subjects (age:63.2±4.6 years; male:96.3%; BMI:26.7±3.2 kg/m²). Double immunofluorescence staining for Protein Gene Product (PGP)9.5 (pan-neuronal marker) and growth associated protein (GAP)-43 (nerve regeneration marker) was applied to quantify intraepidermal nerve fibre density (IENFD) and dermal nerve fibre length. DSPN was diagnosed using modified Toronto Consensus (2011) criteria.

Results: After adjustment for age, sex and BMI, both DSPN groups showed reduced IENFD compared to controls (GAP-43 (DSPN-p/DSPN+p): 3.48±3.28/2.29±2.61 vs 6.19±3.4 fibres/mm; P<0.0001; PGP9.5: 3.81±3.85/2.43±2.86 vs 6.66±3.13 fibres/mm; P<0.0001). Mean dermal GAP-43/PGP9.5 ratio was higher in patients with DSPN (DSPN-p/DSPN+p: 1.07±0.10/1.18±0.28) compared to controls (1.00±0.09) (P<0.05) and in DSPN+p compared to DSPN-p (P<0.05). Linear regression analyses showed a distinct inverse association between the dermal GAP-43/PGP9.5 ratio and IENFD (IENFDGAP-43:ß=-0.375; P=0.001; IENFD-PGP9.5:ß=-0.420; P<0.001).

Conclusion: Dermal nerve fibre regeneration is enhanced in both DSPN entities, but even more in painful DSPN and increases with advancing intraepidermal nerve fibre loss. Thus, dermal nerve repairis preserved in DSPN despite progressive fibre loss, but cannot adequately counteract epidermal neurodegenerative processes, particularly in painful DSPN.

[O3] DELIVERY OF MICRORNA-146A ALLEVIATES PERIPHERAL NERVE DAMAGE AND SUPPRESSES PROINFLAMMATORY GENES IN A MOUSE MODEL OF DIABETES

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Aim: MiR-146a has been implicated in the pathogenesis of diabetic peripheral neuropathy (DPN). The objective of the present study is to investigate the therapeutic role of miR-146a in a mouse model of DPN.

Methods and Results: To assess the effect of miR-146a on peripheral neuropathy in diabetic db/db mice, we administered chemically engineered miR-146a mimics via the tail vein once/ week for 4 weeks. Administration of miR-146a mimics (10 mg/kg) elevated plasma (11.5±1.1 vs 1.0±0.3) and sciatic nerve (11.3±0.9 vs 1.0±0.2) levels of miR-146a compared to the db/db mice treated with mimic control (n=13/group). Electrophysiological recordings showed that the miR-146a treatment markedly increased motor and sensory nerve conduction velocity (MNCV and SNCV) by 29% and 11%, respectively, and significantly decreased thermal sensitivity assayed by tail flick (4.4±0.3s vs 5.7±0.4s) and radial heat plate tests (10.2±0.9s vs 15.4±1.1s), which were associated with reduction of g (axon/myelin) ratio (0.59±0.01 vs 0.62±0.01). The miR-146a mimic treatment significantly increased sciatic nerve blood flow by 40% and the number of intraepidermal nerve fibers (IENF, 15.2±0.6 vs 12.9±0.8 fibers/mm). The miR-146a mimic treatment also significantly decreased diabetes-induced proinflammatory proteins, including IRAK1 (Interleukin-1 receptor-associated kinase 1), TRAF6 (TNF Receptor-Associated Factor 6), ADAMTS3 (a disintegrin and metalloproteinase with thrombospondin motifs 3) and decreased serum cytokine levels of TNFα (1.9±0.7 vs 4.0±0.5pg/ml) and IL-1β (69.9±18.4 vs 111.9±17pg/ml) measured by ELISA.

Conclusion: These data suggest that suppression of diabetes-induced proinflammatory genes by treatment of db/db mice with miR-146a mimics contributes to enhancement of neurovascular function in DPN.

[O4] CAN SLOW BREATHING REVEAL OBSTRUCTIVE SLEEP APNOEA IN TYPE 2 DIABETES AND OBESE PATIENTS?

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Aims: Obstructive sleep apnoea (OSAS), a syndrome caused by cardiorespiratory reflex imbalance, worsens cardiovascular risk in diabetes and obesity. Accurate diagnosis by polysomnography is expensive and requires night hospitalisation. A brief period of slow breathing (SLB), by transiently improving baro-chemoreflex interaction and oxygen saturation (SAT) could shift an ill-balanced cardiovascular/respiratory reflex interconnection, acutely triggering OSAS-related respiratory abnormalities.

Methods: In 66 patients (42 diabetics: age 55±13yr, 21 male, BMI 33.4±7.3 Kg/m^2, HbA_1c 8.03±1.56% and 24 obese: age 50±13yr, 4 male, BMI 39.2±5.3 Kg/m^2) and 20 healthy subjects (age 55±15, 7 male, BMI 22.04±2.3 Kg/m^2) we continuously monitored SAT, respiration (inductance plethysmography) and baroreflex sensitivity (BRS) during spontaneous respiration (5min), 5-min 6cycle/min SLB and 10-min follow-up under spontaneous breathing (POST-SLB). So far 33 patients underwent standard polysomnography (PSG).

Results: Forty patients (26 diabetics and 14 obese) developed apnoeas/hypopneas during POST-SLB (POST-SLB+); considering the 33 subjects undergoing PSG, 27/30 (90%) were true positive, 3/3 (100%) true negative and 3/30 (10%) false negative. At baseline POST-SLB+ had lower SAT ($p=0.003$) and BRS ($p<0.001$) compared to healthy subjects. During SLB all subjects increased SAT ($p<0.001$) and BRS ($p<0.01$) compared to baseline. During POST-SLB, in POST-SLB+ patients SAT fell below ($p<0.0001$) and BRS returned to baseline, whereas in the other patients SAT returned toward baseline and BRS remained higher ($p<0.025$).

Conclusions: A short (20min) simple inexpensive clinical test based upon analysis of cardio-respiratory reflex imbalance can unmask underlying OSAS, due to the post-effects of transiently relieving subclinical hypoxia in diabetes and obesity.

[O5] ASSOCIATION BETWEEN EARLY PERIPHERAL MOTOR UNIT LOSS AND NEURORETINAL DYSFUNCTION IN PATIENTS WITH TYPE 1 DIABETES MELLITUS

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Aims: Early neuroretinal abnormalities have been implicated in the pathogenesis of diabetic retinopathy (DR). However, no data are available on the correlation between this early form of neuropathy at retina level, and peripheral neuropathy. Our study, therefore, was aimed at investigating the potential relation between the number of functional motor unit in peripheral nervous system and neuroretinal function in patients with type 1 diabetes mellitus (T1DM).

Methods: 18 T1DM patients withno symptoms/signs ofperipheral polyneuropathy, without DRor with mild non-proliferative DR, and 14 healthy controls (C) matched for age and gender were enrolled. All subjects underwent the following electrophysiological tests: standard nerve conduction studies (NCS), incremental motor unit number estimation (MUNE) from abductor hallucis (AH), with assessment of AH average SMUP size (aSMUP), and multifocal electroretinogram measuring amplitude density (Amp) and implicit time (IT) of 4 macular quadrants.

Results: No abnormalities of NCS were found in any subject. AH MUNE was significantly decreased in T1DM ($p < 0.0001$). Furthermore a SMUP significantly increased (p 0.007) compared to C. A positive correlation between Amp in nasal quadrant and MUNE (r 0.717, p 0.030) was observed in T1DM patients.

Conclusion: MUNE revealed as a reliable measure in detecting precocious and subclinical rates of motor unit loss and collateral reinnervation in this cohort of T1DM patients. The novelty of our findings lies in that a relationship between neuroretinal dysfunction and early peripheral motor unit decline exists, suggesting that the neuroretina represents a potential “window” to track the early neurogenic process in diabetes.

[O6] HYPERLIPIDEMIA ALTERS ENDOPLASMIC RETICULUM-MITOCHONDRIAL CONTACT SITE FORMATION AND MITOCHONDRIAL RESPIRATORY CAPACITY IN DORSAL ROOT GANGLION SENSORY NEURONS

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Aim: The progression of diabetic neuropathy (DN) correlates with dyslipidemia; therefore, it is essential to understand the impact of lipids on mitochondrial dysfunction in the dorsal root ganglion (DRG) sensory neurons. Since neuronal function depends on mitochondrial ATP, endoplasmic reticulum-mitochondrial (ER-Mt) interactions, and metabolic pathways that converge on mitochondria (Mt), these organelles are central to maintaining neuronal function and bioenergetic homeostasis. We aimed to evaluate the effects of hyperlipidemia on mitochondrial depolarization, mitochondrial bioenergetics, and ER-Mt contact in mouse DRG neurons to identify alterations in mitochondrial function in DN.

Methods: DRG from 60% high fat fed (HF) mice were assessed for ultrastructural changes in ER-Mt contact using transmission electron microscopy. Mouse primary DRG neurons were cultured and treated with palmitate and glucose to model hyperlipidemia and hyperglycemia. Mitochondrial bioenergetics and depolarization were evaluated by measuring DRG neuronal spare respiratory capacity (SRC) using a Seahorse analyzer and loss of TMRM staining, respectively.

Results: DRG from HF mice revealed increased ER-Mt contact in sensory nerve fibers. Loss of TMRM staining in DRG neurons treated with 250 M palmitate indicated increases in mitochondrial depolarization. Measurements of mitochondrial bioenergetics, using a Seahorse analyzer, revealed a decrease in mitochondrial SRC in DRG neurons treated with 250 M PA and 100-400 mM glucose.

Conclusions: We conclude that hyperlipidemia reduces mitochondrial SRC and polarization, which correlates with increased ER-Mt contact sites in hyperlipidemic DRG neurons. These results suggest that hyperlipidemia triggers increase in ER-Mt interactions that may play a role in the progression of DN.

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[O7] DIETARY REVERSAL IMPROVES PERIPHERAL NEUROPATHY IN A MURINE MODEL OF TYPE 2 DIABETES

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Aim: Peripheral neuropathy (PN) is a common complication of type 2 diabetes (T2D) for which no effective treatment currently exists. To determine whether dietary reversal (DR) can benefit mice that resembleaT2D-like phenotype, we investigated the effects of DR using a high fat diet fed mice injected with low-dose streptozotocin (STZ), a novel model of T2D.

Methods: Male C57BL6/J mice were fed either a standard diet (10% kcal fat; CTRL) or a high fat diet (60% kcal fat; HFD). At 12wk a subset of HFD mice were administered with STZ (1x75mg/kg, 1x50mg/kg; HFD-STZ). At 16wk subsets of HF and HF-STZ mice were placed on a 10% kcal fat diet for 8wk (HFD-DR and HFD-STZ-DR, respectively) until study conclusion at 24wk when terminal neuropathy phenotyping was performed on all groups.

Results: By study conclusion HFD mice exhibit signs of impaired glucose toleranceand robust PN, while HFD-DR mice displayed an improved metabolic profile which corresponded with improved peripheral nerve function. As a consequence of STZ administration, HFD-STZ mice develop an initial increase in hyperglycemia compared to HFD mice however PN presentation was that of a similar degree to that seen in HFDmice. Similar to HFD-DR mice, after 8wk of DR HFD-STZ-DR mice had significantly improved metabolic profile and PN was corrected.

Conclusion: DR of HF-STZ mice can improve the metabolic profile and restore peripheral nerve function supporting the idea that dietary intervention is a feasible strategy in improving peripheral nerve health both in patients with T2D.

[O8] SUDOMOTOR DYSFUNCTION AS A MEASURE OF SMALL FIBER NEUROPATHY IN TYPE 1 DIABETES (T1D)

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Aim: To evaluate the association between sudomotor function and cardiovascular autonomic neuropathy (CAN) in T1D.

Methods: This study included 37 T1D (mean age 38±13 years, duration 15±7 years, HbA1c 7.9±1.1%, no known complications at baseline) followed for 12 months, and 40 age-matched healthy controls (HC). Mean ESC of hands (ESCh) and feet (ESCf) were measured with the SUDOSCAN (Impeto Medical). CAN was assessed with heart rate variability (HRV) studies and cardiovascular autonomic reflex tests. Associations between measures of CAN and ESC were estimated using Spearman correlations and longitudinal changes by paired t-test.

Results: At baseline, there were no differences between T1D and HC in ESCh (69.0±14 vs. 69 ±11µS; P=0.84) or ESCf (82±8 vs. 78±9µS; P =0.12). However, some indices of HRV and Valsalva ratio were significantly lower, and the heart rate was significantly higher in subjects with T1D. ESCf and ESCh were correlated with the Expiration/Inspiration ratio and the Valsava ratio (r=0.37, P= 0.02; r=0.34, P=0.04 respectively) at baseline, but no other significant consistent correlations were found between ESC and rest of CAN measures at baseline or 12 months. There was a significant decline in both ESCh and ESCf at 12 months (mean change -7.2 ±11.6, P=0.0006; -2.8 ±7.2, P=0.023 respectively) in T1D.

Conclusion: In patients with T1D and early disease, both hands and feet ESC declined over time. However, the associations between ESC and established CAN measures were inconsistent, suggesting that ESC measures a physiologic change in diabetics but it may not be a direct measure of CAN.

[O9] CORNEAL CONFOCAL MICROSCOPY IS A RAPID REPRODUCIBLE OPHTHALMIC TECHNIQUE FOR QUANTIFYING CORNEAL NERVE ABNORMALITIES

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Introduction: Corneal Confocal Microscopy (CCM) has been proposed as a surrogate end point in clinical trials of new therapies for diabetic neuropathy. However, before it can be used in multicenter trials, fundamental issues such as the effect of adherence to a protocol for image selection, the number of images and the inter and intra observer variability for the quantification of corneal nerve pathology, needs to be established.

Methods: CCM was performed in 35 participants (aged: 49.97 ± 12.47 years) by a single examiner. For each participant, 4 observers (2 expert, 2 novice) used a standardized protocol to select 6 central corneal nerve images to assess the inter observer variability. Observer two selected images on two occasions to assess intra observer variability. To assess the effect of sample size variability, observer one selected 12 CCM images per patient for analysis on a second occasion. Fully automated nerve analysis software (ACCMetrics), developed by our group was utilized to measure corneal nerve fiber density (CNFD), corneal nerve branch density (CNBD) and corneal nerve fiber length (CNFL) and the intra class correlation coefficients (ICC) were computed for all experiments.

Results: ICC and 95% confidence interval (CI) for all observers were 0.93(0.93 0.97) for CNFD, 0.96(0.950.98) for CNBD and 0.95 (0.950.98) for CNFL. ICC and 95% CI for 6 vs 12 images were 0.94(0.880.97) for CNFD, 0.94 (0.890.97) for CNBD and 0.96(0.920.98) for CNFL. ICC and 95% CI for observer two on two occasions were 0.95 (0.910.97) for CNFD, 0.97(0.940.98) for CNBD and 0.97 (0.950.98) for CNFL.

Conclusions: This study shows that implementing a standardized protocol to select CCM images results in high intra and inter observer reproducibility for all nerve fiber parameters and 6 images are adequate for analysis. CCM could therefore be deployed in large multicenter clinical trials with confidence.

[O10] CONCURRENT DIAGNOSTIC VALIDITY OF IN VIVO CORNEAL CONFOCAL MICROSCOPY (IVCCM) TO IDENTIFY DIABETIC POLYNEUROPATHY IN TYPE 1 DIABETES: A POOLED MULTICENTER ANALYSIS

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Aim: Several independent cohorts have implied that IVCCM may serve as a useful proxy measure of diabetic polyneuropathy (DPN). Through an international pooled multicenter analysis, we aimed to confirm the type 1 diabetes-specific concurrent validity and determine diagnostic thresholds for identification of DPN by IVCCM.

Methods: Through an collaborative effort of 5 cohorts, 516 participants (84 adolescent and 432 adults) with type 1 diabetes underwent IVCCM examination concurrently with determination of electrophysiology-based consensus criteria for DPN. Automated image analysis protocols were used to quantify the corneal parameters including, corneal nerve fibre length ($CNFL_{Auto}$). Participants were randomly divided into derivation(n=260) and validation sets (n=256). Concurrent validity and diagnostic thresholds were determined from receiver operating characteristic curves and area-under-the-curve (AUC).

Results: Participants had mean age 42±19 years, mean diabetes duration 21±15 years, and 255(49%) were female. DPN prevalence was 32%. Derivation and validation sets had similar characteristics. In the derivation set, DPN cases had lower corneal parameters values ($p<0.001$ for each compared to controls).$CNFL_{Auto}$ had the highest AUC at 0.77 and its optimal threshold of 12.5mm/mm^2 identified cases with 71% sensitivity and 69% specificity. This threshold identified cases with 68% sensitivity and 68% specificity in the validation set(AUC 0.74).

Conclusions: We confirmed the concurrent diagnostic validity of CNFL for identifying DPN in patients with type 1 diabetes, despite an imperfect reference standard (electrophysiology) for defining DPN. These results strongly support implementation of IVCCM in research trials and the need for longitudinal studies evaluating the predictive validity of this technique.

[O11] CONCURRENT DIAGNOSTIC VALIDITY OF IN VIVO CORNEAL CONFOCAL MICROSCOPY (IVCCM) TO IDENTIFY DIABETIC POLYNEUROPATHY IN TYPE 2 DIABETES: A POOLED MULTICENTER ANALYSIS

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Aim: IVCCM has been proposed as a diagnostic test for diabetic polyneuropathy (DPN) in type 1 diabetes, but its concurrent validity for the detection of large-fibre dysfunction has not been systematically studied in cohorts with type 2 diabetes. We aimed to determine this validity in a pooled multicenter analysis.

Methods: Through an international collaborative effort from 4 separate centers, 471 participants with type 2 diabetes of varying disease duration underwent IVCCM examination concurrently with determination of electrophysiology-based consensus criteria for DPN. Manual image analysis was used to quantify corneal parameters including corneal nerve fibre length ($CNFL_{Manual}$). Participants were randomly divided into derivation (n=238) and validation sets (n=233). Concurrent validity and diagnostic thresholds were determined using receiver operating characteristic curves and area-under-the-curve (AUC).

Results: Participants had mean age 63±10y, mean diabetes duration 12±8y, and 166(35%) were female. DPN prevalence was 51%. Derivation and validation sets had similar characteristics. In the derivation set, DPN cases had lower $CNFL_{Manual}$ than controls without DPN ($p<0.001$). Of the corneal parameters, $CNFL_{Manual}$ had the highest AUC at 0.66 and an optimal threshold of 16.3mm/mm^2 identified cases with 63% sensitivity and 71% specificity. In the validation set, this threshold identified cases with 68% sensitivity and 64% specificity (AUC 0.71).

Conclusions: $CNFL_{Manual}$ has moderate concurrent validity for identifying DPN in type 2 diabetes. The lower performance compared to that observed in type 1 diabetes – which may include further complexity of DPN case definition in older adults with additional metabolic risks - should be explored and examined longitudinally.

[O12] CORNEAL CONFOCAL MICROSCOPY AND OPTICAL COHERENCE TOMOGRAPHY DETECT AXONAL LOSS IN MULTIPLE SCLEROSIS DESPITE NORMAL GLUCOSE TOLERANCE

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Aim: Axonal loss in multiple sclerosis (MS) is increasingly recognised as the main pathological substrate and determinant of progression. Disability scales are insensitive to change and magnetic resonance imaging is limited by low histopathological specificity. In this era of new drugs in MS there is a need for quick and resourceful biomarkers to monitor disease activity and therapeutic benefit. The ocular tissue is abundant in axons and imaging them with corneal confocal microscopy (CCM) and optical coherence tomography (OCT) may provide surrogate measures of global axonal loss in MS.

Methods: 12 healthy age-matched controls and 12 young patients with relapsing-remitting MS underwent standard laboratory testing, CCM markers of axonal loss, OCT and evaluation of their symptoms and signs with the expanded disability status scale (EDSS) (score 0-10) by a certified neurologist.

Results: MS patients had disease duration of 7.3±4.4 years, EDSS of 1.7±1.8, 2.4 ± 2.2 relapses since diagnosis and 7/12 patients had a history of optic neuritis. In controls compared to MS there was no difference in HbA1c (36.3±3.1v34.2±2.4mmol/mol,P>0.05), age (35±8.9v35±4.6,P>0.05) and both groups had noother causes of neuropathy (normal anti-nuclear antibodies). There was a significant reduction in corneal nerve fibre density (38.8±6.2v25.1±5.4fibres/mm^2, P=0.0001), length (27.6±5.2v20.6±5.7mm/mm^2, P=0.0001) and temporal retinal nerve fibre layer thickness (74.7±15.6v52.7±12.6µm, P=0.0009) (figure 1).

Conclusions: Despite normal glucose tolerance, both CCM and OCT detect significant axonal loss, a key component of MS neuropathology. These findings merit further investigation in larger studies.

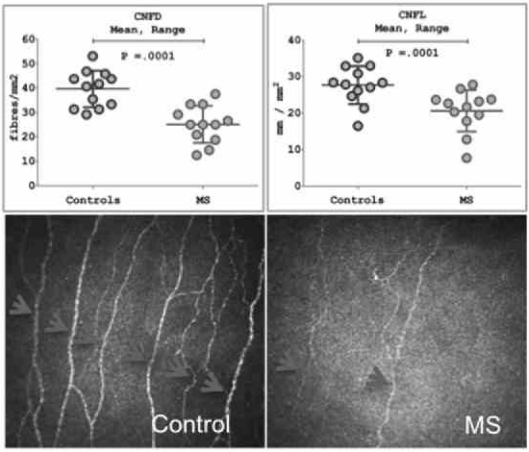

FIGURE 1.

[O13] ETHNIC DIFFERENCES IN SMALL FIBER FUNCTION IN SUBJECTS WITH T2DM

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Sudomotor function and skin blood flow (SkBF) are impaired in subjects with type 2 diabetes (T2DM). Furthermore, ethnic differences have been observed in both measures of small fiber function. The aim of this study was to determine if these differences were compatible with a unifying mechanism for small fiber dysfunction in African Americans (AA).

Sixty five subjects with T2DM were evaluated with the following measures: Neuropathy Impairment Score of the lower legs (NIS-LL); sudomotor function using Sudoscan™ (electrochemical skin conductance (ESC) of the hands and feet); heart rate variability (HRV); SkBF using continuous laser Doppler assessment on the distal lower limb (LL) and quantitative sensory tests (QST) for cold and warm thermal perception thresholds.

We included 32 AA and 31 Caucasian subjects. Demographic characteristics were similar between the groups. AAs had worse sudomotor function (Feet ESC:44.95±4.7367vs 66.37±3.5737; p=0.0006 and Hands ESC:44.32±3.69vs62.73±3.19; p=0.0004), and worse LL skin blood flow (BaselineAUC: 2253.69±143.91vs3200.49±433.60, p=0.03; 44˚CAUC: 9485.7±904.4vs14245.0±1744.5, p=0.02). In addition, AA had significantly worse NIS-LL, pain scores, and QSTs. On univariate regression analysis, feet ESC correlated significantly with NIS-LL, QSTs, and HRV, but did NOT with SkBF 44AUC (r=0.119, p=0.412). On multivariate regression analysis, feet ESC was determined by DM duration, ethnicity, symptom scores and insulin level.

This report shows that both sudomotor function and skin blood flow are significantly more impaired in AA with DM. However, there is no correlation between the two measures suggesting that there are differences in the pathogenesis of microvascular and neuropathic dysfunction, which need to be explored further.

[O14] EARLY DETECTION OF SMALL FIBRE NEUROPATHY BY CORNEAL CONFOCAL MICROSCOPY IN NEWLY DIAGNOSED TYPE 2 DIABETES MELLITUS

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On behalf of CLAHRC-GM Team:
S Epstein, J Arrowsmith, S Hakim, S Issa, Rebecca Spencer, Claudia Soiland-Reyes, Susan Howard, Sarah Cotterill, Catherine Perry, Mike Bresnen, Ruth Boaden, Mitra Tavakoli

Aim: Screening for presence and severity of Diabetic Peripheral Neuropathy with using Corneal Confocal Microscopy in a cohort of newly diagnosed type 2 diabetic patients.

Method: 91 newly diagnosed type 2 diabetic patients (duration less than one year) have been screened for Diabetic Peripheral Neuropathy (DPN) with using corneal confocal microscopy, alongside of 60 age and sex matched healthy control subjects. Retinopathy grading has been done based on national retinopathy screening programme (ETDRS). As part of this screening programme, all patients filled some questionnaires including Diabetic Neuropathy Symptoms profile (DNS) and self-reported questionnaires regards to the history of retinopathy, retinopathy laser treatment, diabetic foot problem, foot ulcer and neuropathy.

Results: Average duration of diabetes was 1 year (1.04± 0.07). 80% of patients had no retinopathy and 19.7% of patients had background retinopathy. 15.3% of patients had symptoms of diabetic neuropathy (DNS>1). There was significant alterations in corneal nerves morphological parameters in patients compare to control subjects including CNFD ($P<0.001$); CNBD ($P=0.007$); CNFL ($P<0.001$), and size of beading along c-nerve fibres ($P<0.001$). CNFDand CNFL were reduced below the 2.5th percentile in 15.5%, and 14.4% of the diabetes patients, respectively. There was no correlation between neuropathy symptoms and severity of alterations of corneal nerves. No correlation has been also found for retinopathy and neuropathy.

Discussion: This study showed the significant level of nerve damage and presence of DPN in newly diagnosed type 2 diabetic patients. As part of a bigger screening programme, feasibility and acceptability of using CCM alongside retinopathy screening have been established. Further studies are needed to assess the role of implication of this technique in primary care.

[O15] ENERGY METABOLISM PERTURBATIONS ASSOCIATE WITH MEASURES OF CARDIOVASCULAR AUTONOMIC NEUROPATHY (CAN) IN TYPE 1 DIABETES (T1D) PATIENTS

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Aim: Metabolite flux as evidenced by circulating metabolite levels have been shown to influence diabetic complications. The aim of this study was to delineate the metabolic perturbations (circulating free amino acids and tricarboxylic acid (TCA) cycle intermediates) in subjects with T1D and its association with measures of CAN.

Methods: Forty subjects with T1D (mean age 35±13 years, 60% females, duration 13±7 years, HbA1c 7.9±1.2%) were enrolled in a 3 year longitudinal cohort study. Mass spectrometry was used for measurement of the TCA intermediates and amino acids at baseline. CAN was assessed with standardized cardiovascular autonomic reflex tests [Expiration/Inspiration (E/I), Valsalva and 30/15 ratios] and heart rate variability (HRV) indices [standard deviation of normal RR interval (SDNN), root mean square of successive RR intervals(RMSSD), low and high frequency power (LF,HF)] at baseline and follow-up.

Results: Using Spearman correlation, higher levels of baseline fumarate were associated with lower baseline CAN parameters (SDNN: r= - 0.463, P =0.003; RMSSD: r= - 0.40, P= 0.01; and E/I ratio r=-0.436, P=0.005). Asparagine and glutamine were positively correlated with baseline CAN measures (SDNN: r=0.417, P=0.007; E/I r=0.429, P=0.006, and SDNN: r=0.511, P=0.001) respectively, even after adjustment for duration, baseline HgA1C, lipids and eGFR (p=0.03). Glutamine was also correlated with SDNN at the 3 year follow up (r=0.447, P=0.005).

Conclusion: These preliminary data suggest that alterations in amino acid metabolism and TCA cycle associate with changes in CAN measures in T1D. Ongoing analyses are further evaluating potential pathophysiologic mechanisms.

[O16] SLOW BREATHING ACUTELY REDUCES REACTIVE OXYGEN SPECIES AND IMPROVES AUTONOMIC AND VASCULAR FUNCTION IN TYPE 2 DIABETES

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Aim: Vagal stimulation is a recently-established antioxidant agent. We tested whether acute vagal stimulation by slow breathing (SLB) could modify the oxidative stressin type-2 diabetes, and whether this was associated with improvements in oxygen saturation (SAT), autonomic (baroreflex sensitivity, BRS) and arterial function (augmentation index, AI75, pulse wave velocity, PWV).

Methods: In 25 type-2 diabetics and 25 controls (age 57±13, 9 male, vs 60±8 yr, 9 male, mean±SD, diabetes duration 9.3±5.4yr, Hba1c 7.0±1.1 mmol/mol) we measured the biological antioxidant potential (BAP® test, Diacron) and reactive oxygen metabolites (d-ROMs® test, Diacron) on fresh venous plasma, SAT, BRS, AI75 and PWV (by continuous blood pressure and electrocardiogram monitoring), at rest (5 min), during SLB (6 cycles/min, 5 min), 5 and 10 min thereafter.

Results: Diabetic patients had lower resting SAT ($p=0.004$) BRS ($p=0.0017$) and similar AI75 and PWV. SLB improved SAT ($p<0.0001$), AI75 ($p>0.03$) in both groups but more ($p<0.05$ or better) in the diabetic group, and BRS only in the diabetic group ($p=0.046$). In the diabetic group the d-ROMs decreased 5 min after SLB, ($p=0.00018$) then returned to baseline after 10 min. No changes were observed in the control group. The BAP test remained higher ($p=0.044$) in the diabetic group at all measures.

Conclusions: SLB acutely reduced ROS without affecting the antioxidant reserve, and improved oxygen saturation, autonomic and vascular function. This antioxidant effect seemed dependent on preexisting oxidative stress as it occurred only in the diabetic group. Hypoxia-induced oxidative stress seems a cause of reversible autonomic dysfunction in diabetes.

[O17] DIFFERENTIAL ASSOCIATION BETWEEN IMPAIRED MAXIMAL AEROBIC CAPACITY AND CARDIAC AUTONOMIC DYSFUNCTION IN RECENTLY DIAGNOSED TYPE 1 AND TYPE 2 DIABETES

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Aim: Both impaired cardiorespiratory fitness (CRF) and reduced heart rate variability (HRV) are predictors of mortality, but their relative roles in recent-onset diabetes have not been established. We sought to determine to which extent CRF and HRV are reduced and interrelated in 163 individuals with type 1 diabetes (T1D) and 188 subjects with type 2 diabetes (T2D) (diabetes duration ⩽1 year) from the baseline cohort of the German Diabetes Study (GDS) and 60 non-diabetic controls (T1D/T2D/controls[median (IQR)]: age:33(26-45)/52(45-59)/45(29-57) years; male: 63%/68%/75%; HbA1c: 6.3(5.8-7.0)%/6.2(5.8-6.7)%/5.2(5.1-5.4)%).

Methods: Fourtime domain and frequency domain HRV measures each, indicating vagal and/or sympathetic modulation over 3 h were determined during a hyperinsulinaemic-euglycaemic clamp. Maximal oxygen uptake (VO_2max) was measured during an incremental exhaustive exercise test.

Results: After adjustment for sex, age, BMI, and smoking, 5 of 8 HRV measures were reduced in T2D vs controls (SDNN:86(69-117) vs 64(51-80) ms;P=0.0003; very low-frequency (VLF) power: 2498(1629-4967) vs 1498(976-2434) ms²;P=0.001), but in T1D only 1 of 8 HRV measures was diminished. VO_2max was lower in T2D(19.3(16.5-22.9) ml/kg/min) than in T1D(25.7(22.5-31.6)ml/kg/min) and controls (27.0(21.8-34.2) ml/kg/min) (P<0.05). Multiple linear regression analysis revealed that VO_2max was independently associated with 7 of 8 HRV indices in T1D (SDNN:ß=0.303, VLF:ß=0.274; P<0.001) and with 4 of 8 HRV indices in T2D(SDNN:ß=0.181, VLF:ß=0.203; P<0.01).

Conclusions: Patients with recent-onset T2D showed reduced maximal aerobic capacity and both diminished vagal and sympathetic HRV modulation indicating broadcardiac autonomic dysfunction. In contrast, CRF and HRV are not disturbed albeit strongly associated in recent-onset T1D.

[O18] SEQUENTIAL COMPRESSION/DECOMPRESSION BY A PULSATING SUIT INCREASES CUTANEOUS MICROCIRCULATORY BLOOD FLOW IN PATIENTS WITH TYPE 2 DIABETES

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Aim: Microcirculation is altered in diabetic patients. In healthy subjects sequential compression/decompression by pulsating suit may induce noninvasively endothelial activation by increasing physiological shear stress. We aimed to evaluate the effects of sequential compression/decompression on cutaneous forearm microcirculation in T2D patients.

Methods: Sixteen T2D patients (53.3±11.4yrs, 6 hypertensives, on oral hypoglycaemic agents, no smoker, free of cardiovascular disease, renal failure, retinopathy, HbA1c 7.1±0.8%) were enrolled in a controlled cross-over study and randomised into two groups: verum (Visit1) and phantom (Visit2, 13±2days after Visit1) compression at 65 mmHg/decompression session (20min) using Stendo® pulsating suit was performed in group 1 and vice-versa in group 2. The pulsating suit generates heart rate-synchronized compression/decompression applied on lower body part (legs-abdomen). Cutaneous forearm microcirculatory flow was measured by laser Doppler flowmetry (Periflux System 5000®) before, during and until 30 minutes after the end of the sessions. Cardiac vagal and sympathetic activity (HF_{HR}, LF_{HR}) were assessed by spectral analysis of heart rate variations.

Results: The 20-minutes area under curves (AUC) calculated during sessions were 1976 (SD: 3938) and -2043 (SD: 8302), respectively in verum and phantom sessions. The mean 40-minutes and 50-minutes AUCs (during Stendo plus 20 and 30 minutes after sessions stopped) were higher for verum (6936 and 7403) than phantom session (-7537 and -10805) ($p<0.01$ for both). No difference for vago-sympathetic activity between sessions.

Conclusion: In T2D patients, sequential compression of the lower body synchronized with each diastole period at physiological pressure increases significantly cutaneous forearm microcirculatory flow, away from pulsatile stimuli with no apparent effect on autonomic activity.

[O19] ROLE OF GLYCEMIC VARIABILITY IN THE CHANGES IN CUTANEOUS MICROCIRCULATORY BLOOD FLOW IN PATIENTS WITH IMPAIRED GLUCOSE TOLERANCE OR TYPE 2 DIABETES

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Aim: Glycemic variability (GV) may be involved in diabetic microangiopathy. We showed that GV was greater in non-diabetic obese patients with slightly elevated HbA1c levels. The aim was here to examine the relations between GV and microcirculatory cutaneous blood flow (CBF) in patients with impaired glucose intolerance (IGT) or type 2 diabetes (T2D).

Patients and methods: We included 19 IGTs and 15 T2Ds on oral hypoglycaemic treatments (HbA1c 5.1±0.6% and 7.1±0.7%, respectively), normotensive, without cardio-vascular history. Forearm CBF was measured by laser doppler (Periflux®) during 3 minutes, 1-hour after a standard breakfast (75g carbohydrates). Coefficient of variation of CBF (CV_{CBF}%) was calculated. During 3-hours after breakfast mean glucose and GV (standard deviation $SD_{glucose}$, CONGA, J-index) were calculated using CGMS. Vascular sympathetic activity (LF_{SBP}) was assessed by spectral analysis of blood pressure variations.

Results: Compared with IGTs, T2Ds had higher mean glucose, CONGA, J-index, and lower mean CBF ($p<0.007$ to <0.0001), with no differences for LF_{SBP}. In total population, mean CBF correlated negatively with $SD_{glucose}$ and J-index ($p<0.01$ and $p<0.05$, even after age and BMI adjustment), but not with mean glucose, and also correlated negatively with HbA1c ($p<0.01$). In multivariate analysis mean CBF remained correlated with $SD_{glucose}$ and J-index independently from HbA1c only in IGTs. CV_{CBF}% correlated negatively with LF_{SBP} ($p<0.01$) and not with glucose parameters.

Conclusion: CBF is lower in T2Ds than IGTs. GV seems to play a greater role than mean glucose and long-term hyperglycemia in peripheral microcirculation, mostly in IGTs. Vascular sympathetic activity is associated with lower vasomotricity.

[O20] CARDIAC AUTONOMIC NEUROPATHY IS STRONGLY ASSOCIATED WITH ABNORMAL CARDIAC REPOLARISATION

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Background and aims: Diabetic cardiac autonomic neuropathy (CAN) is associated with an increased risk of cardiac events and sudden cardiac death. QT variability index (QTVI) is a measure of cardiac repolarisation that is associated with myocardial electrical instability and arrhythmias. We therefore aimed to study the relationships between QTVI and CAN.

Materials and methods: Using O'Brien's tests and baroreceptor sensitivity (BRS) testing, 62 diabetes subjects (37 with T2DM, 38 males) were classified into three groups: 22 with no CAN (No-CAN, 47±15 yrs), 28 subclinical CAN (53±12 yrs) and 12 established-CAN (57±14 yrs). We then analysed QTVI and indices of heart rate variability (HF - parasympathetic and LF - sympathetic) in all subjects.

Results: QTVI was significantly lower in subjects with No-CAN (-0.76±0.62) compared to Subclinical-CAN(-0.11±0.56) and Established-CAN (0.28±0.86; ANOVA $p<0.003$). Parasympathetic and sympathetic activity were significantly higher for No-CAN vs Subclinical-CAN and Established-CAN, LF (2.17±0.58 vs 1.11±0.65 and 0.94±0.52 ms2, respectively; ANOVA $p<0.001$) and HF (2.03±0.59 vs 0.92±0.60 and 0.98±0.53 ms2; ANOVA $p<0.001$). There was a strong negative correlation between QTVI and sympathetic ($\rho=-0.844$) and parasympathetic activity ($\rho=-0.713$; $p<0.001$). Moreover, BRS significantly ($p<0.001$) correlated with QTVI (-0.753), LF (0.758) and HF (0.718).

Conclusion: These results demonstrate a strong association between CAN and cardiac repolarisation abnormalities, which are recognised to increase the susceptibility to cardiac events. Alarmingly there is a clear demonstration of significant abnormalities in early subclinical CAN. Further studies are required to examine if early intensive multifactorial risk factor treatment that has been shown to reduce incident CAN will also have an impact on cardiac repolarisation and arrthythmogenic risk.

[O21] CARDIOVASCULAR AUTONOMIC NEUROPATHY AND CARDIOVASCULAR OUTCOMES IN THE DCCT/EDIC STUDY

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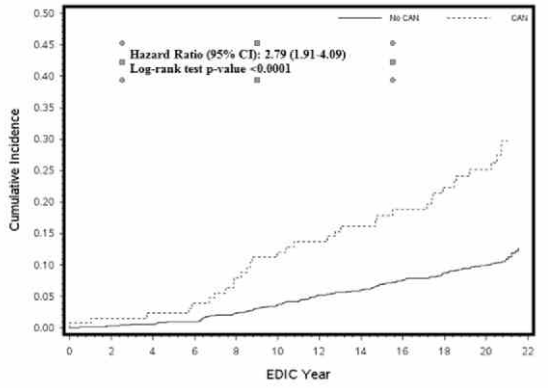
Aim: To examine whether CAN is an independent risk factor of cardiovascular disease (CVD) events during the Diabetes Control and Complications Trial/Epidemiology of Diabetes Interventions and Complications (DCCT/EDIC) in participants with type 1 diabetes.

Methods: Standardized cardiovascular autonomic reflex tests (R-R response to paced breathing, Valsalva maneuver, postural changes in blood pressure) were performed at DCCT baseline, biannually throughout DCCT, and at two time points in EDIC. CVD events were ascertained throughout the study and adjudicated by a review committee. Cox proportional hazards models were used to estimate the effect of CAN on subsequent CVD risk.

Results: There were 299 adjudicated events in 165 participants after DCCT closeout, 132 of 1262 (10%) without CAN experienced 244 CVD events vs. 33 of 131 subjects (25%) with CAN who experienced 55 events (HR=2.79, 95% CI 1.91-4.09 for time to first CVD event) (Figure). In models adjusted for multiple risk factors, the cumulative incidence of the first occurrence of any CVD event during EDIC was significantly higher in participants with CAN at DCCT closeout compared to those without CAN. When analyzed as a continuous variable, R-R variation was significantly lower at DCCT closeout in participants who experienced a CVD event compared to those who did not (p=0.0012).

Conclusion: In the DCCT/EDIC cohort, individuals diagnosed with CAN at DCCT closeout experienced a higher long-term risk of CVD events during follow-up in EDIC, although this association was not independent of historic glycemic exposure, the principal determinant of long-term CVD risk in type 1 diabetes.



[O22] PROGRESSION OR REGRESSION OF CLINICAL NEUROPATHY IN PATIENTS WITH TYPE 2 DIABETES OVER 5 YEAR OBSERVATION PERIOD

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Aim: Natural history of diabetic polyneuropathy is still unestablished. This study is to address the question whether the clinical stage of neuropathy is reversible or not and to determine the factors that influence the progression or regression of the neuropathic deficits.

Methods: From 2,310 patients with type 2 diabetes, 158 patients who had clinical records for consecutive 5 years were evaluated as to the progression or regression of clinical stage of neuropathy.

Results: Overall prevalence of neuropathy was 27% at baseline and unaltered during 5 years. Over the observation period, HbA1c levels decreased from 8.6% to 6.9%, and 12 patients (8%) with abnormal ankle jerk, 13 patients (8%) with subjective symptoms, 18 patients with abnormal touch test (11%) reversed to normal. However, 28 patients (18%) normal for ankle jerk became abnormal, 6 patients (4%) free from symptoms became symptomatic, and 5 patients (3%) developed abnormal touch test. Eight patients (5%) developed from stage I (no neuropathy) to stage II (asymptomatic neuropathy, while 8 patients (5%) with stage II showed regression to stage I. Improvement of above signs and symptoms as well as regression of clinical stage was associated with a decrease in HbA1c and preserved nerve conduction velocities of median and tibial nerves. In contrast, amplitudes (CMAP) were progressively declined even in a group with regressed stage over 5 years.

Conclusion: This study demonstrated that blood glucose control is crucial for the mitigation of neuropathic phenotype and neuropathy develops slowly despite well controlled diabetes with HbA1c 6.9%.

[O23] OCCURRENCE OF DIABETIC FOOT, ISCHEMIC HEART DISEASE AND STROKE BY NCS-SEVERITY OF DIABETIC NEUROPATHY: A 5-YEAR PROSPECTIVE OBSERVATION

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Aim: In 2007 we introduced a staging system of severity of diabetic neuropathy (DN) by nerve conduction study (NCS). The system consists of five stages; NCS-0 (normal): no abnormalities, NCS-1 (mildly abnormal): presence of any delay only of MCV, SCV, or minimal F-wave latency, or presence of a-wave, NCS-2 (moderately abnormal): abnormal decrease in sural SNAP less than 5uV, NCS-3 (severely abnormal): decrease in abductor hallucis muscle (AH)-CMAP to 2-5mV, NCS-4 (ultimately abnormal): AH-CMAP lost or less than 2mVwith trace of sural-SNAP. The system well corresponds to clinical score and intra-epidermal nerve fiber density, as we reported at the DNSG 2015 meeting in Helsigor. We present here preliminary results of 5-year prospective observation on occurrence of diabetic foot (DF), ischemic heart disease (IHD) and stroke (IS) by the NCS staging system.

Methods: In 2007-09, we carried out NCS in 308 diabetics, and categorized them by the NCS grading system:6% was NCS-0, 38% was NCS-1, 38% was NCS-2, 10% was NCS3, and 7% was NCS-4. We then followed them and counted prospectively the occurrence of DF, IHD and ISin 230 patients (mean age 57ys).

Results: Occurrence of DF during the following 5 years by the NCS staging was; NCS-0: 0%, NCS-1: 0%, NCS-2: 1%, NCS-3: 16%, NCS-4:24%. Occurrence any of DF, IHD and/or IS was as follows; NCS-0: 0%, NCS-1: 6%, NCS-2: 31%, NCS-3: 54%, NCS-4 59%.

Conclusion: The present NCS seems to work well not only for diagnosis of the current DN condition, but for prognostic prediction.

[O24] WITHDRAWN

[O25] THE PREVALENCE OF DIABETIC NEUROPATHY AND RISK OF FOOT ULCERATION IN QATAR

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Background: Diabetic peripheral neuropathy (DPN) can lead to foot ulceration and amputation. There are no data on the prevalence of DPN and the risk of foot ulceration in Qatar.

Aims: To define the prevalence of DPNand risk of foot ulceration in secondary care in Qatar.

Methods: 434 (230 males and 204 females) subjects attending the diabetes clinics in Hamad General Hospital and Alwakra Hospital underwent quantification of DPN using a Neurothesiometer.

Results: The average age, duration of diabetes, systolic BP, BMI and HbA1c were:53.2 ± 13.5, 12 ± 8.4years, 137 ± 3.3 mmHg, 32.3 ± 1.1 kg/m^2 and 8.3 ± 0.2 %, respectively. The BMI of the South Asians (29.5 kg/m^2) was lower than in Qatari's (33.3 kg/m^2) and non-Qatari Arabs (38.1 kg/m^2)(P=0.002). The prevalence of DPN(VPT ›15V) was 36% and did not differ significantly between ethnicities. The prevalence of those at high risk of foot ulceration (VPT›25) was 15% in non-Qatari Arabs, 12% in Qatari's and 9% in South Asians.

Conclusion: The prevalence of diabetic neuropathy was comparable to other studies from Europe and the US. A high proportion of patients had unrecognised risk of foot ulceration, which was related to BMI.

[O26] DIVERGENT COURSE OF SENSORIMOTOR AND CARDIAC AUTONOMIC FUNCTION OVER FIVE YEARS IN RECENTLY DIAGNOSED TYPE 1 AND TYPE 2 DIABETES

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Aim: To prospectively assess the changes in sensori motor and cardiac autonomic function and their covariates in recently diagnosed diabetes subjects over 5 years.

Methods: We assessed nerve conduction velocity (NCV), quantitative sensory testing, and heart rate variability (HRV during a hyperinsulinaemic-euglycaemic clamp) at baseline and after 5 years in 73 T1D and 167 T2D patients. Baseline characteristics (T1D/T2D): age: 36.6±12.7/53.2±9.9[SD]years; male: 59/70%; BMI: 24.4±3.6/31.6±5.8kg/m²; diabetes duration: 5.9±3.5/5.5±3.3months; HbA1c: 6.8±1.4/6.4±0.9%. Five-year follow-up: BMI: 25.9±4.3/31.7±5.8kg/m², HbA1c: 7.1±1.1/6.8±1.0%.

Results: After five years, 5 out of 6 NCV measures declined in T2D (e.g. peroneal MNCV: 45.2±4.6 vs 43.2±4.6 m/s; sural SNCV: 45.3±5.3 vs 43.4±5.5 m/s; P<0.0001), whereas no NCV changes were observed in T1D. Vibration sensation deteriorated in both diabetes groups, while cold threshold did not and warm threshold increased only in T1D (all P<0.05). DSPN prevalence increased in T2D patients (19.9% vs 34.0%; P=0.004). Four of 9 HRV measures decreased (e.g.LF(median [25th;75th]): 1267[736;1847] vs 959[539;1466])in T1D, while in T2D 2 of 9 decreased (e.g. LF: 729[364;1259] vs 516[282;1020]) (all P⩽0.001). In T2D ΔHRV of 5 measures was associated with Δfasting glucose (e.g. ΔpNN50: β=-0.401;P=0.00005) and ΔHRV of 2 measures was associated with ΔHbA1c (e.g. ΔpNN50: β=-0.325; P=0.001) and ΔM-value (e.g.pNN50: β=0.258;P=0.015).

Conclusions: Over five years, NCV deteriorated and large fibre dysfunction preceded small fibre dysfunction in recently diagnosed T2D but not T1D, independent of glycaemic control. In contrast, a decline in HRV occurred predominantly in T1D and was associated with worsening of glycaemia and insulin sensitivity in T2D.

[O27] TREATMENT OF TYPE 2 DIABETIC RATS AFTER CHRONIC HYPERGLYCEMIA WITH COMBINATION THERAPY CONSISTING OF ENALAPRIL, α-LIPOIC ACID, AND MENHADEN OIL ON DIABETIC NEUROPATHY

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Aim: The etiology of diabetic neuropathy is multifactorial and an effective treatment will likely require some form of combination therapy. In this study we sought to determine the efficacy of monotherapy vs. the combination of enalapril, α-lipoic acid, and menhaden oil on vascular and neural complications in a high fat fed low dose streptozotocin treated rat, a model of type 2 diabetes.

Methods: Rats were fed a high fat diet for 8 weeks followed by a 30 mg/kg dose of streptozotocin to create a model of type 2 diabetes. Sixteen weeks after the onset of hyperglycemia treatments of 12 weeks were initiated. Prior to and immediately after treatments vascular and neurological endpoints were evaluated.

Results: Prior to treatment diabetic rats had impaired glucose clearance as well as reduced motor and sensory nerve conduction, thermal hypoalgesia, reduction in intraepidermal nerve fiber profiles, decrease in cornea sub-basal nerve fiber length and corneal sensitivity and impairment in vascular relaxation to acetylcholine in epineurial arterioles of the sciatic nerve. Vascular relaxation, nerve conduction velocity and thermal nociception trended to worsen in untreated diabetic rats. Treating diabetic rats with the combination of enalapril, α-lipoic acid and menhaden oil was effective in reversing diabetes induced vascular dysfunction and neural pathology and was more efficacious than either monotherapy.

Conclusions: These studies suggest that a combination therapeutic approach may be most effective for treating vascular and neural complications of type 2 diabetes.

[O28] GABAPENTIN TOPICAL: EFFICIACY AND SAFETY EVALUATION IN DIABETIC PERIPHERAL NEUROPATHY (GATESET)

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Aim: We evaluated the efficacy and safety of the topical preparation containing predominantly gabapentin (8% w/w) in combination with ketoprofen (5% w/w), capsaicin (0.035 % w/w), methyl salicylate (5% w/w) in people with diabetes with peripheral neuropathic pain.

Methods: The patients included were either drug naïve to treatment for neuropathic pain or were on the existing oral therapy with either gabapentin, pregabalin, amitriptyline or duloxetine with a minimum duration of 2 weeks.

Results: 20 patients (12 males, 8 females), mean age 53.7 years. The pain characteristics which were rated high on the Pain Quality Assessment Scale were unpleasant (9.5), sharp (9.25), hot (9.2), intense (8,8). The neuropathy pain scores consistently improved over the weekly follow up, reduced by 52% (Day 0 – 64.35 to 30.88 at the end of 4 weeks) with similar reductions in sub scores- NPS 8 (53%) and NPS 4 (57.4%) ($p<0.0001$). The reductions in the pain scores across NPS, NPS 8 and NPS 4 were comparable ($p=0.2593$ (NS). The % reductions (pre and post treatment score) in individual pain characteristics were; intense pain 53% (8.8, 4.13), sharp 55 % (9.25, 4.19), hot 55% (9.2, 4.13), dull 59% (5.5, 2.25), sensitive 55% (7.85, 4.94), unpleasant 55% (9.5, 4.3), surface pain 65 % (2.45. 1.67), deep pain 60% (6.85, 2.73). The change in the individual pain characteristics significant ($p<0.013$). The patients did not report of any significant side effects.

Conclusions: The change in the pain scores demonstrates that the mechanistic action of topical gabapentin to inhibit peripheral sensitisation translates into meaningful clinical benefits.

[O29] AUTONOMIC NERVOUS SYSTEM DYSFUNCTION AMELIORATES AFTER KIDNEY AND KIDNEY-PANCREAS TRANSPLANTATION

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Aim: We tested the differential effects of kidney or kidney-pancreas transplantation on autonomic function in end-stage renal disease patients.

Methods: In 44 patients undergoing kidney-only (55.6±11.1 years, mean±SD; 30 males) and 12undergoing kidney-pancreastransplantation (36.8±9.1years; 11 males) we measured baroreflex sensitivity (BRS), heart rate variability (HRV, standard deviation of heart period), tissue (NIRS) and arterial (Sat) oxygenation before and four months after transplantation. All kidney–pancreas transplant recipients had type 1 diabetes. Of kidney-only transplanted patients four had type I diabetes and eight type 2 diabetes. All participants were on dialysis before the transplantation. In addition we studied 55 healthy controls (42.0±12.1 years, 33 male).

Results: Before transplantation BRS, HRV and NIRS were more reduced in pancreas-kidney (4.30±2.89, 9.39±7.89, 62.11±0.75, respectively) versus kidney (6.42±5.16,18.70±17.56,62.33±0.84 , respectively) versus control (12.82±6.67, 32.05±14.79, 65.38±1.95, respectively; $p<0.005$ between controls and pancreas-kidney as well as between controls versus kidney-only).

After transplantation the values showed a trend of improvement in the kidney-pancreas group but in the kidney-onlygroup only NIRS was improved (BRS: to 4.69±3.70 in kidney-pancreas and to 6.20±16 in kidney-alone, HRV: to 9.90±7.73 in kidney-pancreasand to 15.96 in kidney-alone; NIRS: to 63.43±2.78 in kidney-pancreas and to 63.13±1.58 in kidney-alone; $p<0.05$ to NIRS change of kidney-only).

Conclusion: All subjects showed a trend of improvement after transplantation. Despite severe baseline autonomic abnormalities, the pancreas-kidney group improved more in terms of autonomic function suggesting that in this respect removal of diabetes was more important than correction of kidney function.

[O30] EFFECTS OF BENFOTIAMINE IN SUBJECTS WITH SENSORIMOTOR DIABETIC POLYNEUROPATHY: A DOUBLE-BLIND, RANDOMIZED, PLACEBO-CONTROLLED, PARALLEL GROUP STUDY OVER 12 MONTHS

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Aim: Diabetic sensorimotor polyneuropathy (DSP) is a frequent diabetic complication, but data on long-term treatment are scarce. Benfotiamine, a vitamin B1 prodrug, has been used for years in the treatment of DSP. The aim of our study was to investigate the effects of benfotiamine on DSP for up to 12 months.

Methods: In this double blind, randomized, placebo-controlled, parallel group study performed in 22 subjects with type 1 or type 2 diabetes mellitus and DSP, study medication was given at a dose of 600 mg/day for 3 months followed by 300 mg/day for further up to 9 months. Investigations of DSP took place at screening, 3, 6 and 12 months. Due to technical reasons the study was prematurely terminated, with 21 subjects being assessed at 6 months and 14 at 12 months.

Results: At 6 months benfotiamine significantly reduced neuropathy symptoms(Michigan Neuropathy Screening Instrument- MNSI questionnaire) compared to placebo (-1.64 vs. +0.30, p=0.036). At 12 months, this improvement was quantitatively greater (-2.57), but failed to reach statistical significance. The pain scale at 6 months compared to the screening visit was reduced in the benfotiamine group while elevating in the placebo group (-1.23 vs. +0.20, p=0.058). Deficits (MNSI examination) did not significantly change during benfotiamine treatment. Whole blood vitamin B1 concentration markedly increased after benfotiamine treatment. The safety profile was comparable between groups.

Conclusions: Treatment with benfotiamine for up to 12 months showed to be safe and significantly improved DSP symptoms after 6 months of treatment.

[O31] BARIATRIC SURGERY IMPROVES AUTONOMIC DYSFUNCTION, AND MARKERS OF INFLAMMATION IN OBESE SUBJECTS WITH TYPE 2 DIABETES

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Autonomic dysfunction has emerged as a major risk factor for the development of cardiovascular disease and diabetes (DM). The aim of this study was to evaluate the impact of bariatric surgery on cardiac and sudomotor autonomic function and on markers of inflammation in obese subjects with and without DM.

Ninety eight patients were evaluated at baseline, 4, 12 and 24 weeks after vertical sleeve gastrectomy (81 subjects) or Roux-en-Y gastric bypass (17 subjects). All subjects were assessed at every visit using Sudoscan™ of hands and feet, time and frequency domain analysis of HRV, and markers of inflammation, including IL-6, PAI-1, leptin and adiponectin.

Ninety-eight subjects completed follow-up (30 non-DM, 34 pre-DM and 34 T2DM). ESC of feet improved significantly in DM subjects (Baseline=59.21±2.70, 12-weeks=66.07±2.32, 24-weeks=69.87±2.05, $p<0.0001$). HRV also improved significantly in DM subjects (sdNN=34.38±2.86, 12-weeks=44.31±3.19, 24-weeks=48.16±3.61, $p<0.001$). Basal heart rate, weight, and percent body fat improved significantly in all groups. Adiponectin levels increased (12.84±1.77 vs 25.00±4.82 µg/ml; $p=0.01$) and leptin levels decreased (53.51±8.92 vs 40.33±8.16 ng/ml; $p=0.01$) at endpoint in DM subjects. Similar results were observed for the non-DM group. Multiple linear regression analysis showed feet ESC improvement was independently associated with baseline A1C, insulin and HOMA2-IR levels; after adjusting for age and gender.

This report shows that bariatric surgery significantly improves both markers of inflammation and cardiac and peripheral autonomic function in obese subjects with DM, independent of baseline weight or body fat. Correction of autonomic dysfunction and improved inflammation may potentially impact morbidity and mortality.

[O32] RESINIFERATOXIN FOR THE TREATMENT OF DIABETIC PERIPHERAL NEUROPATHY

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Objective: TRPV1 is involved in inflammatory thermal sensation and has been shown to play a significant role in DPN. Resiniferatoxin (RTX), a potent agonist of TRPV1 has been shown to be effective in preventing pain transmission by inducing depolarization block of the nerve terminals in the short-term and by nerve terminal desensitization/ablation in the long-term.

Method: STZ-induced diabetic animals were used and thermal sensitivities were determined. Membrane potential and membrane currents were recorded using patch-clamp technique.

Results: RTX activates Transient Receptor Potential Vanilloid 1 (TRPV1) in femtomolar concentrations. TRPV1 is expressed in peripheral terminals is responsible for transducing thermal and chemical nociception. Role of TRPV1 expressed in the central terminals is not clear, however, its activation modulates synaptic transmission and contributes to central sensitization. In this study, we have determined the role of TRPV1 expressed in the peripheral and central terminals using resiniferatoxin (RTX), a potent TRPV1 agonist. A single intraplantar injection of RTX, within two days induced loss of capsaicin-induced nocifensive behavior and enhanced response latency to hot plate, which recovered over a period of two months. RTX treatment resulted in the ablation of peripheral TRPV1 expressing fibers in paw skin, which regenerated over the same time period. We propose that low doses of RTX cream will reduce nociceptive transmission and prevent neuronal activity dependent long-term changes in the spinal cord.

Conclusions: Capsaicin, a TRPV1 agonist, applied topically in a cream form has been shown to improve sensory perception in humans. We propose that ultrapotent TRPV1 agonist to treat DPN, which has the advantage of not inducing burning pain during application and has a longer duration of effect.

[O33] ROLE OF PROINFLAMMATORY REACTION IN DIABETIC POLYNEURIPATHY - IMPACT OF MACROPHAGE ACTIVATION ON THE INSULIN RESISTANCE OF SCHWANN CELLS

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Aim: Enhanced infiltration of macrophages is found in diabetic nerves. The impact of macrophage infiltration on diabetic polyneuropathy (DPN) is not known. We studied how the activated macrophages influence Schwann cells.

Methods: Sciatic nerve from mice rendered diabetic by streptozotocin for 8 weeks were examined for macrophage infiltration and their phenotype. For in vitro experiment, RAW246 macrophages (R0)were differentiated intopro-inflammatory type M1 macrophages (R1)bystimulation with LPS, or anti-inflammatory type M2 macrophages (R2) by IL4. Expressions of iNOS or arginase-1, markers for M1 or M2, were confirmed by real-time PCR. Then, Schwann cells (IMS32) were co-cultured withR0, R1 or R2 in trans-well chamber. After 24 hours, mRNA expressions of inflammation-related molecules of IMS32 were examined. To seethe insulin sensitivity, phospho-Akt expression of co-cultured IMS32 was evaluated after stimulation with insulin.

Results: Sciatic nerve of STZ mice contained many macrophages mainly of M1. Ten-fold increase iniNOS mRNA expression was detected inR1 compared toR0 or R2 ($p<0.01$), whereas arginase-1 mRNA was increased 120 fold in R2 compared toR0 or R1. IMS32 co-cultured with R1exhibited 4 and 3 times greater expressions of iNOS and TNFa than that co-cultured with R0 or R2, respectively. In contrast, arginase-1 was similar among all pairs. phospho-Akt expression was markedly attenuated in IMS32 co-cultured with R1 compared to that with R0 or R2.

Conclusions: The phenotype of infiltrated macrophages exhibited different effects on Schwann cells to modulate insulin sensitivity which may contribute to the development of DPN.

[O34] CHARACTERIZATION OF SPONTANEOUSLY IMMORTALIZED SCHWANN CELL LINES FROM NORMALAND ALDOSE REDUCTASE-DEFICIENT C57BL/6 MICE

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Aim: The increased glucose flux into the polyol pathway via aldose reductase (AR) is recognized as a major contributing factor for the pathogenesis of diabetic neuropathy, whereas little is known about the physiological roles of AR in the peripheral nervous system.

Methods: We established spontaneously immortalized Schwann cell lines from long-term cultures of normal and AR-deficient C57BL/6 mouse peripheral nerves, designated as 1970C3 and IKARS1,respectively. These cell lines were further analyzed for mRNA expression under conditions in the presence or absence of reactive aldehydes (0.5 mM of 3-deoxyglucosone (3-DG), 0.25 mM of methylglyoxal (MG) or2.5 M of 4-hydroxynonenal (4HNE)).

Results: Both 1970C3 and IKARS1 cells exhibited distinct Schwann cell phenotypes, such asspindle-shaped morphology and immunoreactivity for S100 and p75 low-affinity neurotrophin receptor. By using DNA microarray and subsequent real time RT-PCR analyses, we observed significant down-regulation of mRNA expression for the polyol pathway-related enzymes, such as sorbitol dehydrogenase and ketohexokinase, in IKARS1 as compared with 1970C3. In contrast, significant up-regulation of mRNA expression for aldo-keto reductases Akr1b7 and Akr1b8 in IKARS1 as compared with 1970C3 was detected. Furthermore, exposure to 3-DG, MGor4HNE significantly (>2.5 fold) up-regulated the mRNA expression for Akr1b7 in IKARS1, but not in 1970C3. Because we observed no significant differences in the viability between the two cell lines, the detoxification function might be taken over by Akr1b7 in the absence of AR.

Conclusion: 1970C3 and IKARS1can be useful tools for the study of polyol metabolism and functional roles of AR.

[O35] ACTIVATION OF GPR40 AND GPR120 PROTECTS OXIDATIVE STRESS-INDUCED CELL DEATH IN IMMORTALIZED ADULT MOUSE SCHWANN CELLS

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Aim: We previously demonstrated that n-3 polyunsaturated fatty acids (PUFAs) exhibited antioxidant effects in immortalized adult mouse Schwann (IMS32) cells. G-protein-coupled receptor 40 (GPR40) and GPR120 function as a receptor for n-3 PUFAs. The docosahexaenoic acid (DHA) have anti-inflammatory properties mediated through GPR120. GPR40 is involved in glucose-induced insulin secretion. In this study, we investigated whether activation of GPR40 and GPR120 protects neural cells against oxidative stress.

Methods: 1) mRNA expressions of GPR40 and GPR120 were determined by RT-PCR. 2) Cells were pretreated with GW9508 (GPR40/GPR120 agonist), and stimulated by tert-butyl hydroperoxide (tBHP). 3) Cell viability was measured by the MTT assay. 4) mRNA expressions of antioxidative enzymes were determined by quantitative RT-PCR. 5) Luciferase activity was measured by Dual-Luciferase Reporter Assay System.

Results: 1) RT-PCR analysis confirmed expressions of GPR40 and GPR120. 2) Decreased cell viability by tBHP was ameliorated by GW9508. 3) GW9508 increased mRNA of heme oxygenase-1, catalase and glutathione peroxidase. 4) Luciferase activity of Nrf2 was enhanced by GW9508.

Conclusions: These findings indicate that activation of GPR40 and/or GPR120 induces antioxidative enzymes via Nrf2 and would protect neural cells against the hyperglycemia-induced oxidative stress in diabetic neuropathy.

[O36] CORNEAL CONFOCAL MICROSCOPY DEMONSTRATES IMMUNE ACTIVATION AND GREATER CORNEAL NERVE DAMAGE IN PATIENTS WITH TYPE 1 COMPARED TO TYPE 2 DIABETES

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Aim: Immune mediated nerve damage has been postulated in diabetic neuropathy. Corneal confocal microscopy (CCM) allows the quantification of Langerhans cells (LCs) and corneal nerves inpatients. We have quantified the density of LCs and corneal nerve morphology in patients with type 1 (T1DM) and type 2 diabetes (T2DM) using CCM.

Methods: 30 subjects with T1DM (age;57.23±2.0), 37 with T2DM (age;57.72±1.22) and 19 age-matched controls (age;54.25±2.65) underwent CCM. LCs density and corneal nerve morphology were assessed in images obtained from the corneal subbasal nerve plexus.

Results: LCs density (no/mm^2)(62.87±9.76vs. 76.78±14.39vs. 39.31±12.36;P=0.05) was significantly increased in subjects with T1DM and T2DM compared to controls and was comparable between T1DM and T2DM patients. It correlated with BMI (r=0.2, P=0.04) but not HbA1c (P=0.8) or duration of diabetes (P=0.6). Corneal nerve fibre density (NFD) was reduced in T1DM and T2DM compared to controls (21.82±1.28vs.18.57±1.8 vs. 27.20±1.20;P=0.002) and did not differ between T1DM and T2DM (P=0.1). Corneal nerve branch density (NBD)(21.73±2.5 vs.35.38±3.25 vs.36.73±2.94) was significantly reduced in T1DM compared to controls (P=0.001) and T2DM (P=0.002). Corneal nerve fibre length (NFL)(12.11±0.83 vs. 14.07±0.62 vs. 15.95±0.68) was significantly reduced in T1DM compared to controls (P=0.005) and T2DM (P=0.05). LCs' density did not correlate with NFD (P=0.6), NBD (P= 0.5) or NFL(P=0.2).

Conclusion: Corneal LC density is increased in patients with diabetes independent of type and duration of diabetes, HbA1c and severity of corneal nerve damage. There is also evidence of greater corneal nerve damage in T1DM compared to T2DM.

[O37] COMBINED RETINAL/NEUROPATHY/RENAL SCREENING SERVICE: AN EFFECTIVE MODEL FOR EARLY DETECTION OF DIABETIC PERIPHERAL NEUROPATHY

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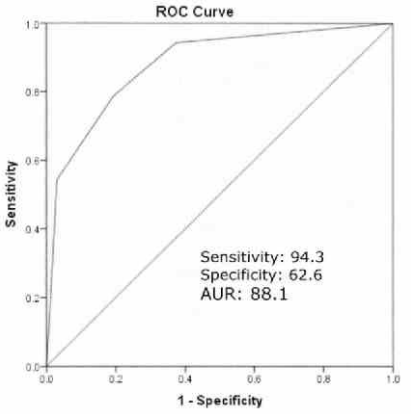
Background and aims: Diabetic foot ulceration and amputations are physically and emotionally devastating as well as being expensive. In the UK, high-uptake retinal-screening has resulted in retinopathy no longer being the commonest cause of working-age blindness. In contrast, diabetic distal symmetrical polyneuropathy (DPN) is diagnosed late using the 10g monofilament (10gMF), foot clinics are bursting with patients and amputations are increasing year-on-year. A more effective model of foot-screening is therefore required.

Materials and methods: Hospital and community-based, one-stop, combined eye/DPN/renal screening service has undergone a feasibility assessment. Patients attending retinal-screening have their feet assessed by a podiatrist whilst the instilled medriatic eye-drop is working. Assessments included: 1) gold-standard Toronto Clinical Neuropathy Score (TCNS, takes 15 minutes), 2) the 10gMF and 3) two state-of-the art, validated, objective and quick measures of neuropathy: DPN-Check - a hand-held device that measures sural nerve conduction velocity and amplitude (3 minutes) and SUDOSCAN that measures sudomotor function (3 minutes).

Results: 180 consecutive diabetic patients, 20.5% of whom have never had their feet examined previously, have so far been evaluated. The prevalence of DPN using TCNS was 31%, massively underestimated by 10gMF (14%). The prevalence of DPN using DPN-check was 55% (91% sensitivity, 73% specificity), 40% using SUDOSCAN (79% sensitivity, 60.3% specificity) and 50.3% using abnormality in either (94% sensitivity, 63% specificity). Both devices co-related with TCNS ($p<0.001$). New diagnosis of painful-DPN was made in 12%. Participants rated the service very highly ($p<0.00$).

Conclusion: Combined eye, DPN and renal screening has high uptake, reduces clinic visits, leads to an early diagnosis of DPN, unmasks painful DPN, and is an effective model for the early diagnosis/management of DPN and foot complications.



Diagnostic performance of combined DPN-check and SUDOSCAN for TCSS-based DPN

[O38] DIFFUSION-TENSOR-IMAGING MR-NEUROGRAPHY FOR THE DETECTION OF POLYNEUROPATHY IN TYPE 1 DIABETES

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Aim: To evaluate if diffusion-tensor-imaging MR-Neurography (DTI-MRN) can detect lesions of peripheral nerves in patients with type 1 diabetes.

Methods: Forty-eight type 1 diabetic patients (12 with severe polyneuropathy (sDPN), 23 with mild/moderate polyneuropathy (mDPN) and 10 without polyneuropathy (nDPN)) and 30 healthy controls (HC) were included. Clinical examinations, nerve-conduction-studies and vibratory-perception-thresholds, determined the presence and severity of DPN. DTI-MRN (voxel size: 1.4x1.4x3mm^3; b-values: 0, 800 s/mm^2) covered proximal (sciatic nerve) and distal regions of the lower extremity (tibial nerve). FA and ADC were calculated and compared to T2 relaxometry and proton-spin-density obtained from a multi-echo TSE sequence.

Results: DTI-MRN could accurately discriminate between DPN, nDPN and HC. The proximal FA was lowest in sDPN (sDPN 0.38±0.04; mDPN 0.43±0.07;nDPN 0.47±0.02; HC 0.48±0.06; p<0.01). In addition, distal FA was lowest in sDPN (sDPN 0.30±0.05; mDPN 0.38±0.06;nDPN 0.41±0.07; HC 0.42±0.07; p<0.01). Likewise, proximal ADC was highest in sDPN with lower values in patients with mPDN and nDPN as well as in HC. The severity of neuropathy was correlated to DTI-MRN demonstrating a strong association of proximal (FA: R^2 = 0.49, p<0.01; ADC: R^2 = 0.15, p = 0.01) and distal nerve lesions (FA: R^2 = 0.32, p< 0.01; ADC: R^2 = 0.19; p-value < 0.01). T2 relaxometry and proton-spin-density did not enable detection of nerve lesions.

Conclusion: DTI-MRN enables detection of DPN by decreasing nerve FA and increasing ADC closely related to the severity of DPN. These alterations are likely to reflect proximal and distal nerve fiber pathology.

[O39] BRAIN MRI ABNORMALITIES IN PATIENTS WITH TYPE 2 DIABETES MELLITUS

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Background and aims: There is a growing body of evidence that brain damage represents another diabetic complication. Changes of cerebral structure and function could be attributed to the influence of the diabetic metabolic milieu. However, the exact brain abnormalities that are associated with type 2 diabetes mellitus (T2DM) need to be further elucidated. Therefore, the aim of this study was to investigate which abnormalities on brain MRI are associated with T2DM.

Materials and methods: We examined93 patients with T2DMwithout history of prior cerebrovascular accidents (mean age 62.3±5.5 years, diabetes duration 9.7±6.7 years, BMI 32.5±10.4 kg/м^2, HbA1c8.1±1.3%) and 18 healthy subjects who served as the control group (mean age 59.5±5.7 years, BMI 29.1±4.0 kg/м^2). All subjects were scanned on a 1.5T MRI scanner. Intracranial volume (ICV), total brain (TBV), total cerebrospinal fluid (CSF), white matter (WM), grey matter (GM), peripheral CSF, lateral ventricular (LV) and white matter hyperintensity (WMH) volume were determined on the MRI scans automatically by kNN-based probabilistic segmentation. Infarct volumes were manually segmented. Volumes were expressed as % of ICV and numbers represent percentages of ICV. Linear regression analyses adjusted for sex, age and education level were performed.

Results: We found a lower TBV (78.8±2.13 vs. 81.3±1.98; p<0.05), a lower WM volume (43.2±1.34 vs. 43.7±1.04%;p<0.05) and a lower GM volume (35.4±2.25 vs. 37.5±2.02%; p<0.05) in patients with T2DM compared to controls. Total CSF volume (21.2±2.13 vs. 18.7±1.98; p<0.05), peripheral CSF volume (19.2±1.78 vs. 17.0±1.93%; p<0.05) and LV volume (2.0±0.91 vs. 1.7±0.71%; p<0.05) were higher in patients with T2DM compared to controls. However, there were no between group differences in WMH volume (0.16±0.18 vs. 0.12±0.13%; p>0.05) and infarct volume (0.2±0.56 vs. 0.03±0.13%; p>0.05). There was a statistically significant negative correlation between longer diabetes duration, on one side, and TBV and WM volume, on the other side. We found a positive correlation between disease duration and LV volume, WMH volume and total CSF volume.

Conclusion: In our study we revealed structural brain abnormalities that are associated with T2DM. These brain abnormalities could underlie the cognitive deficits frequently observed in patients with T2DM.

The study was performed under the grant from EFSD Collaborative Program “New Horizons”.

[O40] THE CORELLATION BETWEEN THE GUILLAIN-BARRÉ SYNDROME AND IMPAIRED GLUCOSE CONTROL

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This year we mark the 100th anniversary since the description of Guillain-Barré syndrome (GBS). At the same time the relation of this neuropathy with diabetes mellitus (DM) was poorly studied in spite that DM is one of most common causes of peripheral neuropathy, and it has been reported that more than 50% of patients with diabetes develop peripheral neuropathy as a complication during their disease course.

Aim: The aim of the study was to study the correlation between evolution and severity of GBS and impaired glucose control.

Materials: There was performed a retrospective study of 36consecutive patients with GBS (21 males and 15 females) of 53,1±4,5 years old hospitalized in the Institute of Neurology and Neurosurgery, Chisinau, Moldova in the period 2013-2015.

The diagnosis was supported by means of electrophysiological investigations and lumbar puncture.

Results: DM was established before the evolution of GBS in one case. Surprisingly in 26 patients (72,2%) it was determined an impairment of the glucose control: in 14 patients (38,9% cases) glycaemia was higher than 7 mmol/l, in other 12 patients (33,3% cases) glucose tolerance was modified. There was not notified a significant difference between the severity of GBS (average 3,8points on Hughes scale assessment in the hyperglycemic group versus 3,7 in the normoglycemic one) and disease evolution.

Conclusions: Impaired glucose control play an important role in the development of GBS. It is necessary to conduct a prospective study to establish the peculiarities of the glucose metabolism in GBS patients.

[O41] MECHANISMS OF DIABETIC NEUROPATHIC PAIN FOCUSSING ON SODIUM CHANNELS

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Neuronal hyperexcitability is a key feature in neuropathic pain and this is probably also the case in painful diabetic neuropathy. Experimental manifestations of neuronal hyperexcitability in pain in general includes: spontaneous discharges in nociceptors, sensitisation of second order neurons in the dorsal horn of the spinal cord, recruitment of silent nociceptors, expansion of receptive fields, and reorganisation patterns in the brain. Sodium channels seem to play a key role in the neuronal hyperexitability. The clinical translation of this array of neuronal hyperexitability to painful diabetic neuropathy is only partly understood. Lowered pain threshold, allodynia, hyperalgesia to one or several sensory modalities and extraterritorial spread of pain are presumed reflections of such neuronal hyperexcitability. However in painful diabetic neuropathy the hyperexcitability signs are often masked by the loss of large and small fibre sensory functions.

The neuronal hyperexcitability has either a peripheral or a central component or a combination of such mechanisms. The use of various blocks or combination of quantitative sensory testing with pharmacological modulation of neuropathic pain are useful tools and aid in distinguishing between peripheral and central sensitisation. In this presentation we will focus on the role of sodium channels blockers to modulate painful diabetic neuropathy. However, the dynamic pattern and plastic changes of the nociceptive system representa limiting factor in distinguishing between peripheral versus more central mechanisms in driving pain in diabetic neuropathy.

[042] THE RELATIONSHIP BETWEEN VITAMIN D AND THALAMIC NEUROCHEMISTRY IN PAINFUL DIABETIC NEUROPATHY

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Background and aims: We have previously demonstrated lower vitamin D levels in painful compared to painless diabetic peripheral neuropathy (DPN). However, the mechanistic basis for this remains unclear. Recent mouse studies have reported an association between vitamin D deficiency and prominent changes in behavior and brain neurochemistry. Thalamic Glutamate / glutamine (Glx) was also found to be lower in DPN compared to non- neuropathic diabetic subjects. The aim of this study was therefore to examine any potential relationship between vitamin D levels, neuropathic pain status and thalamic brain neurochemistry.

Materials and methods: Forty-four patients with type 2 diabetes (T2DM) (14 Painful-DPN, 15 Painless-DPN and 15 No-DPN) and 15 non-diabetic healthy volunteers (HV) were examined by detailed clinical and neurophysiological assessment to determine their neuropathy composite score [NIS(LL)+7 and Douleur Neuropathique 4 score(DN4)]. 25(OH)-Vitamin D was measured between May-September and all subjects had seasonal sunlight exposure and daily activity measured. Single-voxel proton Magnetic Resonance Spectroscopy (H-MRS) was used at 3T to yield thalamic Glx resonance information relative to that of water in each subject (MEGAPRESS; echo time=68ms).

Results: There was no significant difference in age between the study groups (painless-DPN, 59(SD10); painful-DPN, 60(7); no-DPN 57(7) and HV 55(10) years; ANOVA p=0.39). Subjects with painful-DPN (35.8nmol/l) had the lowest vitamin D levels (painful DPN, 35.8(17.1); painless-DPN, 56.1(28.7); No-DPN, 46.8(19.2) and HV, 58.5(27.8); ANOVA p=0.039) and Glx levels 1.27(0.23), 1.37(0.14), 1.34(0.21), 1.45(0.36); ANOVA p=0.28). There was a significant correlation between vitamin D and Glx in patients with painful-DPN only (r=0.69, p=0.03).

Conclusion: We have demonstrated a significant correlation between vitamin D levels and thalamic Glx in patients with painful DPN. This is the first study to demonstrate an association between vitamin D deficiency and neurochemical changes in the brains of patients with painful DPN.

[043] THE PREVALENCE OF PAINFUL DIABETIC NEUROPATHY IN QATAR AND VITAMIN D DEFICIENCY AS A RISK FACTOR

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Background: There are no data on the prevalence of painful diabetic neuropathy (PDN) in Qatar. Vitamin D (25OHD) deficiency is common in patients with diabetes and is associated with PDN.

Aim: To define the prevalence and risk factors of PDNin Qatar.

Methods: 434 (230 males and 204 females) subjects attending the diabetes clinics in Hamad General Hospital and Alwakra Hospital underwent assessment with the DN4 questionnaire.

Results: The average age, duration of diabetes, systolic BP, BMI, HbA1c and 25OHD were: 53.2 ± 13.5, 12 ± 8.4 years, 137 ± 3.3 mmHg, 32.3 ± 1.1 kg/m^2,8.3 ± 0.2 % and 25.14 ± 1.37 ng/ml, respectively. The prevalence of PDNwas 46% and was comparable between men and women, but was higher in those with diabetic neuropathy (VPT >15v) (65%) and hypertension (Systolic BP >140) (71%). 25OHD levels were significantly lower in patients with more severe PDN (DN4 score $\geqslant$ 6): 23.7 ng/ml vs 25.8 ng/ml (P=0.03).

Conclusion: The prevalence of PDN in Qatar is higher than previous studies in Europe and the US. Diabetic patients with neuropathy and hypertension have a higher prevalence of PDN and more severe PDN is associated with lower levels of vitamin D.

[O44] SMALL BUT NOT LARGE FIBRE NEUROPATHY MEASURES DIFFERENTIATE PATIENTS WITH PAINFUL FROM PAINLESS DIABETIC NEUROPATHY

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Aim: To investigate if abnormalities in nerve fucntion and structure, in particular corneal confocal microscopy (CCM) can distinguish patients with painful and painless diabetic neuropathy.

Method: As part of the PROPANE study, 196 diabetic patients (age: 60±12 years; duration of diabetes: 19±15 years) underwent assessment of neurological symptoms (based on Toronto clinical neuropathy score), sensory testing, nerve conduction, vibration (VPT) and thermal (TPT) perception, heart rate variability response to deep breathing and corneal confocal microscopy.

Results: 35% had no pain(NP), 33% had pain without affecting well-being and the quality of life (P-ve) and 32% had pain affecting well-being and quality of life (P+ve). Peroneal and sural nerve conduction velocities and amplitudes and DBHRV did not differ between patients with painful compared to painless diabetic neuropathy. VPT and WT were significantly increased in P-ve (P=0.02, P=0.02) and P+ve (P=0.001, P=0.01) compared to NP, respectively. Corneal nerve fibre density and length were significantly decreased in P-ve (P=0.03, P=0.02) and P+ve (P=0.02, P=0.03) compared to NP, respectively, but there was no difference in corneal nerve branch density.

Conclusion: Both vibration and warm thresholds as well as corneal nerve morphology, but not nerve conduction studies or autonomic function are worse in patients with painful compared to painless diabetic neuropathy, irrespective of the effect on quality of life.

PAINFUL POLYNEUROPATHY IS COMMON BUT LARGELY UNDIAGNOSED IN SUBJECTS WITH AND WITHOUT DIABETES PARTICIPATING IN A NATIONWIDE EDUCATIONAL INITIATIVE (PROTECT STUDY)

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Painful distal sensory polyneuropathy (DSPN) is associated with considerable morbidity and an increased risk of mortality, but neuropathy screening is underutilized in primary care practice. We conducted a nationwide educational initiative to determine the prevalence and risk factors of diagnosed and previously undiagnosed painful and painless polyneuropathy. Among 1,589 individuals participating in the initiative, 643 had no diabetes by history (ND), 113 had type 1 diabetes, and 833 had type 2 diabetes. DSPN was assessed by history and foot examination including pressure (10 g monofilament), temperature (tip therm instrument), and vibration (tuning fork) perception and was classified as possible, probable, and severe if 1 of 3, 2 of 3, and 3 of 3 tests were abnormal. Painful DSPN was defined as the presence of DSPN with pain and/or burning at rest in the feet, while painless DSPN was defined as the presence of paresthesias, numbness, or absence of symptoms. Foot pulses, HbA1c (point-of-care testing), and symptom questionnaires were determined in subsets of participants. DSPN was detected in 49.3%of ND, 43.5%of type 1, and 52.9%of type 2 diabetes subjects. The percentages of subjects with painful DSPN among those with DSPN were 66.7% in ND, 61.5% in type 1, and 61.8% in type 2 diabetes subjects. Among participants with painful polyneuropathy, the latter was reported as previously undiagnosed by 75.8%of ND, 28.5%of type 1, and 60.2%of type 2 diabetes participants. These rates were around 20% higher in subjects with painless DSPN. Among ND participants, 30.1% had HbA1c values of 5.7-6.4%, while 4.1% showed HbA1c levels $\geqslant$ 6.5%. Painful DSPN was associated with HbA1c in type 2 diabetes subjects and in ND individuals who had HbA1c levels $\geqslant$ 6.5%. In conclusion, almost half of subjects with and without diabetes participating in an educational initiative had DSPN which was painful but previously undiagnosed in almost two thirds each. Since the risk of diabetes was increased in one third of participants without known diabetes, effective strategies to reveal both undetected diabetes and neuropathy should be implemented.

PATHOGENETIC THERAPY IN DIABETIC NEUROPATHY – QUO VADIS NEUROPATHY?

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The therapy of diabetes mellitus is based entirely on pathophysiological considerations. Insulin, oral hypoglycaemic agents, antihypertensives, anti-platelet agents and lipid-lowering drugs are considered as pathogenetic oriented, causal treatments. Nonetheless, neuropathy is the only diabetic complication associated with pain. This way, pain relief is also important. The key components of pathogenetic oriented, causal therapy include optimal glycaemic control, management of risk factors, benfotiamine (a transketolase activator and inhibitor of alternative metabolic pathways such as the polyol pathway, hexosamin pathway, PKC pathway and the formation of advanced glycation end products), as well as alpha-lipoic acid being considered as the most powerful antioxidant. Pathogenetic oriented treatment has an impact on neuropathic damage/deficit and disability, while, on the other hand, it has a documented effect on the improvement of neuropathic pain and quality of life as well (Figure 1). The use of symptomatic agents is associated with pain relief and improvement of quality of life, while the progression of neuropathy is not affected (Figure 2).

Figure 1. The impact of pathogenetic oriented therapy of diabetic neuropathy onpain/quality of life and on neuropathic damage/deficit.

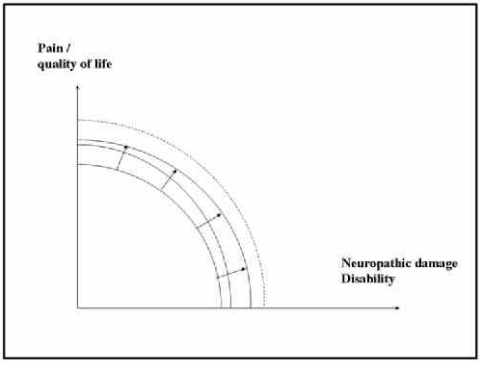
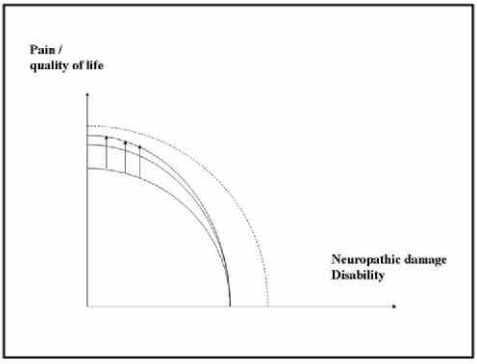


Figure 2. Symptomatic treatment of diabetic neuropathy: improvement of quality of life and pain reduction, no effect on the progression of neuropathy.



The management of diabetes mellitus itself often requires combination therapy with two or three oral hypoglycaemic agents, while hypertension is often treated with even more, different antihypertensive agents. In fact, combination therapy of diabetic neuropathy would be much more often required.

[P1] EFFECTS OF ACUTE GLYCEMIC STRESS ON MEASURES OF CARDIOVASCULAR AUTONOMIC NEUROPATHY (CAN) IN PATIENTS WITH TYPE 1 DIABETES (T1D)

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Objective: To evaluate the effects of acute glycemic stress on measures of CAN, and understand its overall impact on the arrhythmogenesis risk in T1D subjects and various stages of disease.

Methods: Subjects with T1D and age-matched healthy controls (HC) underwent sequentially euglycemic (100±20mg/d/), hyperglycemic (300±20mg/dl) and hypoglycemic (45±10mg/dl) clamp studies, to mimic actual practices in treating T1D. CAN was assessed by time-and-frequency-domain indices of heart rate variability (HRV) derived from continuous ECG recordings during this sequence using the ANX 3.1 (ANSAR Inc. Philadelphia, PA). Blood samples were obtained at 30-min intervals for stress counter-regulatory hormones and metabolomics markers.

Results: We present preliminary data for 7 T1D subjects (mean age 42±17 years, mean diabetes duration 27±11 years, mean HbA1c 8.5±1.3 %), and 3 age-matched HC. There were no differences in indices of HRV between T1D and HC during euglycemia. Time and frequency domains measures of HRV were markedly blunted duringhyperglycemia in all T1D patients, but did not change in the HC (LF/HF ratios, a measure of overall sympathetic/parasympathetic balance were 6.4±6.9 and 4.8±3.6 vs 7.7±11 and 8.0±10, respectively). Similarly there was a higher increase in heart rateduring the hyperglycemic clamp compared to euglycemic clamp (75 vs. 67 bpm) in T1D only. T1D subjects also presented with an increase in the LF/HF ratioduring the hypoglycemic clamp.

Conclusion: This preliminary data suggest that acute glycemic stress is associated with blunting of the overall cardiovagal balance in patients with T1D which may potentially lead to cardiac arrhythmias.

[P2] A PROSPECTIVE STUDY ASSESSING EFFECTS OF SHORT-TERM GLYCAEMIA ON SMALL FIBRE STRUCTURE AND FUNCTION IN NEWLY DIAGNOSED TYPE-1 DIABETES

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Aim: The effects of short-term changes in glycaemia on small fibre neural integrity remain unexplored. In patients with newly diagnosed Type 1 diabetes (T_1DM) this prospective study evaluates and compares the effect of glycaemia on 1) small fibre function (SFF) measured by the LDI (laser doppler imager) $_{FLARE}$ technique and 2) small fibre structure (SFS) assessed by corneal confocal microscopy (CCM).

Methods: We studied 14 patients (7 males; mean age±SD = 27.09yr±9.56) within two weeks of diagnosis of T_1DM and insulin initiation; they were restudied at 6 months after full recovery. Assessments included neuropathy disability scores (NDS), vibration perception threshold (VPT), sural nerve amplitude (SNAP) and conduction velocity (SNCV). SFF was assessed in the foot using the LDI_{FLARE} technique. SFS was measured in the cornea by CCM CNFL, CNBD) and CNFL. 14 age-matched healthy controls (HC: 7 males; 30.1yr±10.3) were studied as comparators.

Results: Compared to baseline, both HbA_{1c} (13.1±1.1 vs 10.2±2.1%; p=0.003) and LDI_{FLARE} areas (8.08±0.98 vs 9.46±1.17 cm^2; p=0.006) improved significantly at 6 months. In contrast, no difference was seen in any CCM parameter (CNFD: 49.65±5.05 vs 48.17±6.23 no/mm2; p=0.66; CNBD: 31.58±2.68 vs 32.89±3.87 no/mm2; p=0.11; CNFL: 19.56±3.01vs 20.75±3.10 mm/mm2; p=0.19). Large fibre parameters (NDS, VPT, SNAP, SNCV) remained unchanged (p=>0.05 for all). There was no change in any neurological parameters in HC at 6 months (p=>0.05).

Conclusion: These results indicate that in T_1DM, SFF assessed by the LDI_{FLARE} is more sensitive to short term changes in glycaemia than SFS assessed by CCM. These differences may be important when choosing between these methodologies for investigating the effect of therapies on small fibre integrity.

[P3] ONE-YEAR PROGRESSION OF RETINAL NEURODEGENERATION IN PATIENTS WITH TYPE 1 DIABETES MELLITUS NOT AFFECTED BY PERIPHERAL NEUROPATHY

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Aim: To examine the role of overall glycemic load and glycemic variability (GV) on the development and progression of retinal neurodegeneration, in type 1 diabetes patients (DM1) with no signs or mild non proliferative diabetic retinopathy, not affected by peripheral neuropathy.

Methods: 19 consecutive DM1 patients were recruited and followed for 1 year, and compared to 13 healthy controls (C). At baseline and after one year, retinal neurodegeneration was evaluated by analysis of all macular neuroretinallayers, and nasal (N)/temporal (T)/superior (S)/inferior (I) quadrants for individual layers, using OCT Heidelberg Spectralis. Metabolic control was measured as HbA1c, and indexes of GV from continuous glucose monitoring. Standard conduction studies (CS) ofsuralis, peroneus and tibialis nerves were also performed.

Results: Retinal nerve fibre layer (RNFL)-N thickness was significantly reduced (p 0.046), while inner nuclear layer (INL)-T thickness (p 0.036) increased, after 1 year, although not significantly different from C.A positive correlation between INL-T and continuous overall net glycemic action (CONGA)-1, -4 hours, was found both at baseline (p 0.035 and p 0.042, respectively) and at follow-up (p 0.015 and p 0.016, respectively). No correlation was observed with HbA1c. No abnormalities of CS were found in any patient.

Conclusion: This is the first longitudinal study demonstrating a pathogenic role of GV on the development of retinal neurodegeneration in DM1 patients. The progressive loss of nerve retinal fibers and the concomitant glial activation may represent an early neuropathic dysfunction, even before the onset of peripheral neuropathic damage.

[P4] ASSOCIATION BETWEEN STRUCTURAL BRAIN ABNORMALITIES AND COGNITIVE FUNCTIONING IN PATIENTS WITH TYPE 2 DIABETES MELLITUS

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Background and aims: Recent clinical and epidemiological studies revealed an association between cognitive impairment, dementia, on the one side, and type 2 diabetes mellitus (T2DM), on the other side. However, the exact association between structural brain abnormalities and cognitive functioning in patients with T2DM is still not entirely clear.

Therefore, the aim of this study was to investigate the association between structural brain abnormalities and cognitive functioning in patients with T2DM.

Materials and methods: We examined 93 patients with T2DM (mean age 62.3±5.5 years, diabetes duration 9.7±6.7 years, BMI 32.5±10.4 kg/м^2, HbA1c 8.1±1.3%). All subjects did not have a history of cerebrovascular accidents or depressive episodes. Cognitive functioning was assessed by means of a standardized psychometric test battery covering the domains Memory, Processing Speed and Executive functioning. All cognitive tests were performed in the morning. There were no episodes of hyperglycemia or hypoglycemia immediately before assessment of cognitive functioning. All subjects were scanned on a 1.5T MRI scanner. Intracranial volume (ICV), total brain (TBV), total cerebrospinal fluid (CSF), white matter (WM), grey matter, peripheral CSF, lateral ventricular and white matter hyperintensity (WMH) volume were determined on the MRI scans automatically by kNN-based probabilistic segmentation. Infarct volumes were manually segmented. Volumes were corrected for ICV. Pearson correlation tests were performed.

Results: We found statistically significant positive correlations between WM, on one side, and the Memoryscore ($r=0.214$, $p<0.05$) and Executive Functioning($r=0.216$, $p<0.05$). Significant negative correlations were found between Processing Speed, on one hand, and WMH ($r=-0.22$, $p<0.05$), and total CSF ($r=-0.236$, $p<0.05$), on the other hand. Moreover, Processing Speed positively correlated with TBV ($r=0.236$, $p<0.05$). The correlations between domain scores and other brain volumes did not reach the level of statistical significance.

Conclusions: Our analysis indicates that WM volume positively correlates with the memory and executive functioning scores while the function of processing speed was negatively affected by WMH and total CSF but positively correlates with the total brain volume. These data could indicate the presence of an association between the structural brain abnormalities and cognitive impairments in patients with T2DM free of clinically significant cerebrovascular disease.

The study was performed under the grant from EFSD Collaborative Program “New Horizons”.

[P5] HIGH FAT DIET-FED FEMALE C57BL6/J MICE DEVELOP EARLY PERIPHERAL NEUROPATHY IN THE ABSENCE OF SYSTEMIC INSULIN RESISTANCE

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Aim: Peripheral neuropathy (PN) is a common complication of observed in patients with impaired glucose tolerance and type 2 diabetes (T2D). As female mice fed a high fat diet (HFD) display a degree of protection against HFD-induced metabolic changes we hypothesized that HFD-fed female mice would also exhibit resistance to developing PN.

Methods: Male and female C57BL6/J mice were fed either a standard diet (10% kcal fat; CTRL) or a high fat diet (60% kcal fat; HFD) from 5wk. At 16wk, 24wk and 36wk,neuropathy phenotyping was performed on all groups complemented with longitudinal metabolic assessment including insulin tolerance testing (ITT). Neuropathy phenotyping consisted of hindpaw latency to heat stimulus, motor and sensory nerve conduction velocity (NCV), and terminal intraepidermal nerve fiber (IENF) counts.

Results: Assessment of insulin resistance through ITT demonstrated that female HFD mice exhibited relatively normal insulin responsiveness early during the disease course while male HFD mice exhibited insulin resistance. Despite this, at 16wk female HFD mice displayeda similar patternof PN to that of their male counterparts with similar fold-changes in hindpaw latency, sensory and motor NCV.

Conclusion: Despite exhibiting resistance to HFD-induced metabolic changes female HFD mice display a robust peripheral neuropathy comparable to HFD-male mice. These data suggest that systemic insulin resistance does not contribute to PN. Current studies are investigating insulin signaling in the peripheral nerve of HFD-fed female mice.

[P6] A 2-YEAR PROSPECTIVE COMPARATIVE STUDY OF CHANGES IN SMALL FIBRE FUNCTION AND STRUCTURE IN SUBJECTS WITH DIABETES AND HEALTHY CONTROLS USING THE LDI_{FLARE} TECHNIQUE AND CORNEAL CONFOCAL MICROSCOPY METHODS

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Aim: The LDI (laser doppler imager) $_{FLARE}$ and corneal confocal microscopy (CCM) are established methods for assessing small fibre function (SFF) and structure (SFS) respectively. This prospective study determines whether either detects changes in small fibre integrity over 2yrs and if so whether these relate to common biomarkers.

Methods: 75 T_1DM patients (mean age ± SD = 41.3yr±14.9), with microangiopathy (MA+; n=43) and without (MA-; n=32), 78 with T_2DM [54.2yr±9.3; MA+ (n=45) and MA- (n=33)] and 75 healthy controls (HC 39.2±14.9) were followed for 2yrs. Baseline and annual tests included lipids, microalbuminuria, retinal screening, SFF by LDI_{FLARE}, SFS by CCM (nerve fibre density), neuropathy disability scores (NDS), and sural nerve amplitude (SNAP) and conduction velocity (SNCV). HbA_{1c} was measured 3 monthly.

Results: At 2yrs, LDI_{FLARE} size reduced in T_1DM by 2.12±8.37% (mean ± SD), in T_2DM by 2.38±7.80% but only 0.57±0.02% in HC ($p< 0.001$ each DM group vs HC). In T_1DM % reduction was greater in MA+ vs MA- groups ($p=0.02$) but not in T_2DM ($p=0.06$).No significant change from baseline was seen in any CCM parameter - T_1DM ($p=0.51$); T_2DM ($p=0.74$) & HC ($p=0.20$). However, there was a greater % reduction in CCM in T_1DM with MA+ vs MA- ($p=0.01$) but not in T_2DM ($p=0.17$).

On multivariate analysis, HbA_{1c} change correlated with % change in LDI_{FLARE} in T_1 and T_2 DM, ($p=0.001$ & $p=0.004$ respectively) and with % change in CCM ($p=0.001$ in both). In T_1 and T_2 DM and HC, % change in LDI_{FLARE} also correlated with triglyceride (TG) change [$p=<0.0001$; $p=<0.01$ & $p=0.0001$ respectively]. CCM change did not relate to TG in any group. SFF or SFS did not correlate with BMI, other lipids or blood pressure (BP). NDS, SNAP, SNCV did not significantly change in any group, or correlate with changes in HbA_{1c}, lipids or BP.

Conclusion: In conclusion, HbA_{1c} significantly affects SFF and SFS in T_1 and T_2 DM. In T_1 and T_2 DM and HC, TG also modulates SFF but not SFS. Long-term studies are required to determine whether such changes are predictive of later clinical DPN.

[P7] CHANGES IN SYMPATHOVAGAL ACTIVITY AND OBSTRUCTIVE SLEEP APNEA AFTER BARIATRIC SURGERY

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Background: Sympathovagal balance is often impaired in obese patients. During sleep, respiratory function is partially controlled by the autonomic nervous system. We aimed to investigate the changes in cardiac autonomic dysfunction (CAD) and obstructive sleep apnea syndrome (OSAS) after bariatric surgery.

Research design and method: Cardiac autonomic function tests were performed in 130 massively obese patients before bariatric surgery and after. Among the 130 patients, 19 were reassessed after surgery (follow-up group). CAD was diagnosed by recording heart rate response to lying-to-standing test and during deep breathing, and defined as at least one abnormal test (CAD+). Sympathetic activity was evaluated by measuring plasma norepinephrine and epinephrine at fasting and after an oral glucose challenge. OSA was evaluated with Epworth sleepiness scale and polysomnography if necessary.

Results: CAD was present in 64.6% of the patients before and 36.8% of those examined after surgery. OSAS was suspected in 42.5% before and 13.7% after surgery. Before and after surgery, suspected OSAS was higher among CAD+ (43.4% pre-op, 19.4% post-op) compared to CAD-patients (34.6% pre-op, 12.2% post-op) ($p<0.05$). In CAD+ patients, OSAS regressed from 43.4% before to 19.4% after surgery. In the follow-up group, CAD was present in 78.9% before surgery and regressed to 26.3% after surgery. Epinephrine and norepinephrine levels at fasting and after glucose were similar before and after surgery in CAD+ ($p>0.05$) and CAD- patients ($p>0.05$).

Conclusion: Weight loss after bariatric surgery is associated with an improvement of both vagal activity and OSAS without modification of sympathetic response.

[P8] ACCURATE AND EARLY DIAGNOSIS OF NEUROPATHY IN ROUTINE CLINICAL PRACTICE USING COMBINED LARGE AND SMALL FIBRE ASSESSMENTS

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Introduction: Lower limb amputations are increasing in UK, mainly due to the late detection of neuropathy. Recently, two point-of-care devices (POCDs), DPN-Check and Sudoscan, that are able measure large- fibre [sural nerve conduction velocity (SNCV) and amplitude (SA)] and small-fibre [sudomotor] functions respectively, have been developed. In a concurrent validity study we sought to investigate whether their combined use would result in better diagnostic performance than either on its own.

Materials and Methods: 160 subjects (57 type 1 diabetes, 65 type 2 diabetes and 38 healthy volunteers) underwent detailed clinical and neurophysiological assessments. Subjects were then grouped into "DPN" (Diabetic Peripheral Neuropathy) and "No-DPN" based on an overall neuropathy composite score (NIS(LL)+7tests). Combined SNCV and amplitude was used to define neuropathy using DPN-Check reference range. Sudomotor function was assessed by measuring foot Electrochemical Sweat Conductance (ESC) using Sudoscan. The concurrent validity of each individual POCD vs. combined performance of both POCDs for diagnosing DPN was assessed.

Results: There was no significant difference in age (mean age±SD years; No-DPN, 55.9±10.8; DPN 58.8±10; healthy volunteers 55.5±9.3). The area under the ROC curve for DPN-Check was0.848 (95% CI: 0.77-0.93) and for Sudoscan foot ESC was 0.79 (95% CI 0.71-0.88). The AUC for combined assessments was higher at 0.88 (95% CI 0.81-0.94). Moreover, the sensitivity and specificity of combining both tests (78.3% and 84.4%, respectively) had better diagnostic performance compared to either test on its own (DPN-Check 74.3% and 84.4%; Sudoscan76.1% and 69.7%).

Conclusions: Combined assessment using DPN-Check and Sudoscan that take about 5 minutes each to perform has better diagnostic utility than either POCD on its own. As DPN involves both large and small nerve fibres the combined annual assessment of both may be important in routine clinical practice in order to detect the disease early when multi-factorial metabolic treatments are likely to work.

[P9] NICLOSAMIDE ETHANOLAMINE UNCOUPLING TREATMENT DOES NOT PREVENT THE DEVELOPMENT OF DIABETES, PERIPHERAL NEUROPATHY OR SENSORY NEURON METABOLIC REPROGRAMMING IN BKS-DBDB MICE

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Aim: Hyperglycemia and hyperlipidemia contribute to diabetic peripheral neuropathy (DPN) in type 2 diabetes (T2D). Niclosamide ethanolamine (NEN) attenuatesthis diabetic phenotype in db/db mice (). The current study investigated the effect of NEN treatment on the development of T2D, DPN, and dorsal root ganglia (DRG) neuron bioenergetic dysfunctionin db/db mice.

Methods: Male BKS-db/db and db/+controls were fed control or NEN-containing chow (AIN-93M ± 1500 ppm NEN) from 6-12 wk. Data were collected at 12 wk. T2D was assessed via body weight, fasting blood glucose, and glycated hemoglobin. DPN was assessed via sensory/motor nerve conduction velocities (NCVs), and thermal hindpaw withdrawal latencies. Mitochondrial function was determined in primary DRG neurons using the Seahorse XF Analyzer.

Results: Unexpectedly, NEN treatment did not lower body weight, and exacerbated hyperglycemia in db/db mice. Treatment did not prevent NCV deficits, and induced thermal hyperalgesia in db/db mice. Mitochondrial oxidative metabolism was down regulated in db/db DRG neurons, with decreased resting ATP production (maintained coupling), and decreased maximal and spare respiratory capacities. Treatment uncoupled mitochondria in db/+ and db/db neurons, and potentiated the db/dbmetabolic reprogramming.

Conclusions: NEN treatment did not improve T2D or DPN phenotypes in db/db mice, suggesting earlier intervention may be required (1). Whether metabolic reprogramming in db/db neurons is a compensatory mechanism to limit reactive oxygen species generation during increased substrate availability, or whether compromised ATP production contributes to nerve dysfunction remain to be determined. However, the data suggest that directly targeting neuronal mitochondria with uncoupling drugs may worsen DPN.

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1. Tao H, Zhang Y, Zeng X, Shulman GI, Jin S: Niclosamide ethanolamine-induced mild mitochondrial uncoupling improves diabetic symptoms in mice. Nat Med 20:1263-1269, 2014

[P10] USE OF CORNEAL NERVE FIBRE LENGTH (CNFL) FOR DIABETIC NEUROPATHY IDENTIFICATION IN OLDER PATIENTS WITH LONGSTANDING TYPE 1 DIABETES

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Aim: CNFL is a valid screening tool for diabetic neuropathy, but has not been systematically evaluated in older adults with longstanding diabetes. We aimed to explore the diagnostic performance of CNFL in a cohort with ⩾50 years of type 1 diabetes (T1D).

Methods: As part of the Canadian Study of Longevity in Diabetes where 150 subjects will undergo deep-phenotyping procedures, to date 48 T1D and 46 age- and gender-matched non-diabetic controls underwent evaluation of symptoms, signs, and electrophysiology to define neuropathy. CNFL was determined by corneal confocal microscopy and diagnostic performance was determined by receiver operating characteristic curves.

Results:T1D participants were mean age 66±7y, had median diabetes duration 54[IQR 52-59]y, 28(58%) female; non-diabetic controls were age 65±8y and 32(70%) female. 41(85%) of T1D participants met neuropathy criteria. Mean sural nerve amplitude for non-diabetic controls (9.5±5.5μV) was similar to T1D without neuropathy (8.4±2.8μV, p=0.83)and was lowest for T1D with neuropathy (3.4±1.6μV, p<0.001 for both comparisons). Mean CNFL for non-diabetic controls (20.0±5.7mm/mm^2) was similar to T1D without neuropathy (18.8±8.9mm/mm^2; p=0.74) and was lower for T1D with neuropathy (9.5±5.4mm/mm^2; p<0.001 for both comparisons). In T1D, area under the curve was 0.81, optimal threshold 13.7 mm/mm^2, sensitivity 78%, specificity 86%.

Conclusion: The diagnostic performance – even the optimal threshold value – for CNFL in older adults with longstanding T1D appears to parallel that observed in younger patients with shorter duration. As age-related changes in CNFL do not appear to impair diagnostic validity, CNFL screening protocols may be applied to broad T1D populations.

[P11] METFORMIN TREATMENT MAY IMPAIR ORTHOSTATIC BLOOD PRESSURE RECOVERY

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Aims: Metformin has been associated with both neuroprotective and neurodegenerative attributes.We aim to investigate the effect of metformin in combination with insulin treatment ondiabetic peripheral neuropathy (DPN) and cardiovascular autonomic neuropathy (CAN).

Methods: The study is a substudy of the CIMT trial, a randomized placebo-controlled multicenter study where 412 patients with type 2 diabetes (HbA_{1c}>7.5% (⩾58 mmol/mol)), were randomized to 18 months of one gram metformin twice daily or placebo in addition to an open-labelled insulin treatment. Outcomes wereorthostatic blood pressure (BP) (30, 90 and 180 seconds after standing),changes in heart rate during deep breathing (beat-to-beat)and vibration detection threshold (VDT).

Results: 15% of all patients had orthostatic hypotension at baseline. 30 seconds after standing systolic BP drop increased by 3.1 mmHg (95% CI 0.5;5.7, p=0.02) and diastolic BP drop increased borderline significantly by 1.2 mmHg (95% CI -0.1;2.4, p=0.06).No other significant findings were seen (figure 1). Beat-to-beat measures decreased insignificantly in the metformin group by1.1 beats per minute (95% CI -2.4;0.1, p=0.07).Non-significant change between groups in VDT were -0.4 volt (95% CI -1.8;1.1, p=0.61).

Conclusions: Metformin in combination with insulin did not improve measures DPN or CAN. However our resultscould indicate thatmetformin may influence orthostatic blood pressure response. These changes may be mediated by changes in autonomic function as metformin treatment caused a trend toward a decreased in beat-to-beat measures at follow-up. Our findings needconfirmation in trails with CAN as primary end point.

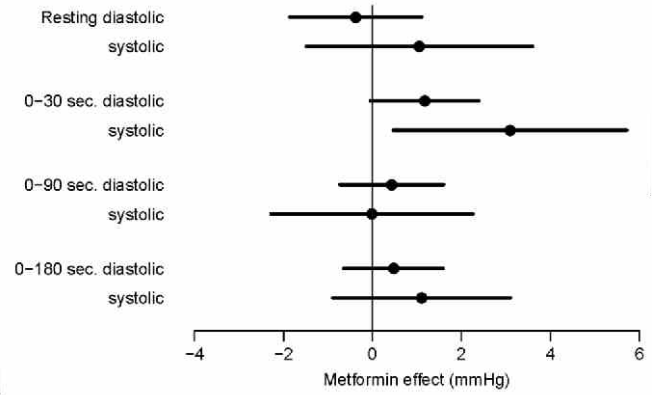

Figure 1.
Summary of the effect of 18 month 1 gram metformin twice daily treatment vs. placebo on resting blood pressure and orthostatic blood pressure measurements.

[P12] PATIENTS WITH EXTREME DURATION TYPE 1 DIABETES T1DM SHOW PROTECTION FROM SMALL FIBRE NEUROPATHY(SFN) DETECTED USING CORNEAL CONFOCAL MICROSCOPY (CCM) AND SKIN BIOPSY

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Aim: To assess the severity and progression of neuropathy in patients with extreme duration (>50 years) T1DM (medallists) compared to T1DM patients awaiting simultaneous pancreas and kidney transplantation (SPK).

Methods: 34 medallists (diabetes duration(DD)-56.1±0.8 yrs) and 36 patients with end stage renal failure awaiting SPK (DD-32.3±1.9 yrs) and 19 control subjects underwent detailed assessment of neuropathy at baseline and annually over 3 years.

Results: Comparing the 3 groups (medallists v SPK v control): Neuropathy disability score (P=0.84), VPT (P=0.27), Peroneal Velocity (P=0.12), Peroneal Amplitude (P=0.93) and warm perception threshold (P=0.12) were comparable between the medallists and SPK. However, IENFD (P=0.05), corneal nerve fibre density (CNFD), branch density (CNBD)(P=0.05) and fibre length (CNFL)(P=0.03) showed significant protection in medallists. HbA1c (P=0.75), cholesterol (P=0.06), and triglycerides (P=0.99) were comparable, but HDL (P=0.003) was significantly higher in medallists. Over 3 years the medallists showed no significant change in any measure of neuropathy.

	Control	Medallist	SPK	P-Medallist v control	P-Medallist v SPK
NDS(0-10)	1.2±0.3	5.6±0.5	5.2±0.6	<0.001	0.843
VPT(volts)	9.7±1.6	25.5±2.3	20.9±2.2	<0.001	0.272
PeronealAmplitude(mV)	4.9±0.3	2.5±1.2	1.2±0.3	<0.001	0.932
PeronealVelocity(m/s)	45.7±0.7	33.7±1.7	31.0±1.8	<0.001	0.122
Cold Threshold($^{\circ}$C)	27.6±0.5	22.3±1.5	16.8±1.9	<0.001	0.112
Warm Threshold($^{\circ}$C)	38.0±0.7	41.1±1.3	43.5±0.9	0.002	0.115
IENFD(no./mm)	8.8±1.0	4.1±0.9	1.8±0.6	0.016	0.05
CNFD(no./mm^2)	28.5±1.8	13.6±1.4	8.7±0.9	<0.001	0.018
CNBD(no./mm^2)	33.4±3.3	16.2±2.6	9.1±1.5	<0.001	0.047
CNFL(mm/mm^2)	16.6±0.9	9.3±0.8	6.9±0.5	<0.001	0.028

Conclusion: Medallists showed a significant protection from SFN compared to T1DM patients awaiting SPK and have ~20 years greater duration of diabetes. However, medallists had a higher HDL-C.

[P13] WITHDRAWN

[P14] CORNEAL CONFOCAL MICROSCOPY (CCM) DETECTS AN IMPROVEMENT IN SMALL FIBRE NEUROPATHY AFTER BARIATRIC SURGERY IN OBESE SUBJECTS WITH TYPE 2 DIABETESMELLITUS (T2DM)

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Aim: To determine the effect of bariatric surgery on neuropathy in obese subjects.

Methods: 32 morbidly obese subjects underwent a comprehensive assessment of large and small fibre neuropathy at baseline and 12 months post bariatric surgery.

Results: 12 months after bariatric surgery, there was a significant improvement in BMI(52.5±1.9 v 35.9±1.7, p<0.0001), HbA1c(50.7±3.1 v 36.7±1.1, p<0.0001), and systolic blood pressure(133.9±3.7 v 123.2±3.0, p=0.002).There was a significant improvement in Neuropathy Symptom Profile(5.2±1.1 v 0.7±0.2, p<0.0001), Neuropathy Disability Score (2.2±0.5 v 0.9±0.5, p=0.006), corneal nerve fibre density(CNFD) (23.0±1.5 v 26.5±1.4, p=0.03), branch density (CNBD) (31.6±3.7 v 39.0±3.3, p=0.04) and fibre length(CNFL) (14.2±0.6 v 15.8±0.8, p=0.04),but no change in other parameters.

At baseline, subjects with (n=15) and without (n=17) T2DM, had comparable CNFD (23.1±2.2 v 22.8 1.6, p=0.6), CNBD (35.9±5.2 v 24.4 ± 3.9, p=0.8) and CNFL (14.4 ± 0.9 v 13.9±0.8, p=0.6). There was a significant improvement in those with T2DM: CNFD(23.1±1.0 v 28.0±1.8, p=0.03), CNBD(35.9±5.2 v 45.5±3.9, p=0.04), CNFL(14.4±0.9 v 16.9±1.1, p=0.007), but not in those without T2DM: CNFD(22.7±1.6 v 23.9±1.8, p=0.5), CNBD (24.44 4.0 v 28.6±3.9, p=0.5), CNFL (13.9±0.8 v 13.8±0.9, p=1.0).

Conclusion: Bariatric surgery leads to an improvement in symptoms and deficits, which can be identified using CCM, but not electrophysiology or QST. Obese subjects with and without T2DM have equivalent amount of corneal nerve damage at baseline, which only improves in those with T2DM. These data strengthen the argument that CCM is a surrogate marker for identifying an early improvement in neuropathy, advocating its use in clinical trials of new therapies for diabetic neuropathy.

[P15] INVESTIGATING FOR INFLAMMATORY MARKERS IN CORNEAL NERVES OF OBESE PATIENTS

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Immune mechanisms have been proposed to play a role in the development at obesity, type 2 diabetes and diabetic neuropathy. The aim of the present study is to assess the role of Langerhans cells (LCs) and Dendritic cells (DCs) as markers of inflammatory in the nerves layer of the cornea in obese patients with and without diabetes mellitus.

Method: 40 obese patients and 20 healthy control subjects underwent full neurological examinations including evaluation of neuropathic symptoms, electrophysiology, quantitative sensory testing, autonomic function tests and corneal confocal microscopy.

Patients stratified into 2 groups: those with diabetes (n= 20; Age= 54±3; BMI= 48.2±3) and those without diabetes (n=20; Age=47±2.3; BMI=50±4). Nerve conduction assessments at Sural and Peroneal nerves did not show any significant difference and they were at the normal range. Quantitative sensory testing showed alterations but it was not at the abnormal level. Small fibre assessments with measuring corneal nerve fibre density (CNFD) ($P=0.001$), branch density (CNBD) ($P<0.001$), length (CNFL) ($P<0.0001$) were significantly reduced. There was no significant difference at corneal nerve parameters between obese patients with and without diabetes. Presence and density of Langerhans cells (LCs) at the nerve fibre layer of the cornea have been measured. The density of LCs was approximately four times higher in obese patients compare to control subjects ($P=0.002$) and higher in those without diabetes compare to diabetes subjects. There was a significant correlation between LCs density and CNFD ($P=0.03$); CNBD ($P=0.008$) and CNFL ($P=0.01$).

These novel findings suggest the potential role of inflammatory markers in obesity and the role of CCM for non-invasive evaluations of these markers.

[P16] CORNEAL CONFOCAL MICROSCOPY: A PROGNOSTIC MARKER FOR STROKE OUTCOME

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Background: Stroke is a leading cause of neurological disability, death and dementia. CT and MRI identify white matter lesions prior to a stroke and overt cerebral infarction after a stroke. Corneal Confocal Microscopy (CCM) is a surrogate end point for peripheral (diabetic neuropathy, CIDP, CIPN) and central (Parkinson's disease, ALS) neuronal damage.

Aim: To determine if CCM can act as a surrogate for pre-stroke cerebral neuronal damage.

Methods: 44 patients with MCA stroke were classified according to the National Institutes of Health Stroke Scale (NIHSS) into those with minimal (NIHSS $\leqslant$ 4) and severe (NIHSS > 4) deficits and underwent CCM to quantify corneal nerve fiber density (CNFD), corneal nerve branch density (CNBD), corneal nerve fiber length (CNFL) and corneal nerve fiber tortuosity (CNTC).

Results: 28 patients (age: 49.9±2.2 yrs) had a NIHSS $\leqslant$ 4 and 16 patients (age 51.6±3.5yrs) had a NIHSS > 4. There were no significant differences in HbA1c (6.5±0.5 v 7.1±0.4, P=0.33), total cholesterol (5.1±0.6 v 4.6±0.2, P=0.33), HDL (1.0±0.0 v 1.2±0.2, P=0.49), LDL (3.4±0.5 v 2.9±0.2, P=0.23), triglycerides (1.6±0.2 v 1.4±0.1, P=0.61) or systolic blood pressure (152.5±6.2 v 165.4±6.6, P=0.18) between both groups. However, stroke patients with NIHSS > 4 had a lower CNFD (P = 0.002) and CNBD (P = 0.026) with increased CNTC (P = 0.04) when compared to patients with NIHSS $\leqslant$ 4.

Parameter	NIHSS $\leqslant$ 4 (Mean ± SEM)	NIHSS >4 (Mean ± SEM)	P Value
Number of Patients	28	16	
Age (years)	49.92 ± 2.19	51.63 ± 3.54	0.667
CNFD (no./mm^2)	28.62 ± 1.16	22.67 ± 1.28	0.002
CNBD (no./mm^2)	92.94 ± 6.45	70.07 ± 6.64	0.026
CNFL (mm/mm^2)	24.94 ± 0.99	21.87 ± 1.24	0.063
CNFT (TC)	0.10 ± 0.01	0.12 ± 0.01	0.048

Conclusion: We propose a corneal confocal predictor index (CPi) for patients, likely to develop greater disability following an MCA stroke, paving the path towards 'personalized medicine'.

[P17] AGREEMENT BETWEEN CLINICAL SCORES OF DIABETIC NEUROPATHY AND NERVE CONDUCTION STUDIES IN ELDERLY TYPE 2 DIABETIC PATIENTS – A CROSS SECTIONAL STUDY

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Aim: We aim to determine the agreement between clinical scores of diabetic neuropathy (DN) and nerve conduction studies (NCS) in elderly patients with type 2 diabetes.

Methods: 121 participants of the ten-year clinical follow-up of the ADDITION-Denmark study underwent NCS and examination using Michigan Neuropathy Screening Instrument (MNSI) and Toronto Clinical Scoring System (TCSS). Presence of DN was based on findings from the NCS. MNSI was considered abnormal if either the questionnaire score was=4 or/and the examination score was=2.5. TCSS was considered abnormal with a score=5. The prevalence of DN was calculated for MNSI, TCSS and NCS, subsequently the joint prevalence was presented in a Venn diagram. Kappa coefficients (κ) of the agreements were computed.

Results: 78 (64%) of participants were men, mean age was 70 years (SD:6.1), mean diabetes duration was 12 years (SD:1.9).30 (25%) participants had DN based on the NCS. MNSI and TCSS were abnormal in 22 (18%) and 25(21%) participants, respectively. In 9% of the participants, MNSI and NCS showed agreement (κ=0.27), an odds ratio of 4.2 (CI:1.6;11.0) for DN when MNSI positive. Similar in 9% of the participants, TCSS showed agreement with NCS (κ=0.23), an odds ratio of 3.2 (CI:1.3;8.0) for DN when TCSS positive. In 13% of participants, MNSI and TCSS showed agreement (κ=0.60) (see fig. 1).

Conclusion: The prevalence of DN derived from MNSI and TCSS was almost identical, although a different set of participants were identified, the agreement was good. There was only a moderate agreement between MNSI, TCSS and NCS.

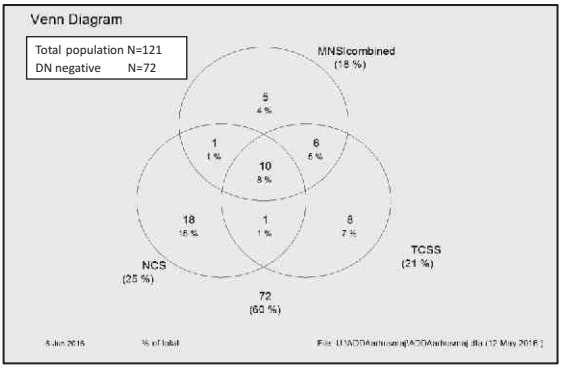

Fig. 1

[P18] SENSITIVITY OF VARIOUS DIAGNOSTIC MARKERS FOR EARLY DETECTION OF DIABETIC NEUROPATHY

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Aim: To determine the optimal diagnostic operating characteristics for diabetic neuropathy in cross-sectional analysis for various neurological examinations

Method: 274 Diabetic patients including 131 T1DM (60% male; Average age 46.5; Duration of Diabetes: 26.8; BMI 26.2; HbA1c: 8.3%) and 143 T2DM (64% male; Average age 63; Duration of Diabetes: 13; BMI 31.7; HbA1c: 7.7%) and 84 age and sex matched healthy control subjects studied in details with battery of neurological examinations including symptoms, neuropathy deficit (NDS), electrophysiology, quantitative sensory testing, autonomic neuropathy, IENFD, corneal sensitivity (NCCA) and corneal confocal microscopy.

Results: 48% of patients had neuropathy (NDS >3)(63 T1DM (48%) and 70 T2DM (49%)). All markers except for NCCA showed a statistically significant diagnostic ability with AUC ranging from 0.58 to 0.81. The best marker was VPT. Using a diagnostic criterion VPT > 11 gave sensitivity and specificity values of 75% and 71% respectively, with a PPV of 70% and NPV of 75%. IENFD <6 gave sensitivity and specificity values of 79% and 44% respectively, with a PPV of 54% and NPV of 70%.CNFD gave sensitivity and specificity values of 72% and 45% respectively, with a PPV of 55% and NPV of 63%. CNFL showed sensitivity and specificity values of 71% and 39% respectively, with a PPV of 52% and NPV of 59%. There was non-significant differences between sensitivity of the various tests between type 1 and type 2 diabetic patients.

Conclusion: The diagnostic validity of various neurological markers for early detection of diabetic neuropathy showed most of neurological markers perform equally which is perhaps due to lack of valid standard reference point for definition of neuropathy.

	AUC (95%CI)	Significance	Optimal cut-off	Sensitivity	Specificity	PPV	NPV
NSP	0.70 (0.63,0.76)	P<0.001	> 2	73%	56%	61%	69%
Left sural amp	0.68 (0.62,0.75)	P<0.001	< 8	71%	61%	61%	71%
Left sural velocity	0.70 (0.63,0.76)	P<0.001	< 46	76%	50%	57%	71%
Left peroneal amp	0.70 (0.64,0.77)	P<0.001	< 3.5	73%	56%	60%	70%
Left peroneal velocity	0.67 (0.61,0.74)	P<0.001	< 44	72%	51%	57%	67%
VPT	0.81 (0.75,0.86)	P<0.001	> 11	75%	71%	70%	75%
CPT	0.75 (0.70,0.81)	P<0.001	< 27	76%	55%	60%	72%
WPT	0.71 (0.65,0.78)	P<0.001	> 39	81%	50%	59%	75%
HRV average	0.79 (0.71, 0.87)	P<0.001	< 9	77%	73%	72%	78%
DB-HRV	0.78 (0.70,0.86)	P<0.001	< 17	76%	74%	72%	78%
IENFD	0.66 (0.57,0.76)	P=0.001	< 6	79%	44%	54%	70%
NCCA	0.57 (0.50,0.64)	P=0.06	> 0.5	71%	38%	51%	59%
CNFD	0.64 (0.57,0.70)	P<0.001	< 28	72%	45%	55%	63%
CNBD	0.58 (0.51,0.64)	P=0.033	< 70	77%	30%	51%	58%
CNFL	0.60 (0.53,0.66)	P=0.007	< 22	71%	39%	52%	59%
CNFT	0.59 (0.52,0.65)	P=0.014	> 16	79%	38%	54%	65%

Table 1. Sensitivity and specificity of various neurological diagnostic markers

[P19] REDUCED CUTANEOUS MICROVASCULAR REPONSE TO TOPICAL CAPSAICIN EVALUATED BY IN VIVO REFLECTANCE CONFOCAL MICROSCOPY AS A POTENTIAL MARKER FOR DIABETIC NEUROPATHY

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Introduction: Altered cutaneous neurovascular reactivity to capsaicin might reflect the dysfunction of small diameter nerve fibers, considered to be first impaired in diabetic neuropathy. In vivo reflectance confocal microscopy (RCM) is a novel imaging technique that enables the noninvasive evaluation of the parameters of cutaneous microvasculature within local capsaicin-induced inflammation.

Aim: The aim of this preliminary study is to assess the vasodilator response of skin microvasculature to topical capsaicin through means of in vivo RCM in patients with diabetes mellitus with and without diabetic neuropathy.

Methods: In this study 14 subjects with diabetes mellitus and 10 healthy volunteers were included. Following clinical and electrophysiological examination, diabetic subjects were distribuited either to the Diabetes with Neuropathy (DN) group (n=8) or to the Diabetes without Neuropathy (D) group (n=6). In vivo RCM using a wave lenghth of 785 nm was used to evaluate the dermal microvasculature for all subjects, before and after 30 minutes of topical capsaicin 1%.

Results: In vivo RCM allowed the evaluation of the neurovascular reactivity changes and showed that a substantially reduced vasodilatory response after capsaicin application in the DN group compared to healthy volunteers. However, when comparing the D group with healthy volunteers no significant differences were observed in the microvascular parameters after 30 minutes of topical capsaicin.

Conclusions: In vivo RCM emphasized a reduced cutaneous vasodilator response to topical capsaicin only in subjects with diabetic neuropathy, suggesting that nerve fibres imparment could explain these observation. Therefore, assessment of the cutaneous neurovascular reactivity though in vivo RCM might be used for the detection of nerve fibre dysfunction in patients with diabetes.

[P20] PREVALENCE OF AUTONOMIC NEUROPATHY IN THE METABOLIC SYNDROME COMPARED TO IMPAIRED GLUCOSE TOLERANCE

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Aim: Autonomic neuropathy is a well recognized complication of type 2 diabetes that is associated with increased morbidity and mortality. However, the presence of autonomic dysfunction has not been well characterized in the metabolic syndrome, which is a combination of medical conditions that increase the risk of developing cardiovascular disease and diabetes. The current study compares the prevalence of autonomic neuropathy in a group of patients with the metabolic syndrome (MetS) compared to a group with impaired glucose tolerance (IGT).

Methods: Cross-sectional data was collected on subjects with the MetS (n=63) and IGT (n=28) who had undergone autonomic testing (the survey of autonomic symptoms (SAS), tilt table, heart rate response to deep breathing, valsalva, and Q-sweat).

Results: Overall the prevalence of autonomic neuropathy was 40.6% in the two groups and 70.6% of subjects had symptoms of autonomic neuropathy on the SAS. There was not a significant difference in the prevalence of autonomic neuropathy, performance on individual tests of autonomic function, or the proportion of subjects with an abnormal SAS between subjects with the MetS compared to those with IGT only.

Conclusions: There is an increased prevalence of autonomic neuropathy in both patients with IGT and the MetS. The prevalence of autonomic neuropathy was not statistically different between subjects with MetS compared to those with IGT.

[P21] IMPLEMENTATION OF CORNEAL CONFOCAL MICROSCOPY FOR SCREENING DIABETIC NEUROPATHY IN PRIMARY CARE: A FEASIBILITY AND ACCEPTABILITY STUDY

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On behalf of CLAHRC (ENA) Team:
CLAHRC Team: R. Spencer, C. Soiland-Reyes, S. Howard, S. Cotterill, C. Perry, M. Bresnen, R. Boaden, M. Tavakoli

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Background: Diabetic Peripheral Neuropathy (DPN) is a common and costly complication of diabetes. Early screening and diagnosis is critical because patients with neuropathy are at greater risk of foot ulcerations. Corneal Confocal Microscopy (CCM) is a relatively new ophthalmic technique which can detect DPN in its earliest stages in a rapid, non-invasive and sensitive way.

Objectives: Investigate the feasibility and acceptability of CCM in primary care optometry practices to screen for DPN during routine diabetic retinopathy screening.

Methods: Four primary care private optometry practices were recruited to a cross-sectional observational study. Optometrists were supplied with CCM (HRT III) equipment and trained over 3 days' workshop. 450 diabetic patients (95% T2DM)were assessed with CCM alongside routine retinopathy screening over 6 months period. Optometrists sent 6 CCM images per patient to the leading centre for quantification of neuropathy.

Patients were assessed for history of foot problems, neuropathy, pain, retinopathy and laser treatments. Questionnaires, qualitative interviews and local records were analysed to assess feasibility and acceptability to optometrists and patients. The role of ethnicity and socio-economic factors also considered.

Results: CCM test were successfully completed for 95% of patients. Overall 97% of patients reported CCM is acceptable, 92% reported it was comfortable, and 97% would agree to do the test again. Optometrists reported the test was easy to perform in 60% of cases, and impossible in 4% of cases due to patient characteristics.

Implications: This was the first clinical study of CCM performed worldwide. This study demonstrated the potential ability and future implementation of CCM for screening DPN in primary care alongside retinopathy programme.

[P22] THE EFFECT OF OMEGA-3 SUPPLEMENTATION ON DIABETIC NEUROPATHY: RESULTS FROM A CLINICAL PILOT TRIAL

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Aim: Diabetic sensorimotor peripheral neuropathy (DSP) is the leading complication in diabetes mellitus (DM). Omega-3 polyunsaturated fatty acids (N-3 PUFA) are integral to the development and maintenance of healthy nerve tissue but have not yet been investigated for their ability to maintain nerve structure and function in DSP.

Methods: Individuals with type 1 (T1DM) and evidence of DSP as determined by a Toronto Clinical Neuropathy Score (TCNS) $\geqslant 1$ were recruited to a 1-year open-label trial of mammalian N-3 PUFA supplementation (10 mL/d; 750 mg EPA, 560 mg DPA and 1020 mg DHA; Auum Inc.) (NCT02034266). The primary outcome is the 1-year change in corneal nerve fibre length (CNFL) measured by in vivo corneal confocal microscopy (IVCCM). Secondary outcomes include nerve conduction studies and quantitative sensory testing.

Results: 40 patients (53% female), aged (mean±SD) 48±14, BMI 28.1±5.8 with diabetes duration of 27±18 years were enrolled. TCNS ranged from no to moderate neuropathy, while 27 (70%) had diagnosed DSP. Mean IVCCM CNFL was 12.0±5.2 mm/mm^2, while normal is thought to be >14.9 mm/mm^2. Seven patients (18%) without DSP were identified as at risk of future DSP with CNFL <14.9 mm/mm^2. Median sural and peroneal nerve conduction velocities were 43.8±11.0 and 38.8±6.6 m/sec.

Conclusion: The baseline characteristics of the 40 participants enrolled in this trial show that they have a broad spectrum of DSP and display evidence of both small and large fibre nerve dysfunction. The trial will finish in July 2016 and results and clinical implications will be presented at NeuroDiab 2016.

[P23] CORRELATION BETWEEN CHRONIC INFLAMMATORY DEMIELINATING POLYNEUROPATHY AND DIABETES MELLITUS

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Aim: Chronic inflammatory demyelinating polyradiculoneuropathy (CIDP) is an entity that describes a group of related neuropathies, all having chronicity, demyelination, inflammation, and immune-mediation in common. CIDP is often associated with other systemic diseases and also seems to be particularly frequent in patients with diabetes mellitus (DM). The connection with diabetes however has recently been challenged.

Methods: We report the case of a 43 year old male patient, diagnosed with Diabetes Mellitus type I four years ago and with diabetic polyneuropathy since two years. The patient complained of progressively intense hyperesthesia, hyperpathia and allodynia of the limbs, fatigue and insomnia for the past two years which prompted the suspicion of an associated disease. Work up included laboratory studies, lumbar puncture and electrophysiological studies (EMG).

Results: Lumbar puncture showed increased protein concentration. EMG findings showed multifocal conduction block, prolonged distal latencies, nerve conduction slowing and dispersion of compound muscle action potential in the examined nerves. We also excluded other aetiologies like Lyme disease, vasculitis, paraneoplasic neuropathy, vitamine B12 and folic acid deficiency, syphilis, Hepatitis C, HIV, paraproteinemia, sarcoidosis, heavy metal intoxications.

Conclusions: The clinical findings and workout showed that CIDP was associated to DM. The association of CIDP with diabetes, therefore, remains an unresolved question that requires large prospective studies.

[P24] NOVEL ROLE FOR THE LIPID-SENSOR LXR (LIVER X RECEPTOR) IN PERIPHERAL SENSORY NEURONS

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Our recent studies showed that the peripheral sensory neurons system - including the nodose ganglia of the vagus nerve and the dorsal root ganglia- could be sensitive to exogenous lipids (Mansuy-Aubert et al., 2015). Unique omega 6 rich diet can ameliorate painful diabetic peripheral neuropathy of diabetic patient. Strong Correlations between dyslipidemia and diabetic painful neuropathies have also been unmasked. These findings strongly suggest that lipids cues can maintain and/ alter peripheral neurons, however, the cellular and molecular basis underlying these recent observations are unclear.

Our recent work suggest that sensory peripheral neurons expressing Nav1.8 can directly respond to cholesterol and fatty acids via the nuclear receptor LXR (Liver X receptor). We showed that the absence of LXR from sensory neurons using tissue deletion specific mice model lead to aberrant sensory nerve structure and altered sciatic nerve function exacerbated when mice are fed a diet rich in saturated fat and cholesterol called Western-Diet. LXRa and b are ligand-activated transcription factors that bind metabolites of cholesterol and fatty acid. Whereas the function of LXRa and b (LXRa/b) in regulating cholesterol efflux (in liver, intestine, adipose tissue, or macrophages) and triglyceride synthesis (in liver) is well characterized, the regulation of LXRa/b in small sensory neurons, their target genes and their physiological function is unknown. Our research on lipid sensors in peripheral neurons may open-up avenue in the understanding of lipids effects on peripheral neurons underlying so-called Diabetic neuropathies.

[P25] WITHDRAWN

[P26] THE RELATIONSHIP BETWEEN INDICES OF OXIDATIVE STRESS AND THE MANIFESTATIONS OF DIABETIC DISTAL POLYNEUROPATHY IN PATIENTS WITH TYPE 2 DIABETES AND NAFLD

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Aim: to study the relationship of some indicators of oxidative stress (diene conjugates (DC) and 8-iso-prostaglandin) and manifestations of diabetic distal polyneuropathy (DDP) in patients with type 2 diabetes mellitus (T2DM) at various stages of nonalcoholic fatty liver disease (NAFLD).

Methods: 79 patients with T2DM at various stages of NAFLD (steatosis – 49, steatohepatitis – 17, fibrosis – 13) and DDP were examined. DC level were determined by spectrophotometry using molar absorption coefficient. The 8-iso-prostaglandin content in serum was determined by enzyme-linked immunosorbent assay. The level of pain was determined by Visual Analogue Scale. The vibration sensitivity is determined by the tuning-fork.

Results: A significant ($p<0.05$) increase of LPO-DC generation in patients with NAFLD at a stage of steatosis (304.7±6.3 nmol/l), steatohepatitis (457.3±2.25 nmol/l) and fibrosis (751.9±9.7 nmol/l) compared to patients without liver disease (212.4±2.1 nmol/l) was revealed. Level of 8-iso-prostaglandin remained stable at all stages of NAFLD in T2DM patients (221.9±109.1pg/ml with steatosis; 121.5±33.7 pg/ml with steatohepatitis; 222.0±11.4 pg/ml with fibrosis) but was significantly higher than in patients without liver disease ($p<0.05$). Pain intensity was 4 points in steatosis, 6 in steatohepatitis and 7 in fibrosis. Vibration sensitivity level was 4.1 points in steatosis, 3.8 in steatohepatitis and 3.4 in fibrosis. The direct relation between DC level and intensity of pain ($r=0.35$; $p=0.04$), and a negative correlation with the level of vibration sensitivity ($r=-0.32$; $p=0.04$) were revealed.

Conclusions: Such indicator of oxidative stress as a level of DC in patients with T2DM and NAFLD can be considered as a marker for the development and progression of DDP depending on the stage of NAFLD.

[P27] INSULIN ENHANCES AMPK ACTIVITY AND MITOCHONDRIAL FUNCTION IN DRG NEURONS

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Aim: There is down-regulation of AMP-activated protein kinase (AMPK) in dorsal root ganglia (DRG) in animal models of type 1 and type 2 diabetes. This may trigger mitochondrial dysfunction and enhance axonal degeneration in diabetes. We hypothesized that loss of insulin signaling in diabetes contributes to loss of AMPK activity in DRG.

Methods: DRG neuron cultures were derived from control or STZ-induced type 1 diabetic rats. Neurons were treated with insulin (10 or 100nM) for short and long-term periods. Downstream genes of insulin signaling were inspected using Western blotting. In parallel, mitochondrial respiration was determined using the Seahorse machine.

Results: Insulin treatment at 10nM or 100nMfor 2-24h increased phosphorylation of AMPK (on T172), P70S6K and acetyl-CoA carboxylase (an endogenous target of P-AMPK) by 2-3-fold ($P<0.05$).Expression of components of mitochondrial Complexes were also raised ($P<0.05$). Similar results were found in control and diabetic cultures. Western blot results did not show any consistent change in expression for T-ERK, ß-actin, pAMPK-S485 and pAkt in response to insulin. Insulin at 10 or 100nM and for 2-6hraugmented mitochondrial oxygen consumption rate, with spare respiratory capacity raised 2-4-fold ($P<0.05$). This occurred in control and diabetic cultures. However, no significant alterations in any parameters were observed with short-term (0, 15, 30 and 60min) insulin treatment.

Conclusions: Insulin can directly enhance mitochondrial function, putatively mediated via activation of AMPK, in cultured rat DRG neurons. High glucose concentration can down-regulate AMPK in neurons, and now the deleterious effect of loss of insulin must also be considered.

[P28] OVER-EXPRESSION OF MUSCARINIC ACETYLCHOLINE TYPE 1 RECEPTOR CAUSES CYTOSKELETAL ABNORMALITIES AND DEFECTS IN MITOCHONDRIAL TRAFFICKING IN ADULT SENSORY NEURONS

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Aim: Muscarinic acetylcholine receptors are a subfamily of G protein-coupled receptor that regulate numerous biological pathways in the central and peripheral nervous systems. It has been shown in a non-mammalian system that neurotransmitters, such as acetylcholine, direct axonal growth during development. Modulation of these cholinergic pathways could be therapeutic for diabetic neuropathy in which sensory nerve terminals are depleted. We have shown that selective or specific muscarinic acetylcholine type1 receptor (M1R) antagonists can induce a dose-dependent elevation in neurite outgrowth. The exact mechanism of M1R-antagonist driven neurite outgrowth is not understood.

Method: To understand the biological function of M1R in peripheral neurons, we have over expressed GFP-M1R inprimary adult dorsal root ganglion (DRG) sensory neurons and studied the physiological as well as molecular consequences.

Results: M1R over expression caused significant ($p<0.005$) depletion of functional mitochondria at the growth coneand a subsequent decrease in neurite outgrowth ($p<0.0001$). The diminished abundance of mitochondria in axons was associated with discontinuity in theβ-tubulin cytoskeleton structure that, in turn, suppressed mitochondrial trafficking. The tubulin-associated cytoskeletal defect was corrected by treatment with muscarinic antagonistspirenzepine and muscarinic toxin 7 which increased coupling oftrimeric G proteinsto the M1R and also causeda sustained release of intracellular[Ca^{2+}]in neurites.

Conclusion: We propose the drug-induced enhancement of the M1R-G-protein complex occupancy and increased intracellular Ca^{2+}concentration coordinate to improve microtubule organization and augment mitochondrial trafficking. This novel mechanism involving M1R influences mitochondrial distribution in nerve terminals and controlsaxonal growth and regeneration.

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[P29] PERIPHERAL NERVE DISTRIBUTION IN PANCREATIC ISLET IN EXPERIMENTAL DIABETIC ANIMAL MODEL

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Aim: The change of sympathetic, parasympathetic and sensory nerve proportion in pancreatic islets has been unclear during diabetes progression yet. The relation and morphologic change of sympathetic, parasympathetic and sensory nerves in pancreatic islet are studied in normal and diabetes rat.

Methods: The pancreas of normal and STZ induced diabetes induced Sprague–Dawley (SD) rats (n = 4-5/group) were fixed by formalin and were dehydrated by sucrose. After cut by freezing microtome into 40 um thick sections, the tissues were stained with protein gene product 9.5, tyrosine hydroxylase and choline acetyltransferase for islet cell, sympathetic, parasympathetic and sensory nerves. All of the stained sections were imaged by confocal microscopy and the images were analyzed to area of sympathetic, parasympathetic and sensory nerves by pixel and calculated the ratio of parasympathetic to sympathetic ratio.

Results: There was no significant difference in the area of sensory and parasympathetic nerves area between normal and diabetic rat pancreatic islets, but the area of sympathetic nerve of diabetic rat was much higher than normal in pancreatic islet ($P<0.05$)The parasympathetic to sympathetic nerve density ratio of diabetic rat was smaller than normal control rats (24 vs 130).

Conclusions: This study demonstrated that sensory and parasympathetic nerve proportion was not different between diabetic and control animal model. However, sympathetic nerve density markedly increased in diabetic animal model.

[P30] NEURONAL OVER EXPRESSION OF SIRT1 PROTEIN TREATS DIABETIC NEUROPATHY

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Aim: NAD^+-dependent SIRT1/PGC-1alpha pathway is critical for regulating mitochondrial oxidative energy metabolism and is associated with neuronal protection. We tested if increasing the SIRT1protein levels in neurons would reverse diabetic neuropathy in a mouse model of type 2 diabetes mellitus (T2DM).

Methods: A doxycycline (DOX)-inducible neuron-specific SIRT1 over expression (SIRT1OE) C57BL6 mouse was generated. SIRT1OE was shut off by feeding DOX (200mg/kg) in the diet. Adult C57BL6 SIRT1OE-Off mice were fed a high fat diet (60% calories from fat) for two months until they developed neuropathy. SIRT1 expression was then activated (SIRT1OE-On, by stopping DOX in the diet but continued to feed HFD for a further two months, then neuropathy was measured. Control SIRT1-Onanimals were fed a control diet (18% calories from fat). Neuropathy endpoints were motor sciatic-fibular nerve conduction velocities (MCV), mechanical allodynia (MA), and intra epidermal nerve fiber density (IENFD). In the dorsal root ganglion neurons (DRG) neurons, NAD+ and SIRT1 protein levels were quantified.

Results: Both MA and MCV improvedin HFD mice when SIRT1 is activated ($P<0.001$ mice at 4 months compared to the 2 month time point). There was no change in control diet (CD) animals. The IENFD in HFD animals with SIRT1-Off was decreased but not in the SIRT1OE-Ongroup ($P<0.001$). In HFD-fed SIRT1OE-off mice, there was a decrease in the NAD^+, SIRT1and PGC-1alpha levels in DRG. SIRT1OE-Onnormalized these levels.

Conclusion: Activation of the SIRT1-PGC-1alpha pathway can reverse neuropathy in a model of T2DM.

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[P31] MECHANISMS UNDERLYING THE NEUROPROTECTIVE ACTIONS OF A NOVEL MESENCHYMAL STEM CELL POPULATION IN A RAT MODEL OF TYPE1 DIABETES WITH DIABETIC NEUROPATHY - ASSOCIATED ALTERED PAIN PERCEPTION

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Aim: Using a Wistar rat model of type-1 diabetes with diabetic neuropathy (DN)-associated altered nociception, we have previously shown that human bone marrow CD362$^+$ mesenchymal stem cells (MSCs) were effective in preventing the development of mechanical hyperalgesia and thermal hypoalgesia. In this study, we investigated possible underlying mechanisms of action of the CD362$^+$-MSCs by evaluating the levels of inflammatory mediators, such as TNF-α and IL-1β, in nervous tissues.

Methods: Type-1 diabetes was induced by intraperitoneal injection of STZ (60 mg/kg). One week after STZ injection, diabetic rats received an intravenous injection of 2x10^{6}CD362$^+$-MSCs, or vehicle solution. Ten weeks after CD362$^+$-MSCs injection, animals were culled and sciatic nerves, spinal cord, and hippocampi were dissected and processed for Western blotting analysis.

Results: STZ-rats, as compared to controls, exhibited increased levels of TNF-α and IL-1β in the sciatic nerve, no significant differences and decreased levels of TNF-α and IL-1β, respectively, in the spinal cord,anddecreased levels of TNF-α and IL-1β in the hippocampus. Administration of CD362$^+$-MSCs to STZ-rats prevented increases of TNF-α but notIL-1β in the sciatic nerve, had no effect in the levels ofTNF-α and IL-1β in the spinal cord, and prevented decreases of TNF-α and IL-1β in the hippocampus.

Conclusions: Our data suggest that the potential therapeutic effects of CD362$^+$-MSCs in DN may be mediated bythe maintenance of normal levels of TNF-α in the sciatic nerve, and of TNF-α and IL-1β in the hippocampus.

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[P32] OBESITY, IN ADDITION TO HYPERGLYCEMIA, IS ONE OF THE MAIN DRIVERS OF POLYNEUROPATHY

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Aim: We aimed to identify the association between individual metabolic syndrome components and polyneuropathy in a large Chinese population.

Methods: We recruited participants from Pinggu, China to complete metabolic and neuropathy phenotyping. Polyneuropathy was defined as those with a Michigan Neuropathy Screening Instrument (MNSI) Examination >/=2.5. Other neuropathy measures included the MNSI questionnaire and monofilament testing. We utilized the National Cholesterol Education Program/Adult Treatment Panel III definition of the metabolic syndrome. Glycemic status was based on glucose tolerance testing. We determined the prevalence of polyneuropathy stratified by glycemic status and the number of metabolic syndrome components. Multivariable logistic regression was performed to evaluate the association of individual metabolic syndrome components with polyneuropathy and number of metabolic syndrome components and polyneuropathy.

Results: Of 4,002 subjects with neuropathy measures, 37.2% had normoglycemia, 44.1% had pre-diabetes, and 18.7% had diabetes. The prevalence of neuropathy was higher in those with pre-diabetes (6.3%) and diabetes (15.3%) than normoglycemia (3.2%) for all definitions of neuropathy ($p<0.0001$). The prevalence of neuropathy was higher as the number of metabolic syndrome components increased but the result was not statistically significant. Diabetes (2.64, 95%CI 1.80-3.86), weight (1.09, 95%CI 1.02-1.17), and height (1.20, 95%CI 1.05-1.37) were independently associated with polyneuropathy when looking at individual components. The number of metabolic syndrome components (1.18, 95%CI 1.04-1.33) were also independently associated with polyneuropathy after adjusting for glycemic status.

Conclusions: The prevalence of polyneuropathy increases with worsening glycemic status. Diabetes, pre-diabetes, and obesity are the likely metabolic drivers of polyneuropathy.

[P33] EFFICACY OF ACUPUNCTURE THERAPY OF GASTROPARESIS IN PATIENTS WITH TYPE 2 DIABETES MELLITUS

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Background and aims: The treatment of patients with diabetic gastroparesis (DG) remains the difficult clinical task. There are some limited data that acupuncture could be of some use for the treatment of these patients. Acupuncture at heterotopic points could improve gastroparesis via excitation of vagal nerves and inhibition of sympathetic nerves. The aim of this study was to compare the efficacy of acupuncture for the management of gastrointestinal symptoms in patients with type 2 diabetes mellitus (DM).

Materials and methods: We studied 32 patients with DG who were randomly allocated into 2 groups: a treatment group (n=16 (5M/11F), mean age was 56,4±10,7 years, DM duration - 12,4±6,7 years) assigned to accupuncture 5 times per week 40 minutes each for 10 days, and a control group (n=16 (7M/9F), mean age - 58,4±9,7 years, DM - 13,1±8,6 years). The severity of DG was assessed by Gastroparesis Cardinal Symptom Index (GCSI) questionnaire and Gastric emptying rate (GER) with 13C-octanoic breath test (13C-OBT) before and after the treatment period.

Results: The treatment with acupuncture resulted in the clinically significant improvement of the severity of symptoms in patients with DG while in the control group there were no positive changes of the signs of DG. In the first group patients was associated with a decrease in scores for cardinal symptoms of the GCSI: nausea by 68,4%, retching by 76,8%, vomiting by 86,7%, stomach fullness by 62,5%, not able to finish a normal-sized meal by 21,2%, stomach visibly larger by 13,4%, loss of appetite by 12,8%, feeling excessively full after meals by 64,7% and bloating by 22.5% ($p<0.05$). Gastric motility was significantly decreased after the end of treatment period - 101.61±3.41 min and 93,2 ± 1.11 min, before after the treatment, respectively, $p<0.05$. In the control group no significant changes of GER were observed after 2 weeks of observation.

Conclusion: Acupuncture therapy is feasible and effective method for the treatment of gastroparesis in patients with type 2 DM.

[P34] TREATMENT OF C57BL/6J TYPE 1 DIABETIC MICE WITH SALSALATE, MENHADEN OIL, THE COMBINATION OF SALSALATE AND MENHADEN OIL, OR RESOLVIN D1 ON NEUROPATHIC ENDPOINTS

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Aim: Treatments to specifically address diabetic peripheral neuropathy have failed. Maintaining near-normal blood glucose through intensive insulin therapy delays symptoms but does not prevent the development/progression of neuropathy. More effective compounds and/or combined treatment approaches are necessary to address the growing burden of diabetic peripheral neuropathy.

Methods: In this study a streptozotocin induced type 1 diabetes model was used in C57Bl/6J mice. Mice were scrutinized for changes in body weight and blood glucose and serum levels of triglycerides, free fatty acids, cholesterol, and resolvin D1 were determined. Motor and sensory nerve conduction velocities and thermal sensitivity were assessed and in vivo corneal confocal microscopy of sub-epithelial nerves and immunohistochemistry of nerves in the cornea and foot pad was performed.

Results: Diabetic mice failed to gain weight and had elevated blood glucose levels. Nerve conduction velocity was slowed, innervation of the foot pad and cornea sub-epithelial and epithelial layers was decreased, and thermal sensitivity was reduced. Monotherapy with salsalate (salicylic acid), menhaden oil, or daily injections of resolvin D1 reduced the pathological signs of diabetic neuropathy. The combination of salsalate and menhaden oil trended to be more beneficial than monotherapy and generated elevated plasma levels of resolvin D1 compared to other groups.

Conclusions: Salsalate triggered elevations in resolvin D1 when combined with fish oil may be a beneficial treatment for diabetic peripheral neuropathy.

[P35] EFFECTS OF ANTIOXIDANT ALPHA-LIPOIC ACID ON QUALITY OF LIFE IN TYPE 2 DIABETIC PATIENTS WITH CARDIAC AUTONOMIC NEUROPATHY

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Introduction: Diabetic cardiac neuropathy, which is characterized by reduced heart rate variability (HRV) and quality of life. We aimed to evaluate the efficacy of the antioxidant alpha-lipoic acid (ALA) on improvement of quality of life in type 2 diabetics with cardiac autonomic neuropathy (CAN).

Methods: In a randomized, double-blind placebo-controlled multicenter trial, type 2 diabetic patients with reduced HRV were randomly assigned to treatment with daily oral dose of 1200 mg ALA (n = 46) or placebo (n = 45) for 6 months. CAN was assessed by the five tests according to the Ewing's protocol and the time and frequency domain of the heart rate variability (HRV) was evaluated. The patients were asked to answer the EuroQol (EQ-5D), and VAS and estimate the quality of life in people with CAN.

Results: All the baseline measures were similar between groups. Both groups of patients with CAD in baseline reported similar low EQ-5D, EQ-5D index (0.79 ± 0.20, ALA vs 0.83 ± 0.11, Placebo, p=0.47) and VAS scores (68.95 ± 12.75, ALA vs 73.07 ± 11.77, Placebo, p=0.91).

After 6 months of treatment with ALA, Change of EQ-5D, EQ-5D index and VAS score were similar in between ALA and placebo groups.

No differences between the groups were noted regarding the rates of adverse events.

Conclusions: High doses of ALA was well-tolerated oral dose of 1200 mg/day for 6 months but had no beneficial effects of quality of life in type 2 diabetes with CAD.

[P36] EFFECTS OF ANTIOXIDANT ALPHA-LIPOIC ACID ON HEART RATE VARIABILITY IN TYPE 2 DIABETIC PATIENTS WITH CARDIAC AUTONOMIC NEUROPATHY

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Introduction: Diabetic cardiac neuropathy, which is characterized by reduced heart rate variability (HRV), frequently coexists with peripheral neuropathy.

We aimed to evaluate the efficacy of oral treatment with the antioxidant alpha-lipoic acid (ALA) in type 2 diabetics with cardiac autonomic neuropathy (CAN), assessed by heart rate variability (HRV).

Methods: In a randomized, double-blind placebo-controlled multicenter trial, type 2 diabetic patients with reduced HRV were randomly assigned to treatment with daily oral dose of 1200 mg ALA (n = 16) or placebo (n = 12) for 6 months. CAN was assessed by the five tests according to the Ewing's protocol and the time and frequency domain of the heart rate variability (HRV) was evaluated.

Results: All the baseline measures were similar between groups, except for the low-frequency band (LF). After 6 months of treatment with ALA, some HRV parameters showed some improvement. The standard deviation of normal-to-normal RR intervals (SDNN; ms) in standing position increased from baseline to 6months by 9.1 ms (-27.9 to 114.5) in the group given ALA and decreased by -7.0 ms (-35.6 to 27.5) in the placebo group (p=0.01 for ALA vs. placebo). Power spectrum in the LF band in standing position increased by 124.8 ms^2 (-73.3 to 965.2) in ALA, whereas it declined by -66.1 ms^2 (-411.9 to 104.1) in placebo (p= 0.08 for ALA vs. placebo). No differences between the groups were noted regarding the rates of adverse events.

Conclusions: High doses of ALA not only well-tolerated oral dose of 1200 mg/day for 6 months but also may slightly improved heart rate variability in type 2 diabetic patients with cardiac autonomic neuropathy.

[P37] THERAPEUTIC EFFICACY OF NSI-189 IN DIABETIC MICE

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Aim: NSI-189 is a novel orally active neurogenic small molecule currently in a Phase 2 clinical trial for major depressive disorder. The aim was to determine efficacy of NSI-189 against indices of neuropathy in mouse models of diabetes.

Methods: Swiss Webster mice with streptozotocin (STZ)-induced diabetes (90 mg/kg ip, 2 consecutive days) or db/db (BKS.Cg-Dock7^{m}+/+Lepr^{db}/J) mice andnon-diabetic littermates were used. STZ-diabetic mice were treated with insulin (sub-cutaneous pellet) or NSI-189 (10mg/kg/day by gavage) from onset or after 8 weeks of untreated diabetes until week 16 of diabetes. db/db mice received NSI-189 between7-34 weeks of age. Nerve function and structure was assessed at regular intervals.

Results: Insulin normalized blood glucose and HbA1c levels in STZ-diabetic mice and prevented nerve conduction slowing, tactile allodynia, paw thermal hypoalgesia, depletion of epidermal and dermal fibers, depletion of corneal stromal and sub-basal nerve plexusfibers and impaired Barnes maze performance. NSI-189 was without discernable effect on general physiology or nerve function in control mice and did not alter severity of systemic diabetes. NSI-189 given from onset of diabetes significantly protected all indices of nerve function and structure compared to vehicle-treated STZ-diabetic mice, while treatment started after neuropathy was established significantly improved all parameters except impaired Barnes maze function. Indb/db mice, the progressive development of MNCV slowing, tactile allodynia and thermal hypoalgesia was significantly reversed by NSI-189after 17-22 weeks of treatment.

Conclusions: As NSI-189 is in clinical trial for other CNS conditions, rapid translation of this therapy to clinical investigation is possible.

[P38] NICOTINAMIDE RIBOSIDEIS A POTENTIAL THERAPYFOR DIABETIC NEUROPATHY

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Aim: To test if treatment with a precursor of NAD^+, Nicotinamide Riboside (NR), would reverse neuropathy in a mouse model of type 2 diabetes Mellitus (T2DM).

Methods: Adult C57BL6 mice were fed a high fat diet (HFD,:60% calories from fat) for two months until they developed neuropathy. Then, 150 mg/kg or 300 mg/kg NR was mixed with HFD and fed every day for 2 months. Control animals were fed a control diet (18% calories from fat). Diets had similar protein and carbohydrate contents. At 2 months, blood glucose levels in HFD-fed mice were >200 mg/dL. Neuropathy endpoints were motor sciatic-fibular nerve conduction velocities (MCV), mechanical allodynia (MA), and intraepidermal nerve fiber density (IENFD). In the dorsal root ganglion neurons (DRG) neurons, NAD^+ levels were quantified by HPLC.

Results: Both MA and MCV improve in HFD mice with NR treatment ($P<0.001$ mice at 4 months compared to the 2 month time point). There was no change in control diet (CD) animals. HFD animals continued to develop neuropathy over the 4 mo. period. At 4 mo., the IENFD was decreased in the HFD but not the NR group ($P<0.001$ HFD mice at 4 months vs baseline).NR treatment decreased HFD-induced increase in triglycerides and non-esterified fatty acids, and normalized impaired glucose tolerance test. In HFD mice, there was a decrease in the NAD^+ level, in SIRT1 activity, and in PGC-1alpha levels in DRG. NR normalized these measurements.

Conclusion: Oral administration of NR can reverse neuropathy in a model of T2DM.

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[P39] POLYNEUROPATHY IN SEVERE OBESE PATIENTS: EFFECT OF THE Y-IN-ROUX GASTRIC BYPASS

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Aim: Polyneuropathy (PN) has been reported as a complication of bariatric surgery (BS). In this study, we compare the frequency of PN before and after Y-in-Roux Gastric Bypass (GB) surgery and identify risk factors in a Brazilian Multicenter for treatment of obesity grades 2 and 3.

Methods: In 97 patients with history of degree 2 and 3 obesity and absence of Diabetes Mellitus in the previous 2 years PN was evaluated by the Michigan Neuropathy Score Instrument (MNSI). Thirty four of the patients were submitted to Y-in-Roux GB in the last 12.3 ± 6.2 months. Patients were evaluated also for their blood levels of B12 vitamin, lipids, glucose and and 25 OH-D vitamin. According to the occurrence of BS and presence (+) /absence (-) of BS and PN, patients were separated in 4 groups.

Results: Frequency of neuropathy was not increased in patients with severe obesity submitted to BS (No BS = 20.6% and BS = 11.7%). Results are presented below.

	No BS (n=63)		BS (n = 34)	
	No BS PN – (n= 50)	No BS PN + (n=13)	BS + PN – (n=30)	BS + PN + (n=4)
Fasting glucose (mg/dL)	94.4 ± 12.5	96.3 ± 13.0	83 .7 ± 6,9	80.5 ± 6.4
HDL-Cholesterol (mg/dL)	45.7 ± 11.9	49.2 ± 13.8	49.8 ± 16.4	35.0 ± 5.6
LDL-Cholesterol (mg/dL)	120.2 ± 28.7	126,76 ± 37,13	88 .2 ± 21.9	119.2 ± 5.1
Trigllycerides (mg/dL)	143.4 ± 62.7	120.2 ± 57.0	86.0 ± 37.0	91.5 ± 7.8
B12 Vitamin (pg/mL)	450.8 ± 183.8	423.2± 37.1	451.1 ± 207.7	553.5 ± 208.0
25 OH D Vitamin (ng/mL)	27.5 ± 9.0	27.6 ± 8.6	27.7± 2.3	30.5 ± 6.4

Conclusion: PN is related to severe obesity. If patients submitted to Y-inRoux GB receive adequate vitamin supplementation, PN frequency probably does not increase.

[P40] SEARCHING THE OPTIMAL WAYS OF SCREENING FOR AUTONOMIC CARDIOVASCULAR NEUROPATHY IN PATIENTS WITH TYPE 1 DIABETES MELLITUS

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Background: Cardiovascular autonomic neuropathy (CAN) increases morbidity and mortality in diabetes and has great predictive power for cardiovascular events.

Purpose: The aim of our study was the searching of new possibilities to optimize the diagnostics of cardiovascular autonomic neuropathy (CAN) in patients with type 1 diabetes mellitus (DM).

Methods: The study involved the examination of 103 randomly type 1 (insulin-dependent) diabetes patients (60 males) with average age 37,1±10,4years, average duration of DM 10,3±3,4 years. It employed tests of autonomic function and 24-h heart rate variability (HRV) spectral analysis of Holter records (VLF, LF, HF). CAN was defined as the presence of at least 3 abnormalities among 7 indices. Special autonomic tests diagnostic tables (ATDT) that calculate R-R intervals ratio during the tests on the basis of ECG data were also used. We investigated the time spent on the calculation the results of tests by one investigator using ATDT (t table) and using standard methods (t stand).

Results: 37 (35.9%) patients were suffering CAN in the research group. 25 cases of CAN (67%) were diagnosed on the basis of the autonomic tests data that were conducted prior to Holter studies. The investigator spent less time using ATDT than using standard methods (ttable=73,8±1,11 sec, tstand=99±2,02sec, $p<0,05$).

Conclusion: The results indicate that the high prevalence of CAN in diabetes mellitus. The investigators can get the acceleration and optimizing the diagnostic process of CAN in patients with type 1 diabetes by using special diagnostic tables.

[P41] LONGITUDINAL CHANGES IN MEASURES OF CARDIOVASCULAR AUTONOMIC NEUROPATHY (CAN) IN TYPE 1 DIABETES (T1D)

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Aim: CAN is an independent risk factor for cardiovascular mortality, known to progress with poor glycemic control as assessed by hemoglobin A1c(A1c). CAN progression in early T1D is not well studied. The aim of this study was to assess longitudinal changes in measures of CAN and their determinants in a relatively healthy T1D cohort.

Methods: Preliminary data are reported for 40 subjects with T1D (age 35±13 years, 60% women, duration 13±7 years, A1c 7.9±1.2% at baseline), no history of cardiovascular complications enrolled in a 3 year longitudinal observational study. CAN was assessed by cardiovascular reflex tests (paced deep breathing, Valsalva, postural changes) and heart rate variability (HRV) analyzed with ANX 3.1 (ANSAR Inc). Measures of CAN included: Expiration/Inspiration (E/I), Valsalva and 30/15 ratios, standard deviation of normal RR intervals (SDNN), root mean square of successive RR intervals(RMSSD), low and high frequency power (LF, HF) of HRV. Longitudinal changes in measures of CAN were evaluated with the paired t-test.

Results: After 24-month, most measures of CAN declined, especially E/I ratio (-0.02±0.006,p=0.03), RMSSD (-5.8±12,p=0.005), deep breathing HF (-9±17,p=0.002), SDNN (-5±17,p=0.063) (Table), which were independent of A1c.

Conclusion: Ongoing analyses are evaluating differences in glucose variability over time and risk factors profiles of T1D subjects who had worsening of CAN compared to those who remained unchanged.

Table: Change in measures of CAN in subjects with T1D

Variable	Baseline	2 year	Change over 2 years	p value
E/I ratio	1.2±0.12	1.1±0.12	-0.02±0.06	0.03
Valsalva ratio	1.3±0.27	1.2±0.25	-0.027±0.30	0.56
Deep Breathing LF, msec	0.85±0.68	1.2±1.4	0.40±1.31	0.055
Deep Breathing HF, msec	23.5±22.8	14.1±13.8	-9.1±17.4	0.002
Deep Breathing LF/HF	0.07±0.098	0.19±0.29	0.11±0.30	0.01
SDNN, msec	53±22.85	47.8±22.4	-5.15±17.0	0.063
RMSSD, msec	37±24.24	31.4±21.2	-5.85±12.3	0.0047

E:I ratio: expiration inspiration ratio, LF: low frequency power, HF: high frequency power, SDNN: standard deviation of RRintervals, RMSSD: root mean square differences of successive RR interval. All data are represented as Mean± Std Dev

[P42] CHARACTERISTICS OF CARDIOVASCULAR AUTONOMIC FUNCTION IN INSULIN PUMP-TREATED TYPE 1 DIABETIC PATIENTS

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Introduction: The long-term hyperglycemia before insulin pump treatment and the following improvementof the glycemic control might influence the autonomic function in type 1 diabetes (DM).

Objectives: The aim of our study was to assesscardiovascular autonomic function at initiation of insulin pump treatment, two months later, as well as 6 years later.

Methods: 13 type 1 DM patients were involved (7 women, 6 men, age: 30.4±2.7 years, duration of DM: 16.5±2.7 years; BMI: 24.2±1; mean±SE). Autonomic neuropathy (AN) was assessed at the first application of insulin pump and 2 months as well as 6 years later by cardiovascular reflex tests (CRT).

Results: Correlations were found between the duration of DM and CRT-s (AN score-duration: $r=0.57$, $p<0.05$; heart rate response to breathing-duration: $r=-0.55$, $p<0.05$). Moderate to severe AN was found, while improvement of total autonomic score was detected two months later (2.85±0.3 vs 1.23±0.3, $p<0.01$). The AN score found six years later was identical to the initial value (AN score: 2.85±0.47). The change of CRT-s was not significant during the follow-up period. The mean HbA1c decreased by 0.7% after 2 months (8.85±0.2% vs 8.12±0.3 %, $p=0.07$) and was even lower 6 years later (8.85±0.2% vs 7.85±0.3 %, $p<0.05$).

Conclusion: Moderate to severe autonomic neuropathy was detected in type 1 diabetic patients at the initiation of insulin pump treatment. The severity of the parasympathetic involvement correlated with the duration of diabetes. Improvement of autonomic function could be confirmed after short-term treatment withinsulin pump. No progression of autonomic nerve dysfunction compared to baseline values was observed after six years of observation.

[P43] INFLUENCE OF CARDIAC AUTONOMIC DYSFUNCTION AND ARTERIAL STIFFNESS ON SUBENDOCARDIAL MYOCARDIAL VIABILITY IN PATIENTS WITH TYPE 2 DIABETES

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Aim: Cardiac autonomic dysfunction (CAD) is characterized by sympatho-vagal imbalance and might thus shorten diastole duration (DD) and impair coronary perfusion. We studied the influence of CAD severity and arterial stiffness on DD and subendocardial myocardial viability (SVI) in type 2 diabetic patients (T2Ds).

Methods: In 42 T2Ds (55.2±12.6yrs, BMI 33.4±7.3kg/m^2, HbA1c 8.04±1.58%) we measured heart rate (HR) and blood pressure (Finapres®) during 5 minutes in supine position. We calculated DD, arterial stiffness (augmentation index and pulse wave velocity), DD%(DD/duration of heart period x100), and SVI (areas under aortic pressure curve during diastole/during systole). CAD was assessed using standard tests (deep-breathing, lying-to-standing, Valsalva) and autonomic score (AS) was calculated.

Results: CAD was absent (AS0), early (AS1), definite (AS2) or severe (AS3) in 7, 14, 15 and 6 patients, respectively. Mean HR was 70.1±11.6,74.9±8.1, 77.8±11.2, 95.0±16.0 bpm in AS0, AS1, AS2 and AS3 ($p<0.01$). DD% correlated negatively with HR ($r=-0.747$, $p<0.0001$) and was lower in patients with higher AS (AS0:61.7±3.3,AS1:59.7±3.9, AS2:56.7±4.1,AS3:52.8±3.6%; $p<0.01$). AS2+AS3 patients showed lower DD% compared with AS0+AS1 patients even after adjusting DD% at HR of 75bpm ($p=0.03$). Also SVI was lower in patients with higher AS (AS0:1.23±0.2, AS1:1.16±0.1, AS2:1.02±0.2, AS3:0.88±0.1; $p<0.01$). SVI correlated strongly with DD% ($r=0.921$, $p<0.0001$) and moderately with augmentation index($r=-0.489$, $p<0.001$).

Conclusions: In T2Ds CAD, expressed as reduced vagal activity, leads to HR acceleration and seems to shorten DD independently of its HR effect. CAD plays a primary role in addition to arterial stiffness in SVI impairment.

[P44] PUPIL DILATATION WITH TROPICAMIDE DOES NOT AFFECT INDICES OF CARDIAOVASCULAR AUTONOMIC NEUROPATHY – THE ADDITION DENMARK STUDY

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Aim: Regularly screening for diabetic cardiovascular autonomic neuropathy (CAN) and retinopathy are internationally recommended as an integral part of patient care. Anticholinergic pupil dilatation may affect the autonomic nervous system and CAN measures. The aim of the study is to investigate whether prior administration of parasympatholytic eye drops (Tropicamide) can influence the results of CAN.

Methods: The study included 179 well regulated type 2 diabetes patients nested in the ADDITION Denmark study with short-term diabetes (duration~5.9 years, mean HbA1c=46.4mmol/mol). 53% were men, mean age was 65.8 years. 7.6% were diagnosed with CAN. CAN was assessed by measures of 2 min. resting heart rate variability (HRV) and three standard cardiovascular autonomic reflex tests (CARTs); the lying-to-standing ratio (30/15 ratio), the deep breathing ratio (E:I) and the Valsalva manoeuvre (VM). HRV was analysed in time-domain and frequency-domain. Time-domain analyses included the root mean square of the sum of the squares of differences between consecutive R–R intervals (RMSSD) and standard deviation of normal-to-normal intervals (SDNN). Frequency-domain analyses included low- and high-frequency power band (LF and HF), total frequency power (Total) and the ratio low-frequency power/high-frequency power (LH-ratio). An unselected subset of study participants received Tropicamide eye drops either before (1-2 hours)(n=65) or after testing for CAN(n=111). Effectively creating a randomised design. Between group differences were assessed by linear regression.

Results: No differences in CARTs nor HRV indices was observed between the two groups (p>0.05)(Figure 1).

Conclusion: Tropicamide pupil dilationone to two hours prior to CAN testing had no influence on measures of CAN in our study. The timing of Tropicamide eye dilation does not need to be taken into account when planning the complications screening programme for patients with diabetes.

CAN measures	Tropicamide before n=65	Tropicamide after n=111	P value
CARTs			
30/15 ratio	1.1 (1.1;1.2)	1.1 (1;1.2)	0.44
E:I ratio	1.2 (1.1;1.2)	1.1 (1.1;1.2)	0.65
VM	1.5 (1.2;1.7)	1.4 (1.2;1.7)	0.71
HRV			
RMSSD (ms)	18.9 (12.5;35.9)	20.5 (11.8;30.7)	0.78
SDNN (ms)	32.8 (21.9;41.9)	29.5 (21;45.1)	0.99
LF (ms^2)	78.9 (23.8;184.3)	68.1 (25.5;125.1)	0.71
HF (ms^2)	42.9 (16.1;114.5)	39.3 (15.6;117.3)	0.96
Totalpower (ms^2)	257.5 (92;542)	231.9 (101;423.8)	0.92
LF/HF ratio	1.8 (0.9;3.6)	1.5 (0.8;2.9)	0.53
Heart rate (BPM)	67.6 (11.0)	68.1 (12.6)	0.80

Figure 1.

Data show medians (IQR) or means (SD) of outcomes and p value for t test of difference between groups with tropicamide drops before and after CAN screening. CAN=cardiovascular autonomic neuropathy, CARTs=cardiovascular autonomic reflex tests, RMSSD=the root mean square of the sum of the squares of differences between consecutive R–R intervals, SDNN=standard deviation of normal-to-normal intervals, LF/HF-ratio=Low frequency power/High frequency power ratioms= milliseconds, BPM=beat per minute. Analyses were adjusted for age, HbA_{1c}, sex and BMI.

[P45] IMPAIRED CARDIOVASCULAR AUTONOMIC FUNCTION AND DIMINISHED VIBRATION PERCEPTION ARE PRESENT AMONG PATIENTS WITH HIGH RISK FOR THE DEVELOPMENT OF TYPE 2 DIABETES MELLITUS SCREENED BY THE FINDRISC QUESTIONNAIRE

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Background and aims: FINDRISC is a validated and one of the most widely used T2DM risk score questionnaire. The aim of our study was to compare autonomic and sensory nerve function among patients with higher future T2DM risk (minimum 12 points in the FINDRISC questionnaire) with healthy conrol subjects.

Materials and methods: Our study in volved 28 patients with higher future T2DM risk (mean age: 60,3±8,2, female 15, HbA1c 5,9 [5,6;6,1], BMI 31 [27,9;34,5]) and 20 healthy control subjects (mean age: 54,3 ± 1,4 , female 10, HbA1c 5,4 [5,1;5,8], BMI 29,5 [26,3;32,4]). Sensory function was evaluated by Neurometer (Neurotron Inc., Baltimore, USA) device, 128 Hz calibrated tuning fork, Semmes-Weinstein monofilament and Q-sense (Medoc Ltd., YamatRishai, Israel) device. Cardiovascular autonomic function was assessed by the five standard cardiovascular reflex tests, 24-hour heart rate variability (HRV) and ambulatory blood pressure monitoring (ABPM).

Results: Patients with higher future T2DM risk had significantly higher vibration perception thresholds on the lower extremities than healthy control subjects (5,8 vs 6,8; p= 0,01). Assessing autonomic function, the total autonomic impairment score was higher (2,1 vs 0,7; p=0,04), while SDANN was lower among patients with higher future T2DM risk compared to controls (133 vs 184, p=0,02). Moreover, patients with higher future T2DM risk had significantly higher scores in the case of the 6th question of the FINDRISC questionnaire which refers to the use of antihypertensive medication (1,5 vs 0,76; p= 0,01).

Conclusion: Our results highlight the importance of early neuropathy assessment, as well as for the development of effective risk reductions trategies among these patients.

[P46] RELATION BETWEEN AUTONOMIC ACTIVITY AND THE POST-PRANDIAL HEMODYNAMIC CHANGES IN HEALTHY INDIVIDUALS

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Aim: We have recently shown that parasympathetic withdrawal in the post-prandial period occurs rapidly and heart rate increase did not depend on the vagal inhibition. Our aim was to examine the relation between autonomic activity and the post-prandial changes in hemodynamics in healthy individuals.

Patients and methods: Data were available in 47 of 49 healthy volunteers. Participants had no cardiovascular risk factors. Measurements were performed at fasting (H0) and 1, 2 and 3 hours (H1, H2, H3) after a standardised breakfast. Tests were performed in supine position with applanation tonometry and Task Force Monitor® device coupled with impedance cardiography. We created two groups according to the median of the difference of the vagal spectrum between H0 to H1.

Results: The group with higher vagal withdrawal (HVW, n=24) was younger (63.2±6.0 vs 67.6 ±4.4 years, p=0.006). Both groups had no differences at fasting or post-prandially in BMI, fat mass, physical activity, microalbuminuria, glycemia, lipids and Low Frequency variations of systolic blood pressure spectrum. Heart rate, arterial stiffness, % diastolic part of the cardiac cycle, myocardial perfusion index, central, peripheral systolic and pulse pressures, were also similar. Subjects with HVW had post-prandially higher stroke volume index (p=0.02), myocardial contractility (p=0.05) and lower indexed peripheral resistance (p=0.009). After adjustment for age, stroke volume index and myocardial contractility were not statistically significant but HVW was still associated with lower peripheral resistance (p=0.04).

Conclusions: In healthy individuals higher post-prandial parasympathetic withdrawal is associated with lower total peripheral resistance indicating a blunted peripheral sympathetic response.

NUTRIVASC study (NCT01579409)

[P47] RELATIONSHIP BETWEEN CARDIAC AUTONOMIC DYSFUNCTION, HIGH BLOOD PRESSURE AND RENAL FUNCTION

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Aim: High blood pressure is involved in the degradation of renal function. We previously showed that cardiac autonomic dysfunction (CAD) promotes the development of hypertension in type 2 diabetes. The aim was here to determine the role of CAD associated with hypertension in impaired renal function.

Methods: We included 428 overweight or obese patients without diabetes. Heart rate variations were analysed during three standardized tests (Valsalva, deep breathing, lying-to-standing). The results were according to age. A 75 g oral glucose load was performed. Dysglycemia (diabetes, fasting hyperglycemia and/or glucose intolerance) was detected. Glomerular filtration rate was calculated (Modification of the Diet in Renal Disease, MDRD).

Results: CAD was found in 194 patients (46.3%). We separated the population into 4 groups: G1: CAD absent or one abnormal test (CAD 0-1) and no hypertension , G2 : CAD 0-1 and hypertension; G3 : CAD confirmed or severe (2-3 altered tests, CAD 2-3) and no hypertension, G4 : CAD 2-3 and hypertension. Systolic, diastolic and pulse pressureswere significantly higher in G4 that in G1 ($p < 0.0001$). MDRD fell significantly from G1 to G4 ($p<0.005$). Fasting and post-load plasma glucose, HOMA insulin resistance index, serum uric acid and triglycerides significantly increased from G1 to G4 ($p< 0.005$; $p<0.0001$, $p=0.046$, respectively).

Conclusions: In patients with hypertension, CAD promotes the appearance of more marked metabolic disorders and contributes to renal function impairment. This suggests a sympathetic hyperactivity associated with greater insulin resistance.

[P48] CARDIOVASCULAR AUTONOMIC DYSFUNCTION PREDICTS HEMOGLOBIN A1CVARIABILITYIN SUBJECTS WITH TYPE 2 DIABETES

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Aim: We examined the association between cardiovascular autonomic neuropathy (CAN) and hemoglobin A1c (HbA1c) variability in subjects with type 2 diabetes.

Methods: Eligible subjects were the type 2 diabetes patients who conducted the cardiovascular autonomic test (AFT) between October 2008 and September 2011. HbA1c measurements after the date of AFT were collected. Finally, subjects with at least 4-year follow-up after AFT and had 6 HbA1c recordings were selected in this analysis. Subjects were categorized by the baseline AFT score; no, early, and severe CAN group. HbA1c variability was measured as the standard deviation (SD) of serial HbA1c measurements (HbA1c-SD), the coefficient of variation of HbA1c (HbA1c-CV), and the adjusted SD of serial HbA1c measurements (adj-HbA1c-SD).

Results: A total of 599 subjects were categorized according to the baseline AFT score. Severe CAN group showed higher Hba1c variability compared with the no CAN group. Multivariable logistic regression analysis showed that severe CAN group was significantly associated with the higher Hba1c variability after the adjusting for the baseline difference (OR [95% CI]; higher HbA1c-SD, 2.108[1.119 – 3.969]; higher HbA1c-CV, 2.264[1.211 – 4.234]; higher adj-HbA1c-SD, 2.166[1.163 – 4.035]).

Conclusions: Severe CAN could be a predictor of future Hba1c variability in subjects with type 2 diabetes. They could have bad influence interactively and go on in a vicious cycle.

[P49] ANALYSIS OF DIURNAL HEART RATE PATTERN IN DIABETIC PATIENTS WITH PERMANENT ATRIAL FIBRILLATION

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Cardiac autonomic neuropathy (CAN) is common and often underestimated long-term complication of diabetes mellitus (DM). CAN has a major impact on CVD, mortality and morbidity in patients with DM. Community studies demonstrate presence of DM in 13% patients with atrial fibrillation (AF). Assessment of heart rate (HR) autonomic regulation is important in further prognosis for DM patients.

Aim: to evaluate ECG based 24 hours HR parameter relevance for death risk assessment among DM patients with permanent AF (PAF)

Materials and methods: cohort of 460 PAF patients exposed to Holter monitoring in 2007-2011 (mean age – 73.9 (9.9), 207 (45%) male), 96 (20.9) patients- diabetics (mean age - 75 (8.5), 41 (42.7%) male). An AF circadian index (AFCI) was calculated from four dichotomizedparameters of diurnal HR changes (day and night time average HR and maximum and minimum HR ratio and difference) and compared between DM and non DM patients and dead and survived patients.

Results: During 5 year follow-up 176 patients (38.2%) died: 52DM patients (54.2%) and 125 -without DM (34.5%), OR=2.24 (1.42;3.54 95% CI). AFCI was higher in DM patients (p-.01) compared with non DM, andin dead DM patients compared with survived (p-.01).

Conlusions: Decrease of AFCI in diabetic PAF patients can be associated with presence of CAN. Decreased diurnal HR variability is associated with higher death risk among PAF patients with DM. Circadian HR pattern needs to be studied in DM patients with PAF for detection of cardiac autonomic failure and inclusion in patients risk assessment.

[P50] PREVALENCE OF DIABETIC NEUROPATHY AMONG PATIENTS WITH TYPE 2 DIABETES MELLITUS IN UZBEKISTAN

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Aim: The work was initiated to study prevalence of diabetic autonomic neuropathy among patients with type 2 diabetes mellitus asper EURODIAB questionnaire.

Materials and methods: Autonomic neuropathy with psycho-autonomic disorders was assessed in 104 patients with type 2 diabetes mellitus undergoing clinical evaluation by means of inquiry as per EURODIAB program modified by Danilov A.B.

Results: In 104 patients, 52 women and 52 men among them, with type 2 diabetes mellitus with mean age 54.6 ± 1.04 years mean duration of type 2 diabetes mellitus was 10.2 ± 0.7 years. Body mass index was 29.9±0.53 kg/m². Glycosylated hemoglobin value (HbA1c) was 9.3±0.3%. According to the findings from our study diabetic polyneuropathy syndrome occurred in 69.2% of cases, 73% of the patients had cardiovascular disorders. Disorders in hidropoiesis could be seen in 91% of the patients, gastrointestinal and respiratory dysfunctions were found in 9.6% and 44.2% of the patients, respectively. Pupilary reflex was found disturbed in 22.7%, urogenital dysfunction could be seen in 37.5%.

Conclusions: Disorders in hidropoiesis manifesting as hyperhidrosis or xeroderma are the most frequent type of diabetic neuropathy in patients with type 2 diabetes mellitus (91%). Of note, cardiovascular disorders could be seen more frequently (73%) than diabetic polyneuropathy syndrome (69.2%). Gastrointestinal disorders were the least frequent (9.6%).

[P51] THE ASSOCIATION BETWEEN VITAMIN D STATUS AND DIABETIC RETINOPATHY

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Aim: Recent clinical and experimental studies have suggested a link between vitamin D deficiency and diabetic complications. However, there were conflicting results in the association between vitamin D deficiency and diabetic retinopathy (DR). We aimed to investigate the association between vitamin D levels and DR.

Methods: A total of 2,064 patients with diabetes were recruited from the Korean National Health and Nutrition Examination Survey (KNHENES) during 2008-2012. All participants participated instandardized interviews, physical andophthalmic examinations. Seven standard retinal fundusphotographs were obtained from both eyes after pupil dilatation. DR was classified as absence of DR, non-proliferative DR (NPDR), and proliferative DR (PDR).

Results: Mean 25(OH)D level was 18.5 ± 6.7 ng/mL. More than half of the participants had insufficient serum 25(OH)Dlevels (< 20 ng/mL). Participants were categorized in to 4 groups according to serum 25(OH)D levels; < 10, 10-19, 20-29, ⩾ 30 ng/mL. The prevalence of DR according to 25(OH)D level was 8.6%, 56.6%, 30.0%, and 4.9%, respectively (p=0.260). There were no differences in prevalence of NPDR and PDR according to 25(OH)D levels. Univariate and multivariate regression analysis showed no association between serum 25(OH)D levels and the presence or severity of DR.

Conclusions: In this cross-sectional study, there was no association between serum 25(OH)D levels and the presence or severity of DR.

[P52] THE ASSOCIATION BETWEEN METABOLIC SYNDROME AND DIABETIC RETINOPATHY

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Aim: Metabolic syndrome (MetS) has been considered as a risk factor for macrovascular complications in people with diabetes. However, the association between MetS and microvascular complications has been less elucidated. Therefore, we aimed to investigate the association of diabetic retinopathy (DR) with MetS and its components.

Methods: A total of 2,116 patients with diabetes were recruited from the Korean National Health and Nutrition Examination Survey (KNHENES) during 2008-2012. All participants participated in standardized interviews, physical and ophthalmic examinations. Seven standard retinal fundus photographs were obtained from both eyes after pupil dilatation. DR was classified as absence of DR, non-proliferative DR (NPDR), and proliferative DR (PDR).

Results: Among participants, 73.3% had MetS. The prevalence of NPDR and PDR were 13.9% and 3.1%, respectively. Age, duration of diabetes, blood pressure and blood glucose level increased according to the DR while BMI decreased. There was no significant difference in the prevalence of MetS according to the DR. Among the components of MetS, only central obesity showed inverse association with the progression of DR. On multiple regression analysis, MetS was associated neither NPDR nor PDR after adjustment for age, sex, duration of diabetes, and HbA1c.

Conclusions: MetS, a hallmark of insulin resistance, was not associated with the presence or severity of DR in Korean.

[P53] DIABETIC PERIPHERAL NEUROPATHY AND SUDOMOTOR DYSFUNCTION AMONG SAUDI PATIENTS WITH NEWLY DIAGNOSED TYPE2 DIABETES MELLITUS

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Aim: To examine diabetic peripheral neuropathy (DPN) and sudomotor dysfunction (SMD)among Saudi patients with newly diagnosed type 2 diabetes mellitus (T2DM).

Methods: This is a cross-sectional study on 125 Saudi patients with newly diagnosed T2DM (<6 months) referred from primary health care centers. Neuropathic symptoms (NS) were assessed using neuropathy symptom-score (NSS). Neuropathic deficits in the feet were determined using neuropathy disability-score (NDS). Scores were derived from testing: 128-Hz tuning fork, neurotip, tendon hammer, cold warm rod.87 participants underwent nerve conduction studies of the right and left sensorysural, motor peroneal and tibial nerves. Patients were subclassified into confirmed or subclinical DPN according to (Tesfaye S,2010). SMD was evaluated in 92 participants using feet-electrochemical skin conductance (ESC). SPSS 20 was used for statistical analysis.

Results: Mean participant age was 45.4±10.3 years. 35.2% had NS; 8.8% had DPN defined as NDS ⩾3. Moderate, elevated risk of SMD was present in 34.8%,17.4% of participants respectively. Confirmed DPN, subclinical DPN were present in 33.8%, 54.4% of participants respectively. NDS ⩾ 3 identified 17.39% of patients with confirmed large fiber DPN but none with subclinical-DPN. SMD (feet-ESC<70µS) occurred in parallel with confirmed DPN in 69.6% of the cases (P<0.006) and in 35.1% of patients with subclinical DPN P<0.101. Isolated SMD occurred in 75% of patients without large fiber DPN (P<0.0001).

Conclusion: DPN is common among studied Saudi patients with newly diagnosed T2DM, placing them at risk of foot ulceration. Strategies for early detection of T2DM and DPN using simple, objective tools are therefore imperative.

[P54] EXPLORING THE ASSOCIATION BETWEEN METABOLIC SYNDROME COMPONENTS AND POLYNEUROPATHY IN AN OBESE POPULATION

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Aim: We determined the polyneuropathy prevalence, stratified by glycemic status, in well characterized obese and lean participants. We also investigated the association of specific metabolic syndrome components and polyneuropathy.

Methods: We performed a cross-sectionalstudy in obese participants from a weight management program and lean controls from a research website. Obese patients were required to have a body mass index ⩾ 35 kg/m^2 or ⩾ 32 kg/m^2 if they had one or more comorbidity. Lean controls met no metabolic syndrome criteria (modified National Cholesterol Education Program/Adult Treatment Panel III definition). Polyneuropathy was defined using the Toronto consensus definition of probable polyneuropathy. The prevalence of polyneuropathy, stratified by glycemic status, was determined, and a Mantel–Haenszel chi-square test was used to investigate for a trend. Logistic regression was used to model polyneuropathy as a function of the metabolic syndrome components.

Results: We enrolled 102 obese participants (44.1% normoglycemia, 30.4% pre-diabetes, and 25.5% diabetes) and 53 lean controls. The polyneuropathy prevalence was 3.8% in lean controls, 11.1% in the obese, normoglycemia group, 29.0%, in the obese, pre-diabetes group, and 34.6% in the obese, diabetes group ($p<0.01$ for trend). Age (OR=1.09, 95% CI 1.02-1.16), diabetes (OR=4.90, 95% CI 1.06-22.63), and waist circumference (OR=1.24, 95% CI 1.00-1.55) were significantly associated with polyneuropathy in multivariable models. Pre-diabetes (OR=3.82, 95% CI 0.95-15.41) approached, but did not reach, statistical significance.

Conclusions: The polyneuropathy prevalence is high in an obese population even in those with normoglycemia. Diabetes, pre-diabetes, and obesity are the likely metabolic drivers of this neuropathy.

[P55] ACCURACY OF ELECTROCHEMICAL SKIN CONDUCTANCE MEASUREMENT FOR THE ASSESSMENT OF SMALL FIBER NEUROPATHY

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Aim: Sudomotor testing has been proposed for the functional assessment of small autonomic fibers. Electrochemical skin conductance (ESC) quantifies sweat gland function simply and rapidly. This study evaluated the repeatability and reproducibility of ESC according to ISO 5725-2.

Methods: 18 healthy volunteers (HV) and 14 patients with type 2 diabetes (PTD2) underwent 6 ESC measurements: two tests on three different devices under usual testing conditions. Measurements were performed in the same order for all subjects. Electrodes were cleaned after each test and patients rested >5 min between successive measurements. Results were expressed as means, standard deviation (SD) and coefficient of variations (CV) for repeatability and reproducibility.

Results: HV had mean age: 37±13 years, mean BMI: 26±4 kg/m^2, 72% males. PDT2 had mean age: 62±9 years, mean BMI: 29±5 kg/m^2, 71% males, mean HbA1C: 7.0±0.9%, and mean diabetes duration: 10.8 years. All PDT2 underwent vibration perception, 10-g monofilament and ankle reflex testing: eight patients were normal, four had one abnormal clinical sign, and two had ⩾2 abnormal results.

Mean hands ESCs were 75.8±7.3 µS in HV and 62.6±10.4 µS in PDT2, while feet ESC were 75.4±5.5 µS in HV and 69.2±9.4 µS in PDT2.

The Table presents ESC repeatability and reproducibility.

	Repeatability SD	CV Repeatability	Reproductibility SD	CV Reproducibility
HV Hands ESC	3.1 µS	4.2 ± 2.7%	3.2 µS	4.3 ± 2.7%
HV Feet ESC	2.1 µS	2.8 ± 1.6%	2.3 µS	3.1 ± 1.5%
PDT2 Hands ESC	4.3 µS	7.1 ± 5.9%	4.5 µS	7.4 ± 6.1%
PDT2 Feet ESC	4.3 µS	6.9 ± 6.3%	4.3 µS	6.9 ± 6.3%

Conclusion: Repeatability and reproducibility of ESC is acceptable in HV and PDT2. Variation is comparable to or lower than other methods of small or large fiber assessment. Based on these results and test objectivity and simplicity, ESC measurement could be considered for patient follow-up and as an endpoint in multi-center trials.

[P56] IS IMPAIRED OLFACTORY FUNCTION A CLINICAL MANIFESTATION OF NEUROVASCULAR DEGENERATION IN TYPE 1 DIABETIC PATIENTS?

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Aim: Type 1 diabetes mellitus (T1DM) is a chronic disease associated with degeneration of the nervous system. Olfactory dysfunction is suggested to be a clinical manifestation of central diabetic neuropathy. The aim of the study was to assess olfactory function in patients with T1DM.

Methods: We included 106 patients with type 1 diabetes (53 men), median age 35 (IQR 28-43) years, disease duration 18.5 (IQR 13-26) years, HbA1c 8.1 (IQR 7.25-9)%. The control group consisted of 30 healthy people. Olfactory function was assessed with "Sniffin' Sticks. For the assessment of odor identification 12 pens with different odors were used and patient should select 1 of 4 presented items which best described each odor for every pen (score 0-12, normosmia: score 11-12). We assessed the metabolic control of diabetes and the presence of diabetic retinopathy, peripheral neuropathy and diabetic kidney disease.

Results: Hyposmia was found in 67.9% of patients with type 1 diabetes compared to 53.3% in control group. Patients with peripheral neuropathy as well as retinopathy showed lower scores in the odor identification test [8 (IQR 7-9) vs 10 (IQR 9-11) scores; p=0.005; 9 (IQR 8-11) vs 10 (IQR 9-11) scores; p=0.03]. Lower olfactory identification score was independently associated with the presence of neuropathy (OR 0.61, 95% CI 0.43-0.85, p=0.003) and retinopathy (OR 0.48, 95% CI 0.28-0.83, p=0.005), after adjusting for gender, HbA1c, BMI, cigarette smoking, LDL cholesterol level.

Conclusion: Olfactory dysfunction is related to the presence of neurovascular degeneration in patients with T1DM.

Grant: Poznan University of Medical Sciences

[P57] SLEEP DISTURBANCE AND DEPRESSION IN PATIENT'S WITH PAINFUL NEUROPATHY

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Aims: Painful Diabetic Neuropathic (DN) is a burdensome disease affecting many important patient related outcomes, including Mood and Sleep. To evaluate the causal relationship between sleep disturbance and depressive symptoms in patients with painful DN.

Methods: Cross-sectional cohort study of 140 painful DN patients from the hospital diabetes register were assessed. The study adopted a multidimensional approach in order to understand sleep disturbance in painful DN. Patients underwent structured interviews, detailed clinical assessments and completed several self-administered questionnaires measuring pain severity (NTSS-6), cognitive processes in relation to pain, affective distress (Hospital Anxiety and Depression Scale) and sleep impairment (Medical Outcome Study Scale). In addition, patients provided demographic information.

Results: 57.6% male gender with a mean age of 61.3 (11.2) years and pain duration of 8.4 (6.0) years. There was a significant positive association between sleep disturbance and pain ($r = 0.40$; $p<0.001$) and depressive symptoms ($r = 0.30$; $p<0.001$). Depressive symptoms were greatest amongst those with both significant sleep disturbance and higher than average pain scores. Mediational analysis revealed that sleep disturbance partially mediates the effect of pain on depressive symptoms from 0.34 ($p<0.001$) to 0.29 ($p<0.001$).

Conclusion: Painful DN has a detrimental effect on pain and sleep. Sleep disturbance is independently associated with both pain severity and depressive symptoms. Poor sleep quality has been found to mediate the relationship between neuropathic pain and depressive symptoms. This study highlights the high prevalence of sleep disorders in neuropathic pain and has important clinical implications in the treatment of patients with painful DN.

[P58] THE EFFECT OF ERECTILE DYSFUNCTION ON QUALITY OF LIFE (QOL) IN A LARGE STUDY OF ROMANIAN MEN WITH SELF-REPORTED DIABETIC NEUROPATHY

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Objective: To evaluate the relationship of autonomic neuropathy (AN) subscale scores on Norfolk QoL-DN (Quality of Life Diabetic Neuropathy questionnaire) and reported erectile dysfunction.

Materials and methods: 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. Patients completed 35 questions related to their own health perception over the previous 4 weeks, resulting in 23,543 completed forms, 10,148 of which were completed by men. Patients also responded to these questions: "Do you have diabetes?", "Do you have neuropathy?", "In the past 4 weeks, have you had a problem with obtaining or maintaining erections?"(Erectile Dysfunction "ED").Autonomic neuropathy (AN) score was extracted from AN domain of the Norfolk QoL-DN questionnaire from patients with self-reported diabetes with and without DN. AN was positive if the subscale score was $\geqslant$ 2, scored on three items in the AN domain:1."vomiting, particularly after meals (but not due to flu or other illness)", 2."diarrhea and/or loss of bowel control", 3."fainting or dizziness when standing".

Results: From 10,148 validated forms, 9898 reported that they had diabetes, of whom 8859responded to the question on ED. Of these, 5704 (64.4%) reported DN and 2459 (43.1%) reported "Yes" to the question on ED. Of 3155 (35.6%) men who reported no DN only 657 (20.8 %) answered"Yes" to the question on ED ($p<0.001$). Of those with AN scores $\geqslant$ 2, 48.9% reported "Yes" to the ED question, compared with 27.9% of those with AN scores$<$ 2($p<0.001$).In considering age, the differences were maintained (21% vs.21.8%). 44.6% of men less than 60 years old with AN scores $\geqslant$ 2, answered "Yes" to the question on ED, compared to 22.8%of those with AN scores$<$ 2($p<0.001$). The mean AN score for those who answered "yes" to the ED question, was 2.13±0.04 compared with 1.25±0.03 for those who answered "no" ($p<0.001$). After multivariate logistic regression adjusted by age, there remains an association between the ED question and AN subscale score higher than 1, OR=2.35 (95%CI 2.14-2.57, $p<0.001$).

Conclusions: Patients with self-reported DN, who answer positively to the ED question, can be identified by a positive response to more than 1 of 3 of the questions in the AN domain of the Norfolk QOL-DN.

[P59] FEMALE SEXUAL DYSFUNCTION WITH SELF-REPORTED DIABETES AND NEUROPATHY ON QUALITY OF LIFE (QOL): A LARGE STUDY ON ROMANIAN PATIENTS

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Background and aims: Objective was to evaluate the relationship of score at autonomic neuropathy (AN) subscale and reported female sexual dysfunction.

Materials and methods: 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. Patients completed 35 questions related to their own health perception over the previous 4 weeks, resulting in 21,656 validated forms of 23,543 completed, of which 11,449 were completed by women. Patients respond also to auxiliary questions like “Do you have diabetes?”, “Do you have neuropathy?”, and “In the past 4 weeks, have you had a problem with vaginal dryness during intercourse?” the question on Female Sexual Dysfunction abbreviated as FSD. Autonomic neuropathy score (between 0-3) was obtain with Norfolk Quality Of Life Diabetic Neuropathy (QoL-DN) scores in self-reported diabetes with and without neuropathy (DN) as one of it's 5 subdomains.

Results: From 11,449 validated forms, 11,221 reported that they have diabetes. The number of women with self-reported diabetes who responded to the question on FSD was 9160.6444 (70.3%) reported neuropathy and 1899 of these (29.5%) reported “Yes” to the question “FSD”. Of 2716 (29.7%) women who denied diabetic neuropathy only 399 (14.7 %) reported “Yes” to the question “A” ($p<0.001$). Of those who replied “Yes” to the question “FSD”, the mean autonomic neuropathy score was 2.37±0.05 compared with 1.85±0.03 of those with”No” to the question “FSD” ($p<0.001$). If we took in consideration the age, the differences were maintain. Even in women younger than 65 years old (ROC curve cut-off), who answered “Yes” to the question “FSD”, the mean autonomic neuropathy score was 2.36±0.07 compared with 1.74±0.04 of those who answered ”No” to the question “FSD” ($p<0.001$).

Conclusions: Self-reported neuropathy increases the incidence of female sexual dysfunction, independent of age. Of the five domains in the Norfolk QOL-DN, greater than 1 in the autonomic domain, significantly increased the likelihood of symptomatic female sexual dysfunction.

[P60] THE IMPACT OF URINARY INCONTINENCE AND SEXUAL DYSFUNCTION WITH SELF-REPORTED DIABETES AND NEUROPATHY ON QUALITY OF LIFE (QOL): A LARGE STUDY ON ROMANIAN PATIENTS

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Background and aims: Objective was to evaluate the impact of self-reported urinary incontinence and sexual dysfunction on quality of life (QoL) scores from Norfolk QoL Diabetic Neuropathy (DN) questionnaire in people with diabetes.

Materials and methods: 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. Patients completed 35 questions related to their own health perception over the previous 4 weeks, resulting in 21,656 validated forms of 23,543 completed. Patients respond also to adjacent questions like “Do you have diabetes?”, “Do you have neuropathy?”, “In the past 4 weeks, have you had a problem with obtaining or maintaining erections?”question on UI (urinary incompetence), “In the past 4 weeks, have you had a problem with vaginal dryness during intercourse?”, “In the past 4 weeks, have you had a problem with involuntary urinating when laughing and coughing?”.

Results: Of 21,656 validated forms, 21,174 people self-reported diabetes. 20,387 people with self-reported diabetes responded to the question on UI. Of those 13,378 (65.6%) self-reported DN and 4657 (34.8%) with DN reported “Yes” to the question on “UI”. Of 6330 (35.4%) subjects who denied DN only 925 (14.6 %) reported “Yes” to the question “UI” (35.4%/14.6%, p<0.001). Patients with diabetes neuropathy without self-reported erectile/female sexual dysfunction and without urinary incontinence had Total Qol scores of 30.46±0.31 compared with people with urinary incontinence and with self-reported erectile/femalesexual dysfunction, but without DN (31.92±1.34, p=0.14). Males with erectile dysfunction, diabetic neuropathy and urinary incontinence had a Total QoL score 5.24 fold higher (53.34±0.85/10.00±0.24) than patients without DN, and without erectile/female sexual dysfunction. On activities of daily living and small fiber neuropathy subdomains, the score was 8.74/8.60 fold higher between these categories.

Conclusions: Quality of life is impaired in people who report erectile dysfunction/female sexual dysfunction and urinary incontinence compared to QoL in people who do or do not report diabetic neuropathy. The presence of neuropathy further impairs QOL. Sexual dysfunction and urinary incontinence greatly impairs total QoL as well as all domains of the Norfolk QoL-DN. Differences between Norfolk QoL-DN (Total and Subscale Scores (Mean ± SE)) in 21,656 Romanian Patients with Self-Reported Diabetes Mellitus for the “Yes”/”No”responses to the question “ In the past 4 weeks, have you had a problem with involuntary urinating when laughing and coughing?”:

[P61] SHOULD WE AVOID THE HANDGRIP TEST IN THE ASSESSMENT OF CARDIOVASCULAR AUTONOMIC NEUROPATHY IN DIABETIC PATIENTS? –EXPLORATORY FACTOR ANALYSIS

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Introduction: Historically, a set of five cardiovascular autonomic reflex tests (CARTs) was considered to be the gold standard of cardiovascular autonomic neuropathy (CAN) assessment. Current guidelines however suggest only the use of four with the omission of the diastolic blood pressure response to sustained handgrip. Thus we aimed to assess the association between the handgrip and the other tests.

Patients and methods: We recruited 353 diabetes patients (age: 60.2±7.4 years; female: 57.2%; BMI: 29.3±2.1 kg/m^2; diabetes duration: 15.6±9.9 years; HbA1c: 8.2±1.9%; type 1 diabetes: 18.1%). We measured the following CARTs: deep breathing test, Valsalva ratio, handgrip test, and orthostatic hypotension test. Definite CAN was defined as $\geqslant$2 abnormal CARTs excluding the handgrip test.

Results: The handgrip test had a sensitivity of 24.6% (95%CI 17.7%-33.1%) and a specificity of 79.4% (95%CI 73.3-84.4%) for the diagnosis of definite CAN. According to exploratory factor analysis, the four examined CARTs showed a 2-factor structure with the handgrip test loading to one factor (factor loading: 0.98) and the deep-breathing test, Valsalva ratio and orthostatic hypotension test clustered on another component with factor loadings 0.68, 0.77 and 0.66, respectively. Handgrip test abnormality showed an independent association with higher initial diastolic blood pressure values (OR: 1.05, p=0.0009) and an independent inverse association with the presence of hypertension (OR=0.42, p=0.006).

Conclusions: According to exploratory factor analysis, there is another independent factor underlying the results of the handgrip test differing from that underlying the results of the other cardiovascular reflex tests. Potential factors influencing handgrip test results could be the presence of hypertension and baseline diastolic blood pressure.

Keywords: diabetes, cardiovascular autonomic neuropathy, handgrip test, hypertension

[P62] CLUSTER ANALYSIS OF SYMPTOMS, PAIN SEVERITY, QUALRITY OF SLEEP AND LIFE IN PATIENTS WITH DIABETIC PERIPHERAL NEUROPATHY IDENTIFIES SUBGROUPS

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Aim: Diabetic peripheral neuropathy (DPN) is a very heterogeneous disease including different features of symptoms and impacts on sleep and quality of life (QOL). The aim of this study is to identify subgroups of clinical features that would enable to distinguish patients with DPN.

Methods: Data from the Korean Diabetes Association Neuropathy Study group in 2010 were used to analyze 1,338 patients with DPN. Cluster analysis and the analysis of the relationship between clustered groups and clinical variables were performed in a set of these patients.

Results: A total of 1,338 patients with DPN were grouped into three clusters based on the Michigan Neuropathy Screening Instrument (MNSI), Brief Pain Inventory-Short Form, visual analogue scales, Medical Outcomes Study Sleep, and EuroQol: asymptomatic (cluster 1, n= 448, 33.5%), mild symptomatic with disturbed sleep dominant (cluster 2, n = 562, 42.0%), and moderate to severe symptomatic with decreased QOL dominant (cluster 3, n = 328, 24.5%). Patients in cluster 1 were younger and less obese that those in cluster 3. While numbness was complained in patients with cluster 2 and 3, burning, prickling, and worse at night or walking were predominant symptom in patients with cluster 3. These clinical profile-based subgroups correlated with the data from the scales of pain, sleep, and QOL.

Conclusion: These cluster analyses further endorse the basis that symptomatic and comprehensive subgrouping of patients with DPN to tailor to personalization of evaluation and treatment.

[P63] ABSENT ANKLE REFLEXES – STILL A SPECIFIC SIGN OF DIABETIC POLYNEUROPATHY IN THE ELDERLY – A CROSS-SECTIONAL STUDY

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Aim: It remains unknown, whether absent ankle reflexes in elderly diabetic people, reflects the presence of diabetic neuropathy (DN), or can be explained by ageing. We aimed to determine whether absent ankle reflexes are a reliable sign of DN compared to nerve conduction studies (NCS), in an elderly population with screen-detected type 2 diabetes.

Methods: 121 participants of the ten-year clinical follow-up of the ADDITION-Denmark study, underwent NCS of three motor (Median, Peroneal, Tibial) and three sensory (bilateral Sural and Median) nerves. Activity of ankle reflexes was determined in a sitting position. From the NCS, categorization of DN was done by criteria of Dyck, requiring abnormal conductivity in more than one nerve (amplitude, velocity or F-latency > 2SD), at least including the Sural nerve. The test characteristics of bilateral absent ankle reflexes were calculated against NCS.

Results: 78 (64%) of participants were men, the median age was 70 years (IQR: 66; 75), 30 participants (25%) presented with DN. 14 (12%) showed absent ankle reflexes bilaterally. 8% without DN had absent ankle reflexes, whereas 23% with DN showed absent ankle reflexes. This yielded a sensitivity of 23%, a specificity of 92%, a positive predictive value of 50%, and a negative predictive value of 79%. A statistically significant association between absent ankle reflexes and NCS was found in a chi-squared test with p-value 0.020.

Conclusion: Our findings indicate, that absent ankle reflexes in the elderly, should continue being considered a reliable sign of DN, although the sensitivity of this test is low.

[P64] NEUROLOGICAL AND ELECTRODIAGNOSTIC EVALUATION OF PATIENTS WITH DIABETIC NEUROPATHY

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Aim: The aim of our study is to describe the different forms of peripheral nerve involvement in patients with diabetes mellitus (DM).

Methods: We examined all the diabetic patients referred to our center in the last two years; after the clinical neurological examination they were referred for electromyographic evaluation (nerve conduction studies with/without needle EMG).

Results: In most of the patients we found evidence of other forms of neuropathy than the distal symmetric sensory polyneuropathy. Most of them consisted in carpal tunnel syndrome, and other entrapment neuropathies (ulnar nerve at the elbow), but other forms of sensory-motor polyneuropathies, radiculopathies, were also seen.

Conclusion: Careful neurological examination and electromyographic studies when needed, can be very useful in the correct diagnosis and treatment orientation of patients with diabetic neuropathy. Red flags that should arise suspicion are: change in disease pattern, focal symptoms, important motor function involvement.

[P65] NERVECHECK: FOR THE ASSESSMENT SENSITIZATION TEST IN DIABETIC PERIPHERAL NEUROPATHY

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Objective: DPN prevalence up to 50 % and half has asymptomatic neuropathy. It is important to evaluate sensory subtype's deficits (SSD). Cutaneous application of L-menthol 40%(L-m) in healthy subjects (HS) induces cold sensitization of transient receptor potential melastatin 8 (TRPM8). SSD and threshold points (Thr P)can be measured by the Nerve Check quantitative sensory testing (QST). Implement a cold perception threshold (CPT) sensitization for clinical phenotyping of subtypes dysfunctions on TRMP8, A δ- and C-fibers in diabetic type 2 (DM2) without DPN.

Methods: 55 subjects,18 HS, 14 DM2 without DPN (G1), 13 DM2 with DPN (G2).Toronto criteria and NerveCheck selecting DPN groups. Subjects evaluated through CPT and after 10, 20, 40 min (´)L-m sensitization and Thr Pby levels method with 5 ST (ºC): 22, 4; 17, 8; 9,8 and void stimulus.

Results: Medians (percentile= 5th, 95th), Mann–Whitney U: P = 0.05 (*), P = 0.001 (**), CPT (CPT grading)HS = 6 (6, 6); G1 = 6 (3, 6); G2 = 2 (0, 6). CPT_sensitization TRMP8 (CPT grading)HS = 10' 2(2, 3); 20´ 4 (3, 5); 40´6 (6, 6). G1= 10´ 2(2, 4); 20´ 2 (2, 3); 40´4 (3, 6). (*). G2= 10´2 (2, 3); 20´ 4 (3, 6); 40´3 (0, 6) (**).

Conclusion: NerveCheck during clinical sensitization cold test may be a useful tool to detect clinical dysfunction of TRMP8, A δ- and C-fibers in DM2with or without DPN.

[P66] THE UTILITY OF POINT-OF-CARE SURAL NERVE CONDUCTION DEVISE (DPN-CHECK) FOR IDENTIFICATION OF DIABETIC NEUROPATHY – A CROSS SECTIONAL STUDY

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Aim: Conventional nerve conduction studies (NCS) are provided as gold standard for diagnosis of diabetic neuropathy (DN). However, NCS are time consuming and expensive. Recently, a more rapid and accessible point-of-car nerve conduction device (DPN-Check) has been developed that measures both sensory conduction velocity and amplitude of sural nerve. We aimed in this study to examine the utility of DPN-check compared to NCS in a large cohort of participants with screen-detected type-2 diabetes.

Methods: From the ADDITION-Denmark ten-year follow-up study, 121 participants (median age:70) were included. Conventional NCS and DPN-check were done by blinded examiners. Participants underwent NCS of three motor (median, peroneal, tibial) and three sensory (bilateral sural and median) nerves. The NCS results were compared to laboratory controls. From NCS, DN was classified by Dyck's criteria. DPN-check results were compared to reference values of the devise. For DPN-check, abnormality on both sural nerves was required for DN. DPN-check results were calculated against NCS which was taken as gold standard.

Results: 30 participants (25%) presented with DN by NCS while 44 participants (36%) presented with DN by DPN-check. In 26 participants both tests showed DN and in 73 both tests were normal. This yielded a sensitivity of 87%, a specificity of 80%, a positive predictive value of 59% and a negative predictive value of 95%. A statistically significant association between abnormal DPN-check and NCS was found (chi-square,$p<0.001$).

Conclusions: DPN-check may provide a rapid and cheap screening of diabetic neuropathy, however abnormal results need to be confirmed by conventional NCS.

[P67] ASSOCIATION BETWEEN MIR499 GENE POLYMORPHISM AND DIABETIC NEUROPATHY IN TYPE 2 DIABETES

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Background: MicroRNAs (miRNAs) are non-coding RNAs that regulate gene expression. Genetic variants (such as Single-Nucleotide Polymorphisms, SNPs) in miRNA genes may be involved inthe deregulation of target gene expression. The miR499 is a novel miRNA, mainly expressed in the muscle, heart, and brain, and implicated in cardiovascular disease, cancer, rheumatoid arthritis, and metabolic syndrome.

Aim: To investigate whether the miR499 A/G rs3746444SNP is associated with susceptibility to diabetic polyneuropathy (DPN) and/or cardiovascular autonomic neuropathy (CAN) in type 2 diabetes.

Methods: In 150 type 2 patients (age 63.8±8.1 years, duration 12.7±9.5 years, BMI 30.8±5.2 Kg/m^2, 89 males) the rs3746444 was investigated by TaqMan genotyping assay. Cardiovascular tests, MNSI-Q and MDNS for neuropathic symptoms and signs, VPT, and Thermal Thresholds (TT) were used for CAN and DPN assessment.

Results: AA, AG, and GG genotypes were present in 56%, 38%, and 6% of patients, respectively. After ANOVA analysis and adjustment for sex, age, BMI, duration, and HbA1c, GG genotype was associated with higher insulin dose (P=0.030), CAN score (P<0.0001), MDNS (P=0.010), and VPT (P=0.004)in comparison with AA and AG genotypes. Moreover, GG genotype was associated with the presence ofearly CAN (Chi^2=9.75, P=0.006, OR 7.57, 95% C.I. 1.8-32.2), confirmed CAN (Chi^2=13.1, P=0.006, OR 9.92,95% C.I. 1.8-32.2), and abnormal TTs (Chi^2=7.65, P=0.01, OR 11.4, 95% C.I. 1.3-98.1).In a logistic regression analysis, including sex, age, BMI, duration, HbA1c, insulin dose, physical activity, LDL cholesterol, systolic BP, eGFR, retinopathy, and GG genotype as independent variables, CAN was predicted by duration (OR 1.1, CI 95% 1.01-1.19, P=0.031) and GG genotype (OR 35.8, CI 95% 2.7-467, P=0.006) (r^2=0.36). In a multiple regression analysis with the same variables, GG genotype was the major determinant of CAN score (P=0.001, adjusted r^2=0.27). The association with DPN was lost in multivariate analyses.

Conclusions: This novel association of miR499rs3746444SNP with CAN susceptibility, albeit requiring replication in larger cohorts, might suggest a role of miR499 in cardiovascular autonomic dysfunction in diabetes.

[P68] EEG ASPECTS IN RENAL HEMODIALYSIS: COMPARISON OF DIABETIC VS. NON-DIABETIC PATIENTS

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Hemodialysis sessions are accompanied for a short time interval by abrupt changes of the serum ionic values. Blood pH has major importance, knowing that discrete changes could modulate the permeability of the blood brain barrier (BBB). (Vanhatalo et al., 2002; Nita et al., 2004). The permeability of the BBB could be recorded by EEG as very slow waves. (Tetrault et al., 2008).

In this paper we compared the amplitude and frequency EEG features of a patient with diabetus melitus (DM) and a patient without diabetus mellitus (non DM). We recorded wake scalp EEG, respecting 10-20 system, during 4 hours of dyalisis.

Before dialysis session, both patients had EEG with fast activity (>10 Hz) and relatively low amplitude: peak-to-peak maximum amplitude was 114,4 μV for the DM patient (with standard deviation 12,14 μV), while for the non DM patient the value was 223,2 μV (with standard deviation 24,97 μV). These values establish the starting point (inter-individual variability) for the comparison between the two patients. The patient with DM has a maximum amplitude that represents 51% compared with the maximum amplitude of the non DM patient . Comparising the standard deviation, the report was 49%.

After the dialysis session, both patients produced very slow oscillations on EEG (<0,1 Hz) with great amplitudes, suggestive for compromised BBB. More than that , the maximum amplitude was 1,2 mV in DM patient, compared with only 0,8 mV in the non DM patient. This represents an absolute increase with 50% and a relative increase of 194% (considering that the patients have been started from the same EEG max amplitude before dialysis). Except the very slow waves, the features of the EEG were not changed in the two patients: standard deviation were 12,14 μV in DM patient, and 24,97 μV in nonDM patient, keeping a ratio of 49%.

These results suggest that during the hemodialysis, the diabetic patient suffers a more pronounced opening of BBB compared with the non-diabetic patient.

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AUTHORS INDEX