33rd Neurodiab Annual Meeting 28 September - 1 October 2023 Thessaloniki, Greece

Final Program

Scientific program endorsed by EASD

SCIENTIFIC PROGRAM

DAY 1 - Thursday 28 September 2023

Time	Topic	Speakers/Chair
14:00 - 14:45 (45')	**Introduction**	Vincenza Spallone and Triantafyllos Didangelos
	Opening Ceremony	Greetings from Aristotle University Authorities and Greek Minister
14:45 - 16:15 (90')	**Oral session Young Investigator Award 1** (OR.O1-OR.O5, OR.07)	Chairs: Abd Tahrani (Birmingham, UK), Prashant Vas (London, UK)
16:15 - 16:35 (20')	Coffee break	
16:35 - 16:50 (15')	**Lecture**	
	In memory of Aaron (Arthur) Vinik	Solomon Tesfaye (Sheffield, UK)
16:50- 17:20 (30')	**Invited lecture 1**	Chair: Gidon J Bönhof (Düsseldorf, Germany)
	1. Exercise and diabetic neuropathy	Ilias N. Migdalis (Athens, Greece)
17:20 - 18:35 (75')	**Oral session Young Investigator Award 2** (OR.O8-OR.12)	Chairs: Fabiana Picconi (Rome, Italy), Sanjeev Sharma (Ipswich, UK)
18:35 - 19:05 (30')	**Lifetime achievement award ceremony**	Soroku Yagihashi (Hirosaki, Japan) presented by Mark Yorek (Iowa City, US) Jiro Nakamura (Nagakute, Japan) presented by Hideki Kamiya (Nagakute, Japan) Ilias N. Migdalis (Athens, Greece) presented by Triantafyllos Didangelos (Thessaloniki, Greece)

SCIENTIFIC PROGRAM

DAY 2 - Friday 29 September 2023

Time	Topic	Speakers/Chair
8:00 – 8:30 (30')	**Invited lecture 2**	Chair: Niels Ejskjaer (Aalborg, DK)
	1. New risk factors and mechanisms: the impact of the exposome	Christian Herder (Düsseldorf, Germany)
8:30 - 10:30 (120')	**Oral session Young Investigator Award 3** (OR.13-OR.17)	Chairs: Mitra Tavakoli (Exeter, UK), Bruce Perkins (Toronto, Canada)
	Oral session 1 (OR.18-OR.20)	Chair: Uazman Alam (Liverpool, UK)
10:30 - 10:50 (20')	Coffee break and Exhibition	
10:50 - 11:20 (30')	**The Göran Sundkvist Young Investigators Award for Clinical Science**	Chairs: Vincenza Spallone (Rome, Italy) and Triantafyllos Didangelos (Thessaloniki, Greece
	Corneal confocal microscopy: ophthalmology meets neurology	Maryam Ferdousi (Manchester, UK)
11:20 - 12:20 (60')	**Symposium 1**: Large observational studies in type 1 diabetes: lessons learnt	Chairs: Rodica Pop-Busui (Ann Arbor, US), Soroku Yagihashi (Hirosaki, Japan)
	1. DCCT/EDIC perspective	Barbara Braffett (Rockville, US)
	2. T1D Exchange perspective	Kara Mizokami-Stout (Ann Arbor, US)
	3. Unmet needs in type 1 diabetes	Bruce Perkins (Toronto, Canada)
12:20- 13:20 (60')	**Sponsored Symposium by Wörwag Pharma GmbH & Co. KG** Two underdiagnosed and undertreated complications of diabetes: DSPN & CAN – recent findings and unmet need	Chair: Péter Kempler (Budapest, Hungary)
	1. Treatment routine of DSPN: implementation in clinical practice- still a long way to go?	Dan Ziegler (Düsseldorf, Germany)
	2. Impact, diagnosis, and management of CAN: Recent advances	Vincenza Spallone (Rome, Italy)
13:20 - 14:15 (55')	Lunch	

SCIENTIFIC PROGRAM

DAY 2 - Friday 29 September 2023

Time		Speakers/Chair
14:15 - 15:20 (65')	**Poster session Young Investigators Award 1** (P.01-P.10)	Chairs: Kara Mizokami-Stout (Ann Arbor, US), Soroku Yagihashi (Hirosaki, Japan)
	Poster session 1 (P.11-P.21)	Chairs: Anne-Marie Wegeberg (Aalborg, Denmark), Chong Hwa Kim (Bucheon, Korea)
	Poster Session 2 (P.22-P.32, P.62)	Chairs: Mark Yorek (Iowa City, US), Stephanie Eid (Ann Arbor, US)
15:20 - 16:20 (60')	**Sponsored Symposium** **By Impeto Medical** Diagnostic and Clinical Utility of Sudoscan	Chair: Triantafyllos Didangelos (Thessaloniki, Greece), Brian Callaghan (Ann Arbor, USA)
	1. US research development on the technology	Carolina Casellini (Norfolk, US)
	2. The use of Sudoscan in the early diagnosis of DPN	Dinesh Selvarajah (Sheffield, UK)
	3. The French clinical experience and its evolution at home	Jean Pascal Lefaucheur (Créteil, France)
16:20 - 17:20 (60')	General Assembly	

SCIENTIFIC PROGRAM

DAY 3 - Saturday 30 September 2023

Time	Topic	Speakers/Chair
8:00 - 8:30 (30)	**Invited lecture 3**	Chair: Mark Yorek (Iowa City, US)
	1. Treatments from animals to humans: the limitations and prospects of translational research	Paul Fernyhough (Winnipeg, Canada)
8:30 - 9:45 (75')	**Oral session 2** (OR.21-OR.25) Longitudinal observations	Chairs: Christina Brock (Aalborg, Denmark), Thomas Tegos (Thessaloniki, Greece)
9:45 - 10:15 (30')	**The Angelika Bierhaus Young Investigators Award for Preclinical Science**	Chairs: Vincenza Spallone (Rome, Italy) and Triantafyllos Didangelos (Thessaloniki, Greece)
	1. Functional significance of HIF1a activation in the manifestation of type 2 diabetic neuropathic pain	Richard Hulse (Nottingham, UK)
10:15 - 10:35 (25')	Coffee break and Exhibition	
10:35 - 12:00 (85')	**Symposium 2**: New approaches to diagnosis	Chairs: Rayaz Malik (Doha, Qatar), Andrea Truini (Rome, Italy)
	1. Artificial intelligence-based prediction models	Uazman Alam (Liverpool, UK)
	2. Small fiber measures	Troels Staehelin Jensen (Aarhus, Denmark)
	3. Pain phenotyping	Andrea Truini (Rome, Italy)
	4. Autonomic testing	Anna Körei (Budapest, Hungary)
12:00 - 13:00 (60')	**Sponsored Symposium by P&G HEALTH** Diagnosis of DPN – How to shift the paradigm from treating painful DPN to diagnosing early?	Chair: Shazli Azmi (Manchester, UK)
	Welcome and intro	
	Diabetic neuropathy: The Good, the Bad and the Ugly	Rayaz Malik (Doha, Qatar)
	Improving DPN screening uptake – case studies from Europe and South-East Asia	Solomon Tesfaye (Sheffield, UK)
	Discussion	
	Wrap-up, thank you, closing remarks	
13:00 - 14:00 (60')	Lunch	

SCIENTIFIC PROGRAM

DAY 3 - Saturday 30 September 2023

Time	Topic	Speakers/Chair
14:00 - 15:00 (60')	**Poster session Young Investigators Award 2** (P.33-P.42)	Chairs: Gabriela Radulian (Bucharest, Romania), Eirik Søfteland (Bergen, Norway)
	Poster session 3 (P.43-P.51)	Chairs: Aleksandra Araszkiewicz (Poznan, Poland), Ioannis Petropoulos (Doha, Qatar)
	Poster session 4 (P.52-P.61)	Chairs: Ariel Odriozola (Barcelona, Spain), Alexander Strom (Düsseldorf, Germany)
15:00 - 15:45 (45')	**Symposium 3**: Electrical stimulation as a therapeutic tool	Chair: Gerry Rayman (Ipswich, UK)
	1. For neuropathic pain	Solomon Tesfaye (Sheffield, UK)
15:45 - 16:55 (70')	2. For gastrointestinal symptoms	Christina Brock (Aalborg, Denmark)
	Symposium 4: Joint meeting Neurodiab - PNS: Insights into the nerve damage in diabetic neuropathy	Chairs: Brian Callaghan (Ann Arbor, US), Dinesh Selvarajah (Sheffield, UK)
	1. The role of Schwann cell-axon interactions in metabolic disease	Stephanie Eid (Ann Arbor, US)
	2. The role of mitochondria and bioenergetic failure in painful neuropathy	Daniela Menichella (Chicago, US)
16:55 - 17:40 (45')	3. The role of nerve vessels	Zoltan Kender (Heidelberg, Germany)
	Oral session 3 (OR.26-OR.29)	Chairs: Maryam Ferdousi (Manchester, UK), Praveen Anand (London, UK)

SCIENTIFIC PROGRAM

DAY 4 - Sunday 1 October 2023

Time	Topic	Speakers/Chair
8:30 - 9:45 (75')	**Oral session 4** (OR.30-OR.34)	Chairs: Lynn Ang (Ann Arbor, US), Tamás Várkonyi (Szeged, Hungary)
9:45 - 10:15 (30')	**Invited lecture 4**	Chair: Peter Kempler (Budapest, Hungary)
	1. Reversing neuropathy: recent evidence and mechanisms	Praveen Anand (London, UK)
10:15– 10:40 (25')	Coffee break and Exhibition	
10:40 - 11:40 (60')	**Oral session 5** (OR.35-OR.38)	Chairs: Shazli Azmi (Manchester, UK), Christos Savopoulos (Thessaloniki, Greece)
11:40 - 12:40 (60')	**Symposium 5**: Unexplored territories of neural control	Chairs: Paul Valensi (Paris, France), Carla Greco (Modena, Italy)
	1. Gut microbiota	Virginie Mansuy-Aubert (Lausanne, Switzerland)
	2. Female sexual function	Eirik Søfteland (Bergen, Norway)
12:40 – 13:00 (20')	Closing Remarks	Vincenza Spallone and Triantafyllos Didangelos

Oral sessions

28 September 2023
14:45 - 16:15

Oral session Young Investigators Award for the Best Oral Presentation 1
(OR.O1-OR.O7) (Epidemiology, biomarkers, and assessment of diabetic polyneuropathy)

Chairs: Abd Tahrani (Birmingham, UK) and Prashant Vas (London, UK)

OR.01 Liver fibrosis indices are related to diabetic peripheral neuropathy in individuals with type 2 diabetes mellitus
Carla Greco (Modena, Italy)

OR.02 Abnormal combined DPN-check and Sudoscan results predict all-cause mortality in people with diabetes: the Sheffield Prospective Study
Mohummad Shaan Goonoo (Sheffield, UK)

OR.03 Determinants of corneal nerve morphology in an unselected population-based cohort from Qatar
Ioannis Petropoulos (Doha, Qatar)

OR.04 Longitudinal changes in serum neurofilament light chain levels in type 2 diabetes and diabetic polyneuropathy
Laura Linnea Mää9ä (Aarhus, Denmark)

OR.05 Changes in sciatic nerve structural integrity and cross-sectional area are associated with distinct peripheral sensory phenotypes in individuals with type 2 diabetes
Zoltan Kender (Heidelberg, Germany)

OR.07 New observational windows of neuropathic damage in type 2 diabetic patients
Marika Menduni (Rome, Italy)

Oral sessions

28 September 2023
17:20 - 18:35

Oral session Young Investigators Award for the Best Oral Presentation 2
(OR.08-OR.12) (Brain, pain, treatment, and epidemiology of autonomic neuropathy)

Chairs: Fabiana Picconi (Rome, Italy) and Sanjeev Sharma (Ipswich, UK)

OR.08 Cerebral structural alterations after chronic opioid pharmacotherapy treatment in painful-diabetic peripheral neuropathy
Gordon Sloan (Sheffield, UK)

OR.O9 Comparison of central parasympathetic and cutaneous responses to insulin-induced hypoglycemia
Maria Bitsch Poulsen (Aalborg, Denmark)

OR.10 Risk of diabetic microvascular complications, heart failure, hospitalisation and all-cause mortality with SGLT2i and GLP1-RA in type 2 diabetes: a real-world data study
Aikaterini Eleftheriadou (Liverpool, UK)

OR.11 Cardiovascular autonomic function in long COVID-19 individuals with and without diabetes
Lynn Ang (Ann Arbor, US)

OR.12 Sex differences in the inverse associations of monocyte counts and neutrophil-to-lymphocyte ratio with heart rate variability: the Maastricht Study
Haifa Maalmi (München-Neuherberg, Germany

Oral sessions

29 September 2023
08:30 – 09:45

Oral session Young Investigators Award for the Best Oral Presentation 3
(OR.13-OR.17) (Autonomic neuropathy assessment)

Chairs: Mitra Tavakoli (Exeter, UK) and Bruce Perkins (Toronto, Canada)

OR.13 Sweat gland nerve fiber density and association to sudomotor function, symptoms, and risk factors in adolescents with type 1 diabetes
Vinni Faber Rasmussen (Randers, Denmark)

OR.14 Symptoms of autonomic neuropathy in 25% of people with diabetes from the north Denmark region using the Composite Autonomic Symptoms Score-31
Anne-Marie Wegeberg (Aalborg, Denmark)

OR.15 Determinants of orthostatic hypotension in type 1 diabetes: neurogenic or non-neurogenic?
Ilenia D'ippolito (Rome, Italy)

OR.16 Normative thresholds of cardiovascular autonomic function: the LOFUS study
Marie MB Christensen (Herlev, Denmark)

OR.17 Validation of indicator plaster Neuropad for the detection of autonomic neuropathy in patients with diabetes mellitus
Ioanna Zografou (Thessaloniki, Greece)

Oral sessions

29 September 2023
09:45 – 10:30

Oral session 1 Epidemiology and assessment of diabetic polyneuropathy (OR.18-OR.20)

Chairs: Uazman Alam (Liverpool, UK)

OR.18 Sex differences in severity of diabetic peripheral and autonomic neuropathy
Eleni Karlafti (Thessaloniki, Greece)

OR.19 Investigating the role of obesity and metabolic markers for the presence and severity of peripheral neuropathy in type 2 diabetes, pre-diabetes (IGT) and healthy subjects
Mitra Tavakoli (Exeter, UK)

OR.20 New normative reference data for Rydel-Seiffer tuning fork vibration thresholds and diagnostic performance of Neuropathy Disability Score to detect diabetic polyneuropathy
Gidon Bönhof (Düsseldorf, Germany)

Oral sessions

30 September 2023
08:30 – 09:45

Oral session 2 Longitudinal observations (OR.21-OR.25)

Chairs: Christina Brock (Aalborg, Denmark) add Thomas Tegos (Thessaloniki, Greece)

OR.21 Natural course of declining nerve function during the first 10 years of well-controlled recently diagnosed type 2 diabetes
Alexander Strom (Düsseldorf, Germany)

OR.22 Long-term abnormal corneal nerve morphology predicts progression of neuropathic deficits in type 2 diabetes
Georgios Ponirakis (Doha, Qatar)

OR.23 Elevated diabetic ketoacidosis risk following ulcer or amputation in T1D: 34 year follow-up of DCCT/EDIC
Bruce Perkins (Toronto, Canada)

OR.24 The influence of chronic kidney disease on diabetes neuropathy – results of the 5-year longitudinal Ipswich NeuroDiab study
Sanjeev Sharma (Ipswich, UK)

OR.25 Bidirectional association between diabetic peripheral neuropathy and vitamin B12 deficiency: two longitudinal 9-year follow-up studies using a national sample cohort
Tae Sun Park (Jeonju, South Korea)

Oral sessions

30 September 2023

16:55 – 17:40

Oral session 3 Pain treatment (OR.26-OR.29)

Chairs: Maryam Ferdousi (Manchester, UK) and Praveen Anand (London, UK)

OR.26 Opening of KV7 channels activates AMPK and mimics aspects of antimuscarinic drug action in adult sensory neurons
Paul Fernyhough (Winnipeg, Canada)

OR.27 Responders to neuropathic pain treatment have greater target engagement of dopamine receptor systems: a resting-state functional magnetic resonance imaging study in painful diabetic neuropathy
Dinesh Selvarajah (Sheffield, UK)

OR.29 LX9211 in individuals with painful diabetic peripheral neuropathy: results from a randomized, double-blind, placebo-controlled, parallel-group, multicenter study
Rodica Pop-Busui (Ann Arbor, US)

Oral sessions

1 October 2023
08:00 – 09:45

Oral session 4 Brain and autonomic neuropathy (OR.30-OR.34)

Chairs: Lynn Ang (Ann Arbor, US) and Tamás Várkonyi (Szeged, Hungary)

OR.30 Olfactory function and measurements of rhinencephalon structures upon magnetic resonance imaging in adults with type 1 diabetes are related to diabetic peripheral neuropathy
Aleksandra Araszkiewicz **(**Poznan, Poland)

OR.31 The impact of autonomic and peripheral diabetic neuropathy on cognitive function in older type 2 diabetic patients
Marika Menduni (Rome, Italy)

OR.32 Soluble urokinase plasminogen activator receptor is associated with cardiovascular autonomic neuropathy in type 1 diabetes
Christian Stevns Hansen (Herlev, Denmark)

OR.33 Changes in diastole duration during five minutes of deep breathing in overweight or diabetic patients with obstructive sleep apnoea syndrome
Paul Valensi (Paris, France)

OR.34 No certain association between autonomic nerve dysfunction and the incretin effect
*Sondre Meling (*Stavanger, Norway)

Oral sessions

1 October 2023
10:40 – 11:40

Oral session 5 Disease-modifying treatment (OR.35-OR.038)

Chairs: Shazli Azmi (Manchester, UK) and Christos Savopoulos (Thessaloniki, Greece)

OR.35 Dietary reversal and/or exercise correct peripheral neuropathy in a mouse model of diet- induced obesity
Diana Rigan (Ann Arbor, US)

OR.36 Imeglimin, a new oral hypoglycemic agent, improves hyperglycemia and hypoglycemia-induced cell death and mitochondrial dysfunction in Schwann cells
Koichi Kato (Nagoya, Japan)

OR.37 Improvement of cardiovascular autonomic function in patients with metabolic syndrome with and without diabetes after a physical training program
Tamás Várkonyi (Szeged, Hungary)

OR.38 The impact of obstructive sleep apnoea treatment on peripheral neuropathy in patients with type 2 diabetes: results from a 2-year feasibility RCT
Esraa Makhdom (Birmingham, UK)

Poster sessions

29 September 2023
14:15 - 15:20

Poster session Young Investigators Award for the Best Poster Presentation 1
(P.01-P.10) (Epidemiology and mechanisms)

Chairs: Kara Mizokami-Stout (Ann Arbor, US) and Soroku Yagihashi (Hirosaki, Japan)

P.01 Predictors of diabetic peripheral neuropathy: systematic review and meta-analysis
Sher Mein Chew (Singapore, Singapore)

P.02 A heavy burden of amputation caused by diabetic neuropathy for the health care system of Georgia
Rusudan Kvanchakhadze (Tbilisi, Georgia)

P.03 Investigating the association between neuropathy and cardiovascular disease in patients with diabetes
Raabya Pasha (Manchester, UK)

P.04 The difference in diabetic peripheral neuropathy prevalence in two distinct editions of the European futsal championship for people with diabetes
Daniel-Tudor Cosma (Horezu, Romania)

P.05 Longitudinal changes in corneal small nerve fibre morphology in Parkinson's disease: a corneal confocal microscopy study
Ayesha Malik (London, UK)

P.06 Characterising cognitive deficits and transcriptomic changes in the hippocampus of male Wistar rats with prediabetes
Hasan Alshatti (Manchester, UK)

P.07 Activation and reprogramming of human Muller cell line MIO-M1 exposed to high glucose and glucose variability: an in vitro study
Benedetta Russo (Rome, Italy)

P.08 The impact of PCSK9 inhibition on the development of peripheral neuropathy
Ali Jaafar (Réunion, France)

P.09 Pericyte-astrocyte crosstalk mediating altered microvascular blood flow in diabetic neuropathic pain
Lydia Hardowar (Norngham, UK)

P.10 Perception threshold tracking reveals different small nerve fiber function in subgroups of people with diabetic peripheral neuropathy
Johan Røikjer (Aalborg, Denmark)

Poster sessions

29 September 2023

14:15 – 15:20

Poster session 1 Epidemiology and care organization (P.11-P.21**)**

Chairs: Anne-Marie Wegeberg (Aalborg, Denmark) and Chong Hwa Kim (Bucheon, Korea)

P.11 Association between general and abdominal obesity in type 2 diabetes with diabetic neuropathy: results from a National Health Insurance Service–National Sample Cohort, 2015
Seon Mee Kang (Chuncheon, South Korea)

P.12 Association between liver fibrosis and cognitive impairment in elderly patients with type 2 diabetes
Maria Del Pilar Sanchis Cortes (Palma de Mallorca, Spain)

P.13 The role of hypertriglyceridemia in the development of diabetic neuropathy (DPN) in patients with type 2 diabetes in Georgia by Sudoscan
Tamar Maghradze (Tbilisi, Georgia)

P.14 Link between small fiber neuropathy and depression in patients with diabetic polyneuropathy: a corneal confocal microscopy study
Hidayah Afzal (Manchester, UK)

P.15 Is diabetic neuropathy affected by lipoprotein a? A retrospective epidemiological study in an Egyptian cohort
Hani Naiem Ibrahim (Cairo, Egypt)

P.16 Diabetic neuropathy status of patients with or without ischemic heart disease, a retrospective epidemiological study in an Egyptian cohort
Hani Naiem Ibrahim (Cairo, Egypt)

P.17 Statistics of diabetic neuropathy in Georgia
Tamar Gogoberidze (Tbilisi, Georgia)

P.18 Understanding the management of diabetic neuropathy: a national survey of healthcare professionals in the United Kingdom
Raksha Ravishankar (London, UK)

P.19 Assessing diabetic neuropathy clinical practice guidelines using the AGREE II Framework
Umama Ahmed (London, UK)

P.20 Study protocol for Developing a Core Outcome set for Diabetic nEuropathy clinical trials (DECODE)
Sasha Smith (London, UK)

P.21 The role of the pharmacist in the screening for diabetic neuropathy – partially results from the "See the sweet part of life" campaign
Daniel-Tudor Cosma (Horezu, Romania)

Poster sessions

29 September 2023 | 14:15 – 15:20

Poster session 2 Mechanisms of nerve damage and possible targets (P.22-P.32, P.62)

Chairs: Mark Yorek (Iowa City, US) and Stephanie Eid (Ann Arbor, US)

P.22 Prediabetes impairs Schwann cell-axon communication via the lactate shuttle
Crystal Pacut (Ann Arbor, US)

P.62 Type 2 diabetic neuropathic pain is dependent upon Hypoxia Inducible Factor 1 alpha mediated activation of dorsal horn neurons
Richard Hulse (Nottingham, UK)

P.23 Peripheral nervous system-specific Kcnj11-deficient mice develop dysfunction of peripheral nerves
Tsubasa Mizuno (Aichi, Japan)

P.24 Dimethyl fumarate improves NRF-2 mediated anti-oxidant response to ameliorate functional and molecular deficits in experimental diabetic neuropathy
Ashutosh Kumar (Nagar, India)

P.25 TRPM3 activation mediates stimulatory effects of muscarinic receptor antagonism on mitochondrial function and axonal outgrowth in diabetic peripheral neuropathy
Paul Fernyhough (Winnipeg, Canada

P.26 Beta-arrestin-biased agonism at the M_1 muscarinic receptor of adult sensory neurons
Paul Fernyhough (Winnipeg, Canada)

P.27 Could be methylglyoxal the culprit of the diabetes-induced Parkinson's disease?
Miquel Adrover (Palma, Balearic Islands, Spain)

P.28 Efficacy of pyruvate and benfotiamine against mouse and cell culture models of diabetic neuropathy
Kazunori Sango (Tokyo, Japan)

P.29 Transplantation of dental pulp stem cells ameliorates hindlimb skeletal muscle atrophy and peripheral nerve dysfunction in diabetic rats
Keiko Naruse (Aichi, Japan)

P.30 Three-dimensional pathological analysis of DRG neurons in experimental diabetic polyneuropathy
Hiroki Mizukami (Hirosaki, Japan)

P.31 Co-culture of lined dorsal root ganglion neurons and Schwann cells as a useful tool for the study of diabetic neuropathy
Shizuka Takaku (Tokyo, Japan)

P.32 Systemic biomarkers of microvascular alterations in type 1 diabetes associated neuropathy and nephropathy
Evangelia Baldimtsi (Linköping, Sweden)

Poster sessions

30 September 2023
14:00 – 15:00

Poster session Young Investigators Award for the Best Poster Presentation 2 (P.33-P.42)
(Autonomic neuropathy and treatment)

Chairs: Gabriela Radulian (Bucharest, Romania) and Eirik Søfteland (Bergen, Norway)

P.33 Blood oxygen saturation and associations with autonomic and peripheral neuropathy in diabetes
Rasmus Budde Brødsgaard (Herlev, Denmark)

P.34 Hypertriglyceridemia and cardiovascular autonomic function in patients without diabetes: a cross-sectional study
Bilal Bashir (Manchester, UK)

P.35 Heart failure in patients with type 2 diabetes mellitus and coronary artery disease with and without cardiovascular autonomic neuropathy
Olha Monashnenko (Kyiv, Ukraine)

P.36 Assessment of diabetic autonomic neuropathy using pupillometry and corneal confocal microscopy in patients with diabetes and concurrent sexual dysfunction
Zara Linn (Manchester, UK)

P.37 The effect of global nox4 deletion on peripheral nerve function in a mouse model of diet- induced obesity and prediabetes
Andrew Carter (Ann Arbor, US)

P.38 Effect of B vitamins on neurite regeneration in a 3D co-culture model of neurodegeneration
Christian Viel (Schwalbach am Taunus, Germany)

P.39 The anti-diabetic drug troglitazone activates TRPA1 in sensory neurons
Mohua Kibria Mumu (London, UK)

P.40 Differential effects on corneal nerve fiber regeneration with different GLP-1 receptor agonists in children and adults with obesity
Hoda Gad (Doha, Qatar)

P.41 Alleviation of autonomic dysfunction measured as pressure pain sensitivity at the sternum improves empowerment and quality of life in type 2 diabetes: a randomized trial
Sofie Hecquet (Herlev, Denmark)

P.42 Neuromuscular electrical stimulation for the treatment of diabetic sensorimotor polyneuropathy: a prospective, cohort, proof-of-concept study
Sasha Smith (London, UK)

Poster sessions

30 September 2023
14:00 - 15:00

Poster session 3 Small fiber and autonomic neuropathy (P.43-P.51)

Chairs: Aleksandra Araszkiewicz (Poznan, Poland) and Ioannis Nicholaos Petropoulos (Doha, Qatar)

P.43 Early corneal nerve loss in children with melanocortin 4 receptor (MC4R) gene mutation related obesity
Hoda Gad (Doha, Qatar)

P.44 Early corneal nerve loss in children with obesity and type 2 diabetes
Hoda Gad (Doha, Qatar)

P.45 Corneal confocal microscopy as a marker to monitor the progression of small fibre neuropathy in people with and without cardiac autonomic neuropathy
Liam Davidson (Manchester, UK)

P.46 Relation between advanced glycated end products and sympathetic activity in overweight patients with obstructive sleep apnoea syndrome
Paul Valensi (Paris, France)

P.47 Cardiac Autonomic Neuropathy and Progressive Renal Decline in Patients with Type 1 Diabetes: A 15-year follow up study
Dinesh Selvarajah (Sheffield, UK)

P.48 Is recovery of cardiovascular autonomic neuropathy possible in type 1 diabetes? A 5-year follow-up study
Ilenia D'ippolito (Rome, Italy)

P.49 Cardiovascular Autonomic Neuropathy is a risk factor of arterial stiffness in Type 2 diabetes
Seongsu Moon (Daegu, South Korea)

P.50 Comparison of each test of cardiovascular reflex tests in the diagnosis of diabetic cardiovascular autonomic neuropathy
Chong Hwa Kim (Bucheon, South Korea)

P.51 Transcutaneous vagal nerve stimulation for treating gastrointestinal symptoms in people with diabetes: a randomized, double-blind, sham-controlled, multicentre study
Anne-Marie Wegeberg (Aalborg, Denmark)

Poster sessions

30 September 2023
14:00 - 15:00

Poster session 4 Diagnosis and treatment of diabetic neuropathy (P.52-P.61)

Chairs: Ariel Odriozola (Barcelona, Spain) and Alexander Strom (Düsseldorf, Germany)

P.52 Corneal nerve sensitivity: early detection of diabetic peripheral neuropathy (DPN)
Mark Yorek (Iowa City, US)

P.53 Proposal of a new objective diagnostic criterion with versatility for diabetic peripheral neuropathy
Tatsuhito Himeno (Aichi, Japan)

P.54 The morphological analysis of lower limb nerves using ultrasonography is useful to evaluate diabetic polyneuropathy
Yuka Shibata (Aichi, Japan)

P.55 A randomized, double-blind, placebo-controlled 52-week study to assess the effects of liraglutide on somatic and autonomic nerve function in subjects with type 2 diabetes mellitus *Carolina Casellini* (Norfolk, US)

P.56 Association of neuropathic deficits with pharmacological interventions inducing weight change in type 2 diabetes
Georgios Ponirakis (Doha, Qatar)

P.57 Glucagon-like peptide 1 agonists and diabetic neuropathy: a literature review
Prodromos Bostantzis (Kavala, Greece)

P.58 Glycemic changes afer treatment with moxonidine or ramipril in overweight patients with dysglycemia and mild-to-moderate hypertension
Paul Valensi (Paris, France)

P.59 The impact of obstructive sleep apnoea treatment on pain in patients with type 2 diabetes: results from a 2-year feasibility RCT
Esraa *Makhdom* (Birmingham, UK)

P.60 A randomized, double-blind, placebo-controlled, parallel, 12-week, phase 2a study of topical pirenzepine (WST-057) or placebo in type 2 diabetes mellitus patients with painful diabetic neuropathy
Carolina Casellini (Norfolk, US)

P.61 Real-world evaluation of OpSite topical dressing in painful diabetic neuropathy
Dinesh Selvarajah (Sheffield, UK)

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ΕΛΛΗΝΙΚΗ ΙΑΤΡΙΚΗ ΕΠΙΘΕΩΡΗΣΗ

- **Πρόγραμμα και Περιλήψεις του 33ου Συνεδρίου της Ομάδας Εργασίας για την Διαβητική Νευροπάθεια της Ευρωπαϊκής Διαβητολογικής Εταιρείας**
  Program and Abstracts from the 33st Annual Meeting Of the Diabetic Neuropathy Study Group (NEURODIAB) of the European Association for the Study of Diabetes (EASD)

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Αθήνα, 8 Σεπτεμβρίου 2023

Το νέο Διοικητικό Συμβούλιο όπως αυτό διαμορφώθηκε από τις εκλογές της Εταιρείας Παθολογίας Ελλάδος, που έλαβαν χώρα την τελευταία μέρα του 6ου Πανελλήνιου Συνεδρίου της, Κυριακή 25 Ιουνίου 2023 είναι τα εξής:

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Άρθρο Σύνταξης
Editorial

Αγαπητές και αγαπητοί Συνάδελφοι,

Καταρχήν ευχόμαστε καλή Ακαδημαϊκή χρονιά με υγεία.
Στο παρόν τεύχος του περιοδικού μας, που είναι επετειακό, έχουμε την ιδιαίτερη τιμή και χαρά να φιλοξενούμε στις σελίδες του δύο σπουδαία θέματα.

Πρώτον είναι το 6ο Πανελλήνιο Συνέδριο Παθολογίας της ΕΠΕ που πραγματοποιήθηκε από τις 23 Ιουνίου έως 25 Ιουνίου 2023, στο Royal Olympic Hotel, με μεγάλη επιτυχία και συμμετοχή τόσο με προσωπική παρουσία όσο και διαδικτυακή. Ταυτόχρονα διεξήχθησαν και οι αρχαιρεσίες για την εκλογή νέου Δ.Σ της Εταιρείας μας, η σύνθεση του οποίου δημοσιεύεται στις σελίδες του παρόντος τεύχους καθώς και φωτογραφίες του συνεδρίου. Το πρόγραμμα του Συνεδρίου είναι αναρτημένο στην ιστοσελίδα της Εταιρείας.

Δεύτερον, όπως ακριβώς πριν 2 χρόνια, το πρόγραμμα και τις περιλήψεις των εργασιών του 33ου Συνεδρίου της Ομάδας Εργασίας για την Διαβητική Νευροπάθεια (DIABETIC NEUROPATHY STUDY GROUP, NEURODIAB), της μεγαλύτερης ομάδας εργασίας για τη Διαβητική Νευροπάθεια παγκοσμίως, το οποίο θα πραγματοποιηθεί για δεύτερη φορά στη Θεσσαλονίκη, υπό την αιγίδα της Εταιρείας Παθολογίας Ελλάδος (ΕΠΕ), από 28 Σεπτεμβρίου έως 1 Οκτωβρίου 2023 στο ξενοδοχείο ELECTRA PALACE.

Ευελπιστούμε το παρόν τεύχος να αποτελέσει πηγή ερευνητικής έμπνευσης και εκπαίδευσης για τους νεότερους αλλά και τους παλαιότερους Συναδέλφους.

Ευχόμαστε μία παραγωγική Ακαδημαϊκή χρονιά σε κάθε επίπεδο, υγεία σε όλους μας και δύναμη να ανταπεξέλθουμε στους δύσκολους καιρούς που έρχονται, όχι μόνο λόγω της πανδημίας που βιώνουμε τα 2 τελευταία χρόνια, αλλά και των δυσμενών συγκυριών για τη χώρα μας, με ακραία φυσικά φαινόμενα, όπως οι πολλές εστίες πυρκαγιάς και οι πλημμύρες στο Θεσσαλικό κάμπο.

Με συναδελφικούς χαιρετισμούς,

Η Πρόεδρος
Δρ. Παγώνη Ματίνα

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28 SEPTEMBER - 1 OCTOBER 2023

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ORAL SESSIONS

OR.01 | LIVER FIBROSIS INDICES ARE RELATED TO DIABETIC PERIPHERAL NEUROPATHY IN INDIVIDUALS WITH TYPE 2 DIABETES MELLITUS

Carla Greco[1], Stefano Boni[1], Silvia Coluccia[1], Eleonora Zanni[1], Massimiliano Colzani[1], Chiara Pacchioni[2], Manuela Simoni[1], Fabio Nascimbeni[3], Simonetta Lugari[3], Daniele Santi[1]

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Objectives: The role of non-alcoholic fatty liver disease (NAFLD) and liver fibrosis in diabetic polyneuropathy (DPN) remains unclear. We evaluated the correlation of liver fibrosis and steatosis with DPN in type 2 diabetes mellitus (T2DM).

Methods: 63 T2DM subjects (mean age 58.52 ± 12.97 years, duration 9.31 ± 8.96 years, HbA1c 59.37 ± 14.47 mmol/mol, 42 males – 66.7%) underwent clinical evaluation of DPN by Michigan Neuropathy Screening Instrument (MNSI), Michigan Diabetic Neuropathy Score (MDNS) and Diabetic Neuropathy Index (DNI). NAFLD was evaluated by predictive tools: Fatty Liver Index (FLI) and Hepatic Steatosis Index (HIS) and confirmed by ultrasonography (US). Liver fibrosis risk was evaluated by scores Fibrosis-4 (FIB-4), NAFLD Fibrosis, aspartate aminotransferase to alanine aminotransferase (AST/ALT) ratio, AST to platelet ratio index (APRI). The fibrosis has been investigated using Fibroscan.

Results: DPN was detected (DPN+) in 41.3% of the cohort (26 patients). DPN+ subjects were older (p<0.001), with longer diabetes duration (p=0.008) and characterized by higher prevalence of impaired urinary albumin excretion (p=0.011), chronic kidney disease (p=0.023) and heart failure (p=0.021). No association was identified between DPN and non-invasive predictive tools of NAFLD. Liver US was performed in 57 subjects (90.5%) and identified steatosis in 49 (86%). No significant difference was found in NAFLD prevalence comparing DPN+ and DPN- (86.4 vs 85.7%, p=0.633), also considering high-grade steatosis alone. Among fibrosis scores, FIB-4, NAFLD Fibrosis and AST/ALT ratio scores were higher in DPN+ vs DPN- (p=0.004, p=0.008 and p=0.040, respectively). MNSI score was directly related to FIB-4 score (Rho: 0.300, p=0.019) and to AST/ALT ratio (Rho: 0.437, p<0.001). MDNS score was significantly directly related to age (Rho: 0.380, p=0.002), disease duration (Rho: 0.296, p=0.019), serum glucose (Rho: 0.334, p=0.007), NAFLD fibrosis score (Rho: 0.419, p<0.001), and FIB-4 score (Rho: 0.276, p=0.031). DNI score was significantly, directly related to age (Rho: 0.451, p<0.001), disease duration (Rho: 0.341, p=0.006), serum glucose (Rho: 0.294, p=0.019), and NAFLD fibrosis score (Rho: 0.285, p=0.029). Finally, liver stiffness by Fibroscan has been investigated in 22 subjects (34.9%) demonstrating an overall prevalence of liver fibrosis of 31.8%. Although fibrosis appears more prevalent in DPN+ vs DPN- (50 versus 25%), the small sample size does not allow to reach statistical significance (p=0.267).

Conclusions: Although in a small sample, relation between DPN and the liver fibrosis risk has been documented. This finding requires validation in larger studies and considering expansion of elastographic evaluation or biopsy gold standard diagnosis.

Table 1. Non-invasive biomarkers of liver fibrosis in T2DM subjects according to the presence of DPN.

	DPN⁻ (n = 37)	DPN⁺ (n = 26)	p
Non-invasive biomarkers of fibrosis			
FIB-4 score (mean ± SD)	1.17 ± 0.55	1.71 ± 0.86	***0.004***
FIB-4 high risk score (%)	1 (2.9)	3 (11.5)	0.203
NAFLD Fibrosis score (mean ± SD)	1.06 ± 1.73	2.12 ± 1.05	***0.008***
NAFLD Fibrosis high risk score (%)	20 (60.6)	24 (92.3)	***0.005***
AST/ALT ratio (mean ± SD)	0.87 ± 0.23	1.12 ± 0.66	***0.040***
AST/ALT ratio high risk score (%)	1 (2.7)	4 (15.4)	0.088
APRI score (mean ± SD)	0.35 ± 0.29	0.36 ± 0.24	0.848
APRI high risk score (%)	5 (14.3)	5 (19.2)	0.430

OR.02 | ABNORMAL COMBINED DPN-CHECK & SUDOSCAN RESULTS PREDICT ALL-CAUSE MORTALITY IN PEOPLE WITH DIABETES: THE SHEFFIELD PROSPECTIVE STUDY

Mohummad Shaan Goonoo[1], Dinesh Selvarajah[1], Oliver Binns-Hall[2], Gordon Sloan[1], Jeremy Walker[2], Solomon Tesfaye[3]

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Aims: Diabetic peripheral neuropathy (DPN) has been associated with increased mortality; however, data is not available for objectively-diagnosed DPN using point-of-care-devices (POCDs). We therefore examined the predictive validity of POCD-diagnosed DPN for increased mortality in a prospective study.

Methods: A total of 245 consecutive people with diabetes (17 type 1 diabetes, age 62.3+14.3) attending retinal-screening had all annual review health checks in a One-stop Screening Service. DPN assessments included Toronto Clinical Neuropathy Score (TCNS) evaluation, 10g-monofilament test(10g-MFT) and two validated, objective POCDs, DPN-Check (handheld device measuring sural nerve conduction velocity/amplitude), and SUDOSCAN (measuring sudomotor function). Mortality data was collected at a 7-year follow-up. Kaplan-Meier survival curves and Cox-proportional hazards models were generated to assess associations of DPN measures with all-cause mortality.

Results: At follow-up, 52 [21.2% (SE 6.8%)] had died. Those who died were older at screening [72.4(10.9) vs 59.6(13.9) years; (p<0.001)]. The prevalence of screen-detected DPN was 12.6% (SE 4.4%) for 10g-MFT, 27.7% (SE 8.2%) for TCNS and 33.4% (SE 9.1%) for combined POCDs. In crude Kaplan-Meier analyses all-cause mortality risk was greater in patients with abnormal TCNS (p<0.001) and POCDs (p<0.001) but was equivalent in patients with normal or abnormal 10g-MFT (p=0.21). After adjusting for age, HbA1c and Total Cholesterol, only abnormal POCDs was significantly associated with all-cause mortality [HR 1.18(p=0.04, 95%CI 1.00:1.39) vs TCNS [HR 1.33(p=0.06, 95%CI 0.99:1.78)].

Conclusions: This is the first prospective study showing abnormal combined DPN-Check and SUDOSCAN results predict all-cause mortality after adjusting for other risk factors. However, 10g-MFT and TCNS that diagnose DPN late did not predict all-cause mortality.

OR.03 | DETERMINANTS OF CORNEAL NERVE MORPHOLOGY IN AN UNSELECTED POPULATION-BASED COHORT FROM QATAR

Ioannis Nikolaos Petropoulos, Georgios Ponirakis, Hoda Y. Gad, Areej Baraka, Einas Elgassim, Rayaz A. Malik

Research Division, Weill Cornell Medicine - Qatar

Objectives: The goal of a biomarker like corneal confocal microscopy (CCM) in a screening setting is to identify small fiber neuropathy. To achieve this robust reference values are needed, preferably derived from independent population cohorts. The Qatar Biobank is a population-based prospective cohort of 25,000 individuals designed to assess the relationship between genetics, lifestyle factors and disease incidence. We have recently implemented CCM and aimed to determine factors influencing corneal nerve morphology in an unselected population from Qatar Biobank.

Methods: 211 participants without (n=168; 92 males/76 females) or with (n=43; 28 males/15 females) diabetes mellitus (DM) (Type 1/2: 2/41) in the CCM substudy underwent assessments for peripheral neuropathy [vibration perception threshold>15 volts; DN4>4], and CCM for estimation of corneal nerve fiber density (CNFD) and length (CNFL). Additionally, age, COVID-19 history, anthropometric and biochemistry (bilirubin, calcium, cholesterol, low/high density lipoprotein cholesterol, triglycerides, urea, uric acid, c-peptide, ferritin, folate, free T3, free T4, testosterone, thyroid stimulating hormone, vitamin B12, vitamin D, c-reactive protein, HbA1c) data were collected. Correlation analysis was performed to assess for

significant associations between CCM parameters and clinical or demographic parameters. Subsequently, significant parameters were fitted into a multiple linear regression model. Subgroup analysis was performed to assess the effect of COVID-19 history and DM on CCM parameters.
Results: Mean participant age was 44.20 ± 13.41 years with no significant difference between participants with and without DM (P>0.99). Neuropathy was confirmed in 2/211 participants, who were excluded from further analysis. There was a significant correlation between CNFD and age (r=-0.20, P=0.006), creatinine (r=-0.18, P=0.01), folate (r=-0.14, P=0.05), free T3 (r=0.22, P=0.001), vitamin D (r=-0.16, P=0.02) and HbA1c (r=-0.23, P=0.0008). There was a significant correlation between CNFL and age (r=-0.21, P=0.003), calcium (r=-0.16, P=0.02), creatinine (r=-0.21, P=0.002), folate (r=-0.17, P=0.01), free T3 (r=0.20, P=0.003), vitamin D (r=-0.18, P=0.009), and HbA1c (r=-0.24, P=0.0007). Multiple regression analysis showed that a model with creatinine (P=0.009/P=0.002), FT3 (P=0.003/0.009), vitamin D (P=0.04 for CNFL only) and HbA1c (P=0.03/0.02) as independent variables predicted a significant amount of CNFD (R2=0.12) and CNFL (R2=0.14) respectively. There was no difference in CNFD and CNFL according to COVID-19 history. Participants with DM had significantly lower CNFD (P=0.003) and CNFL (P=0.01) compared to participants without DM independent of COVID-19 history.
Conclusions: In an unselected population-based cohort we have determined meaningful factors influencing corneal nerve morphology. These should be considered when calculating age-adjusted reference values to identify corneal nerve abnormalities.

OR.04 | LONGITUDINAL CHANGES IN SERUM NEUROFILAMENT LIGHT CHAIN LEVELS IN TYPE 2 DIABETES AND DIABETIC POLYNEUROPATHY

Laura Linnea Määttä[1], Signe Toft Andersen[2], Tina Parkner[3], Claus Vinter Bødker Hviid[4], Daniel Witte[2], Troels Staehelin Jensen[1]
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Objectives: There is a lack of easily applicable objective tools facilitating detection and follow-up of diabetic polyneuropathy (DPN). We aimed to investigate longitudinal serum levels of the axonal biomarker neurofilament light chain (s-NfL) in people with type 2 diabetes (T2D) to clarify the potential of s-NfL as a biomarker for DPN.
Methods: We performed a nested case-control study of a subgroup of the ADDITION-Denmark cohort of people with screen-detected T2D examined clinically 5 and 10 years after their diabetes diagnosis (N=178). Based on Toronto criteria for clinically confirmed DPN at the 10-year examination, we divided the group into participants with (+DPN) and without DPN (-DPN). Biobank serum samples from both time points were analyzed for s-NfL using single-molecule array (Simoa®). Difference in s-NfL change over time (Δs-NfL) between the groups, as well as the association between Δs-NfL and change in DPN risk factors and eGFR, were evaluated.
Results: Median s-NfL levels increased from the 5- to the 10-year examination both in +DPN participants (11.3 ng/L [IQR 9.54; 15.6] to 18.8 ng/L [IQR 14.4; 27.9], p<0.001, N=39) and in -DPN participants (10.2 ng/L [IQR 7.49; 13.7] to 15.4 ng/L [IQR 11.7; 20.1], p<0.001, N=139). The increase in s-NfL in +DPN participants was greater than in -DPN participants (median Δs-NfL 7.4 ng/L [IQR 3.8; 12.9] vs. 4.7 ng/L [IQR 2.8; 8.1], p=0.03). Linear modelling of Δs-NfL adjusted for 5-year s-NfL, time between the 5-and 10-year follow-up, age, sex, ADDITION-randomization group, BMI and eGFR showed that +DPN participants had 17.4% (95% CI 4.3; 32.2) higher Δs-NfL than -DPN participants. The risk of DPN increased with higher yearly Δs-NfL (OR 1.41 [95%CI 1.08; 1.84] per 1 ng/L/year higher s-NfL in the fully adjusted model) although s-NfL at 5-year follow-up was not predictive of DPN after adjustment for covariates (OR 1.04 [95%CI 0.97; 1.12] per 1 ng/L higher s-NfL). Increasing weight and BMI were associated with lower Δs-NfL (4.6% [95%CI 1.2; 8.0] lower Δs-NfL per 5 kg weight increase and 5.6% [95%CI 1.9; 9.2] lower Δs-NfL per 2 kg/m2 BMI increase) whereas decreasing eGFR was associated with higher Δs-NfL (5.1% [95%CI 1.8; 8.6] higher Δs-NfL per 5 ml/min/1.73m2 eGFR reduction).
Conclusion: S-NfL levels increased more in +DPN than -DPN participants over time, suggesting that s-NfL may have utility as a biomarker for DPN development. Furthermore, changes in weight, BMI and eGFR need to be considered when interpreting development of s-NfL levels.

OR.05 | CHANGES IN SCIATIC NERVE STRUCTURAL INTEGRITY AND CROSS-SECTIONAL AREA ARE ASSOCIATED WITH DISTINCT PERIPHERAL SENSORY PHENOTYPES IN INDIVIDUALS WITH TYPE 2 DIABETES

Dimitrios Tsilingiris[1], Christoph Mooshage[2], Lukas Schimpfle[1], Alba Sulaj[1], Ekaterina von Rauchhaupt[1], Julia Szendroedi[1], Stephan Herzig[3], Peter Nawroth[1], Martin Bendszus[2], Sabine Heiland[2], Felix Kurz[4], Johann Jende[2], Stefan Kopf[1], Zoltan Kender[1]
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Objectives: To investigate the relationship of peripheral sensory phenotype of the lower extremity with the structural integrity of the ipsilateral sciatic nerve among individuals with type 2 diabetes mellitus (T2DM).
Methods: We examined 76 individuals with T2DM (mean age 64.7± years, 28.9% females). All participants underwent detailed clinical and electrophysiological assessments. Participants were categorized into four sensory phenotypes (healthy, thermal hyperalgesia-TH, mechanical hyperalgesia-MH, sensory loss-SL) via a standardized sorting algorithm based on quantitative sensory testing (QST) of the right foot. As a measure of nerve structural integrity, the fractional anisotropy (FA) of the right sciatic nerve was obtained through diffusion-weighted magnetic resonance neurography (MRN). MRN-derived sciatic nerve cross-sectional area (CSA) was also measured. Comparisons were made across the four sensory phenotypes, with post-hoc pairwise tests.
Results: On the basis of QST of the right foot 16, 24, 17 and 19 participants were categorized as healthy, TH, MH and SL, respectively. There were no differences across the groups with regards to clinical, demographic, and laboratory characteristics. There was a gradual decrease of FA across the groups, culminating in the lowest values among those with SL [443.6 vs. 436.5 vs. 395.4 vs. 381.9, p(ANOVA)= 0.005, p=0.024 and 0.029 for SL vs. healthy and TH, respectively], while an opposite trend was observed for CSA [p(ANOVA)= 0.011]. The MH and SL phenotypes were associated with lower FA and higher CSA values vs. the healthy phenotype. The association for SL persisted after adjustment for sural nerve conduction velocity, but not after adjustment for sural nerve action potential (SNAP). After adjustment for SNAP, only MH was associated with a higher CSA. The presence of either MH or SL vs. Healthy or TH was predicted by lower FA (OR 0.988, 95% c.i. 0.978–0.997, p=0.011) and higher CSA (OR 1.131, 95% c.i. 1.019–1.256, p=0.021) independently of one another.
Conclusions: A gradually diminishing sciatic nerve structural integrity indexed by FA is observed with sensory phenotypes of increasing severity, likely reflecting progressive fiber loss. Increasing sciatic nerve diameter precedes overt fiber and sensory loss and may be useful as an early clinical biomarker.

OR.07 | NEW OBSERVATIONAL WINDOWS OF NEUROPATHIC DAMAGE IN TYPE 2 DIABETIC PATIENTS

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Objective: The aims of our study are to evaluate the relationship among retinal neurodegeneration (RN), mild cognitive impairment (MCI) and diabetic peripheral (DPN) or cardiac autonomic neuropathy (CAN), and to evaluate whether neuroretina study could provide useful information to identify patients with type 2 diabetes (T2D) at risk of neuropathy and dementia.
Materials and methods: 64 patients with T2D (65-90 years), with a disease duration greater than 5 years, with mild or no diabetic retinopathy and without previous history of stroke or neurodegenerative diseases, were enrolled. All patients were classified as MCI or controls (C), according to the Montreal Cognitive Assessment Test (MoCA). The participants underwent retinal microperimetry that measures the average threshold macular sensitivity (ATMS), electroretinography (ERG) that asses the Implicit Time (IT) and SD-optical coherence tomography (SD-OCT), that measures the thickness of retinal layers.
Diabetic neuropathy was assessed in patients with MCI: Michigan Neuropathy Screening Instruments (MNSI), vibration perception threshold (VPT) and thermal perception thresholds to detect DPN and the cardiovascular autonomic tests to detect CAN. Then, MCI patients were subdivided according to neuropathic characteristics into DPN+ or DPN- and into CAN+ or CAN-.
Results: IT was significantly longer (30,6 ms vs 28,7 ms p=0,03 and 31,1 ms vs 26,5 ms, p=0,03), and ATMS was significantly lower (25,5 db vs 26,8 db, p=0,04) in MCI patients compared to C. We found a positive correlation between MOCA test score and ATMS (r=0,3, p =0,02).
In the MCI-group, patients DPN+ showed a significant reduction in the GCL+IPL average thickness 75,4 vs 64,4), compared to DPN-. We also observed a negative correlation between VPT and the GCL+IPL thickness (r =-0,04, p=0,01).
In the MCI-group, patients CAN+ showed a significantly longer IT compared to those CAN- (respectively 32,3 vs 30,2, p=0,03). We observed a positive correlation between systolic blood pressure delta, assessed during orthostatic hypotension tests, and IT (r=0,03, p=0,02). No significant differences were observed in the C group.
Conclusion: RN is observed in T2D subjects with MCI. In the MCI group, there were significant associations among retinal morphological and functional alterations and signs and symptoms of both DPN and CAN. These results suggest that the neuroretina could represent an important observation point for the study of neuropathic damage.

OR.08 | CEREBRAL STRUCTURAL ALTERATIONS AFTER CHRONIC OPIOID PHARMACOTHERAPY TREATMENT IN PAINFUL-DIABETIC PERIPHERAL NEUROPATHY

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Objectives: Opioid medications are commonly used to treat Painful-Diabetic Peripheral Neuropathy (Painful-DPN). It is increasingly recognised that opioid medications lead to significant adverse effects, including addiction and mortality. Additionally, alterations in cerebral structure and function have been associated with opioid use; however, this has not been explored in patients with Painful-DPN. We therefore performed a neuroimaging study to determine the effect of long-term opioid treatment (>6-months) on cerebral structure in Painful-DPN.
Methods: A total of 56 participants with Painful-DPN were recruited (17 on long-term opioid treatment [O+] and 39 not on opioid treatment [O-]). Participants underwent detailed clinical and neurophysiological assessments and Magnetic Resonance Imaging (3T, Phillips Medical Systems, Holland). Brain morphometric analysis was performed using Freesurfer (https://surfer.nmr.mgh.harvard.edu/).
Results: O+ participants were prescribed the following opioid treatments: codeine (n=3, 18%), tramadol (n=5, 29%), morphine modified release (n=1, 6%), buprenorphine (n=1, 6%), and combination treatment (n=5, 29%). O+ participants had a longer duration of diabetes, greater HbA1c, higher pain severity and higher scores on Hospital Anxiety and Depression scales compared to the O- group. Participants in the O+ group had a greater mean caudate volume (O+ 3.5mL ± 0.4; O- 3.2 ± 0.4mL, p=0.034); mean insula volume (O+ 6.3 ± 0.8; O- 5.9 ± 0.6, p=0.049) and mean insular vertices (O+ 3,286 ± 411; O- 3055 ± 282, p=0.018).
Conclusions: This is the first study to examine the impact of opioids on cerebral structure in Painful-DPN. We demonstrated alterations in insular cortical and caudate morphology. Thus, opioids may alter affective/attentional pain processing (insular cortex) and brain regions associated with binge/intoxication (caudate nucleus). These results may have important clinical implications for uncovering the effects of long-term prescription opioid use on brain structure in Painful-DPN.

OR.09 | COMPARISON OF CENTRAL PARASYMPATHETIC AND CUTANEOUS RESPONSES TO INSULIN-INDUCED HYPOGLYCEMIA

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Objectives: In response to hypoglycemia, the autonomic nervous system upregulates the sympathoadrenal outflow to increase glucose production in the liver. However, this natural defence is often compromised in patients with insulin-dependent diabetes. Therefore, this study aimed to observe the sympathetic and parasympathetic response and recovery to insulin-induced hypoglycemia in both healthy participants and participants with diabetes without complications.
Methods: Six insulin-dependent participants without complications and six age and gender-matched healthy volunteers were included in this explorative cross-sectional study. Baseline measurements of ECG, skin blood flow, ECG-derived cardiac vagal tone (parasympathetic measure) and blood glucose were obtained before an intravenous bolus of soluble insulin was injected. Measurements were repeated at 30, 60, 120 and 240 minutes.
Results: Groupwise comparison found that insulin-induced hypoglycemia significantly reduced cardiac vagal tone and increased heart rate but had no effect on skin blood flow in healthy and people with insulin-dependent diabetes at the time of hypoglycemia. The between-group comparison found no difference in cardiac vagal tone or skin blood flow at baseline or at the time of hypoglycemia. However, the recovery of cardiac vagal tone was delayed in the diabetes group compared to the healthy controls. Meanwhile, the heart rate was not.
Conclusion: Cardiac vagal tone, the efferent branch of the neurocardiac regulation, responded consistently to insulin-induced hyperglycemia. This contrasts with the measure of sympathetic function, skin blood flow, which had no response in healthy controls and participants with diabetes calling attention to the differential sympatho-excitatory effect of insulin. Moreover, no immediate compromised counter-regulation of hypoglycemia was evident. However, the recovery of cardiac vagal tone was significantly delayed indicating impaired central parasympathetic regulation in participants with diabetes prior to the potential presence of complications.

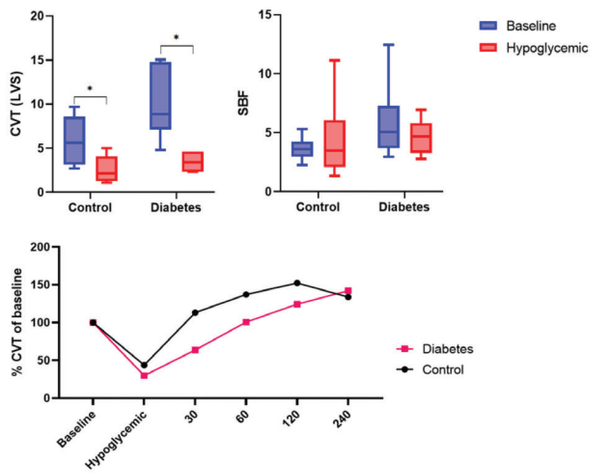

Figure 1. Boxplots of the in change cardiac vagal tone (CVT) and skin blood flow (SBF) from baseline to insulin-induced hypoglycemia and the recovery of CVT.

OR.10 | RISK OF DIABETIC MICROVASCULAR COMPLICATIONS, HEART FAILURE, HOSPITALISATION AND ALL-CAUSE MORTALITY WITH SGLT2I AND GLP1-RA IN TYPE 2 DIABETES: A REAL-WORLD DATA STUDY

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Objective: To assess the relationship of sodium-glucose cotransporter-2 inhibitors (SGLT2i) and glucagon-like peptide-1 receptor analogues (GLP1-ra) on 5-year risk of diabetic neuropathy, autonomic neuropathy, diabetic retinopathy and macular oedema, hospitalisation and all-cause mortality in type 2 diabetes.

Methods: This is a retrospective cohort analysis of six million people with type 2 diabetes across 85 healthcare organisations using a global federated health research network (TriNetX, Boston, USA). Two intervention cohorts (SGLT2i, n=126,171 ; GLP1-ra, n=164,024) were compared against a control cohort (no SGLT2i/ GLP1-ra, n=1,665,412). Propensity score matching for age, sex, ischaemic heart disease, microvascular complications, HbA1c <7% and >7%, and use of pioglitazone was used to balance cohorts 1:1. A sub-analysis comparing the two intervention cohorts was also performed.

Results: Intervention cohorts (both SGLT2i and GLP1-ra) demonstrated a reduced relative risk (RR, 95% confidence interval [95%CI]) compared to the control cohort at 5 years for macular oedema (SGLT2i: 0.55, 0.51-0.59. GLP1-ra: 0.80, 0.76-0.84), heart failure (SGLT2i: 0.55, 0.54-0.57. GLP1-ra: 0.63, 0.61-0.65), hospitalisation (SGLT2i: 0.64, 0.64-0.65. GLP1-ra: 0.65, 0.65-0.66) and all-cause mortality (SGLT1i: 0.38, 0.37-0.40. GLP1-ra: 0.39, 0.38- 0.40). Contrary to the GLP1-ra cohort, the SGLT2i cohort demonstrated a reduced risk compared to the control cohort at 5 years for diabetic neuropathy (SGLT2i: 0.86, 0.84-0.89. GLP1-ra: 1.19, 1.16-1.22), autonomic neuropathy (SGLT2i: 0.83, 0.76-0.92. GLP1-ra: 1.08, 1.00-1.17) and diabetic retinopathy (SGLT2i: 0.71, 0.67-0.74. GLP1-ra: 1.06, 1.02-1.10). When directly comparing to SGLT2i, the GLP1-ra cohort demonstrated an increased RR at 5 years in neuropathy (1.42, 1.39-1.47), autonomic neuropathy (1.28, 1.17-1.40), diabetic retinopathy (1.48, 1.41-1.55), macular oedema (1.49, 1.38-1.60), heart failure (1.16, 1.12-1.20), hospitalisation (1.04, 1.03-1.06) and all-cause mortality (1.09, 1.06-1.13).

Conclusions: SGLT2i and GLP1-ra both reduce the risk for macular oedema, heart failure, hospitalisation and all-cause mortality in people with type 2 diabetes over 5 years. Additionally, SGLT2i therapy reduces the risk for further microvascular complications including neuropathy, autonomic neuropathy and retinopathy. SGLT2i therapy was associated with the greatest risk reduction in diabetic microvascular complications as well as heart failure, hospitalisation and all-cause mortality. Future randomised controlled trials of SGLT2i and GLP1-ra should incorporate sensitive surrogate biomarkers of diabetic microvascular disease to validate these findings and if validated, in particular SGLT2i should be considered higher in the treatment algorithm for the general patient with type 2 diabetes.

OR.11 | CARDIOVASCULAR AUTONOMIC FUNCTION IN LONG COVID-19 INDIVIDUALS WITH AND WITHOUT DIABETES

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Coronavirus disease 2019 (COVID-19) has been associated with a broad spectrum of long-term complications. These include the development and progression of severe autonomic dysfunction, particularly among people with diabetes mellitus. We sought to identify the impact of long COVID-19 on cardiovascular autonomic function in individuals with and without diabetes.

Objectives: Coronavirus disease 2019 (COVID-19) has been associated with a broad spectrum of long-term complications. These include the development and progression of severe autonomic dysfunction, particularly among people with diabetes mellitus. We sought to identify the impact of long COVID-19 on cardiovascular autonomic function in individuals with and without diabetes.

Methods: We evaluated cardiovascular autonomic (CAN) function in a cross-sectional study in 47 adults with long COVID-19 with (N=21, mean age 61 years, 43% women, mean A1c 6.2%) and without type 2 diabetes mellitus (T2DM) (N=26, mean age 58 years, 65% women) and compared them with T2DM without COVID-19 (N=45, mean age 57 years, 42% women, mean A1c 7.8%). CAN was assessed with cardiovascular autonomic reflex tests (30:15 ratio, E.I ratio, Valsalva ratio) and indices of heart rate variability (SDNN, RMSSD). We used pairwise comparison and Analysis of Covariance (ANCOVA) both adjusted for age, gender, race, and BMI to compare the groups.

Results: In a pairwise comparison higher heart rate (HR) and lower CAN measures (SDNN, RMSSD, Valsalva) were found in T2DM with COVID-19 compared to T2DM without COVID-19. Lower HR and lower Valsalva were found in COVID-19 individuals without T2DM compared to T2DM without COVID-19. When comparing the three groups, lower Valsalva were found in COVID-19 individuals with and without T2DM compared to T2DM without COVID-19.

Conclusions: These data suggest that COVID-19 exacerbates CAN in patients with T2DM and impacts CAN in people without T2DM at a magnitude similar to that of T2DM patients.

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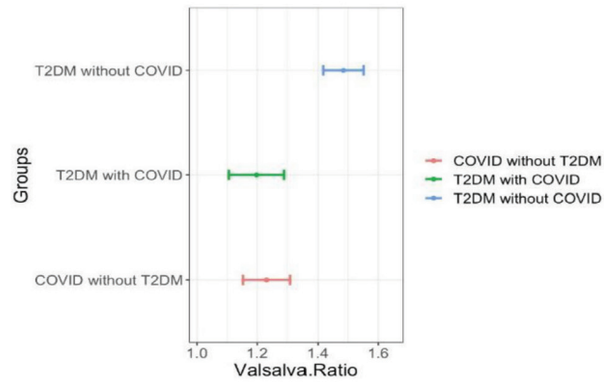

OR.12 | SEX DIFFERENCES IN THE INVERSE ASSOCIATIONS OF MONOCYTE COUNTS & NEUTROPHIL-TO-LYMPHOCYTE RATIO WITH HEART RATE VARIABILITY: THE MAASTRICHT STUDY

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Objectives: Higher levels of inflammatory biomarkers are associated with lower heart rate variability (HRV), an index of impaired autonomic function. We hypothesised that higher leukocyte subsets are also associated with lower HRV in people with and without diabetes.
Methods: We used data from The Maastricht Study (a population-based study oversampled with individuals with type 2 diabetes). Automated white blood cell counts were obtained from baseline blood samples, and HRV was measured with a 24-h electrocardiogram. Time and frequency domains were calculated using z-scores of 7 and 6 time and frequency HRV indices, respectively. We used linear regression models adjusted for anthropometric, metabolic, lifestyle and clinical covariates to assess the associations of each leukocyte subset (per 1-standard deviation (SD) increase) with HRV domains.
Results: We included 1,888 individuals (mean±SD age 60±8 years, 49% women, 28% with type 2 diabetes). 1-SD increases in neutrophil and monocyte counts were associated with lower HRV time and frequency domains in all participants before and after adjustment. The association between monocytes and time domain was modified by sex, with a significant negative association among women but not among men (Pinteraction=0.041). Sex stratification also revealed a negative association between neutrophil-to-lymphocyte ratio (NLR) and HRV in women (β (95% CI) for time and frequency domains were -0.09 (-0.14, -0.04) and -0.08 (-0.13, -0.03)), but not in men (Pinteraction=0.006 and 0.035, for time and frequency domains, respectively). No associations were found for basophils, eosinophils and lymphocytes. Diabetes status did not modify these associations.
Conclusions: Higher neutrophil and monocyte counts and higher NLR are associated with lower HRV, particularly in women, indicating that the cross-talk between the immune and autonomic nervous systems may differ between men and women.

OR.13 | SWEAT GLAND NERVE FIBER DENSITY AND ASSOCIATION TO SUDOMOTOR FUNCTION, SYMPTOMS, AND RISK FACTORS IN ADOLESCENTS WITH TYPE 1 DIABETES

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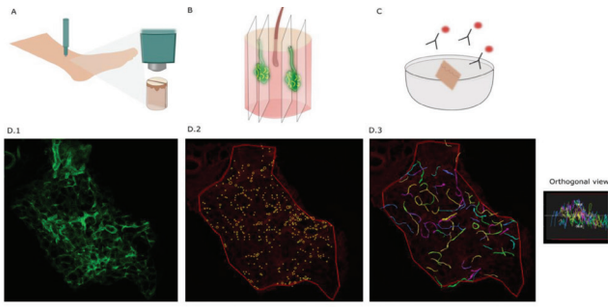
Objectives: To quantify sweat gland nerve fiber density (SGNFD) in adolescents with a type 1 diabetes (T1D) duration above five years. In addition, to investigate associations between SGNFD, quantitative sudomotor axon reflex test (QSART), and possible risk factors for abnormal tests indicating sudomotor neuropathy.
Methods: Cross-sectional study where sixty adolescents with T1D and 23 control subjects were included. Clinical data, biochemical data, QSART, and skin biopsies from the distal leg were obtained. Skin tissue was immunostained and imaged by confocal microscopy. Quantification of the sweat gland volume and three-dimensional reconstruction of the nerve fibers were performed using a design-unbiased technique.
Results: In total, 452 sweat glands (SG) were analyzed with a mean of 5.5 SG per individual. Adolescents with T1D had a significant reduction of maximum and mean values of total nerve fiber length (NFL) and SGNFD compared to controls (NFL p<0.01, p=0.03; SGNFD p<0.01, p=0.02, respectively). Sweat gland volume (SGv) was similar between groups (p=0.24). Higher NFL was associated with both higher SGv and SGNFD (r=0.77 and r=0.78, both p values <0.05) and a trend toward higher NFL leading to higher sweat response was observed (r=0.24, p=0.07). No association between SGNFD and QSART was found (r=0.16, p=0.21). In cases with reduced SGNFD, SGv, and NFL, the sweat response was reduced or absent. Height, systolic blood pressure, total daily insulin dose, and basal/total insulin dose were positively correlated to sweat response, while low-density lipoprotein, and HbA1c (mean last 5 yrs) were negatively correlated to sweat response (all p values <0.05). Other microvascular complications and high cholesterol levels increased the relative risk for reduced SGNFD.
Conclusion: Adolescents with T1D have significantly reduced NFL and SGNFD, but not SGv compared to control subjects. Evaluating all three parameters; NFL, SGv, and SGNFD were important for understanding the association with sweat responses obtained by QSART. Three-dimensional reconstruction of sudomotor innervation adds important information about the distribution of structural nerve damage and allows for distinguishing between structural and functional changes indicating sudomotor autonomic dysfunction.



Sweat gland nerve fiber density = total nerve fiber length in sweat gland / sweat gland volume

OR.14 | SYMPTOMS OF AUTONOMIC NEUROPATHY IN 25% OF PEOPLE WITH DIABETES FROM THE NORTH DENMARK REGION USING THE COMPOSITE AUTONOMIC SYMPTOMS SCORE-31

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Objectives: Autonomic neuropathy is a severe complication of diabetes, estimated to affect around 45% of the population based on the DCCT/EDIC and ADDITION studies. Clinical manifestations, such as dizziness, gastrointestinal discomfort, incontinence, and altered vision, initially cause frustration, while long-term complications increase morbidity and mortality. Currently, assessment of autonomic neuropathy is not implemented in clinical guidelines or annual visits. We aimed to investigate symptoms of autonomic neuropathy in a representative cohort of people with type 1 and type 2 diabetes in the North Denmark Region using the Composite Autonomic Symptoms Score (COMPASS)-31 questionnaire.

Methods: All adults with diabetes in the North Denmark Region (n=29.155), identified based on ICD-10 codes and The National Health Insurance Service Registry, were invited to an online survey through secure digital mail. The survey consisted of the Danish version of COMPASS-31, the Michigan Neuropathy Screening Instrument (MNSI), Short Form (SF)-36, and information on essential clinical characteristics. Participants were stratified based on their COMPASS-31 scores: low (score below 15), medium (score between 15-30), or severe (score above 30).

Results: 7.386 people, 25% of the registered population of people with diabetes in the North Denmark Region, completed the COMPASS-31. Of these, 14% (1.049) had type 1 and 86% (6.337) had type 2 diabetes. Based on COMPASS-31 stratifications, 55% had low scores, 23% had medium scores, and 22% had severe scores. There was no difference in age, sex, disease duration, and body mass index between the COMPASS-31 strata, though slightly more people with type 2 diabetes had medium to severe symptom scores compared to type 1 diabetes (see Table 1). The total MNSI score and the fraction with pain increased while the health-related quality of life decreased with COMPASS-31 score severity. The distribution of data for individual sub-domains of COMPASS-31 can be seen in Figure 1.

Conclusion: Presence of autonomic symptoms coincided with previous estimates and was accompanied by other symptoms of systemic neurodegeneration. These results emphasize the need for enhanced focus on autonomic symptoms in clinical practice. COMPASS-31 scores are not directly linked to a diagnosis but could be implemented as a screening tool. This cohort will be followed prospectively to investigate symptom development and changes.

	Type 1			Type 2		
COMPASS-31 score	low	medium	severe	low	medium	severe
Number (%)	652 (62%)	202 (19%)	195 (19%)	3.431 (54%)	1.473 (23%)	1.433 (23%)
Age (years)	58 [48;68]	56 [46;70]	61 [49;69]	68 [60;74]	66 [58;73]	66 [58;73]
Gender (female)	42%	49%	45%	38%	40%	41%
Disease duration (years)	26 [14;40]	24 [12;40]	25 [12;40]	9 [4;15]	10 [5;15]	10 [5;16]
Body mass index (kg/m^2)	25.7 [23.2;28.7]	25.5 [23.4;29.4]	25.9 [23.1;29.8]	29.1 [25.9;32.9]	29.9 [26.5;33.9]	30.4 [27.0;34.7]
MNSI score	1 [0;2]	2 [1;4]	5 [2;8]	1 [0;2]	2 [1;3]	4 [2;6]
Peripheral pain	14%	35%	62%	16%	33%	60%
SF-36 score	69 [61;72]	61 [48;68]	46 [35;58]	68 [56;72]	59 [45;68]	45 [35;57]

Table 1. Non-invasive biomarkers of liver fibrosis in T2DM subjects according to the presence of DPN.

	DPN$^-$ (n = 37)	DPN$^+$ (n = 26)	p
Non-invasive biomarkers of fibrosis			
FIB-4 score (mean ± SD)	1.17 ± 0.55	1.71 ± 0.86	***0.004***
FIB-4 high risk score (%)	1 (2.9)	3 (11.5)	0.203
NAFLD Fibrosis score (mean ± SD)	1.06 ± 1.73	2.12 ± 1.05	***0.008***
NAFLD Fibrosis high risk score (%)	20 (60.6)	24 (92.3)	***0.005***
AST/ALT ratio (mean ± SD)	0.87 ± 0.23	1.12 ± 0.66	***0.040***
AST/ALT ratio high risk score (%)	1 (2.7)	4 (15.4)	0.088
APRI score (mean ± SD)	0.35 ± 0.29	0.36 ± 0.24	0.848
APRI high risk score (%)	5 (14.3)	5 (19.2)	0.430

OR.15 | DETERMINANTS OF ORTHOSTATIC HYPOTENSION IN TYPE 1 DIABETES: NEUROGENIC OR NON-NEUROGENIC?

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Objectives: The study aimed to investigate the determinants of orthostatic hypotension (OH) in a population with type 1 diabetes (T1D), and the usefulness of a new bedside index of cardiac baroreflex function to discriminate neurogenic from non-neurogenic OH.

Methods: In 124 participants with T1D [age 41.4±12.3, duration 22.0 (IQR 14.0-31.5) years], we performed three heart rate based cardiovascular reflex tests (HR-CARTs) and OH test and assessed diabetic polyneuropathy (DPN), clinical history and variables. We defined OH as a systolic blood pressure fall (ΔSBP) ≥20 and ≥30 mmHg in presence of supine SBP <140 and ≥140 mmHg, respectively, and confirmed cardiovascular autonomic neuropathy (HR-CAN) in presence of 2 abnormal HR-CARTs. We used the ΔHR/ΔSBP ratio, i.e., the change in heart rate by the fall in SBP after standing, to classify OH as neurogenic or non-neurogenic according to a value <0.5 or >0.5 bpm/mmHg, respectively.

Results: OH was present in 25 participants (20%), 9 with normal HR-CARTs, and was associated with lower HR-CARTs (P=0.0003, P<0.0001, P=0.0368), with higher scores of neuropathic symptoms (P=0.0034) and signs (P=0.0433), with higher HbA1c (P=0.0027), and with the presence of confirmed HR-CAN (P<0.0001) and DPN (P=0.0052). OH was not associated with the use of interfering-drugs in OH testing (i.e., diuretics, nitrates, alpha-lytic, sympatholytic agents, and beta-blockers). Table shows a multivariate logistic regression analysis for OH.

ΔSBP showed good diagnostic accuracy for confirmed HR-CAN [area under the ROC curve (AUC) 0.792±0.056 (95% CI 0.682-0.902), sensitivity of 50%, and specificity of 87%]. In a sensitivity analysis, excluding participants with interfering-drugs, AUC increased to 0.818±0.059, sensitivity to 58% and specificity to 91%. Values of the ΔHR/ΔSBP ratio ≤0.5 bpm/mmHg were found in 13 out of 25 participants with OH. AUC of the ΔHR/ΔSBP ratio, in discriminating among participants with OH those with and those without confirmed HR-CAN, was 0.708±0.107 (95% CI 0.498-0.919), with sensitivity of 67% and specificity of 61%. When excluding participants with interfering-drugs, AUC increased to 0.869±0.083, sensitivity to 69%, and specificity to 83%.

Conclusions: CAN is the main independent determinant of OH and OH keeps high specificity for confirmed CAN. ΔHR/ΔSBP ratio has a fair diagnostic accuracy for neurogenic OH, although less than is described at the cut-off of 0.5 bpm/mmHg with tilt table test in non-diabetic conditions of autonomic failure. The usefulness of this index of baroreflex function, easily achievable in the clinical setting, deserves to be further investigated in diabetes.

Table. Multivariate logistic regression analysis with OH as the dependent variable. Model 1 includes age, sex, diabetes duration, body mass index, and the use of drugs interfering in OH testing; model 2 includes confirmed HR-CAN, HbA1c, DPN, and retinopathy in addition to the variables of model 1.

	Model 1				Model 2			
Variables	Odds ratio	95% CI	R^2	P	Odds ratio	95% CI	R^2	P
Confirmed HR-CAN (yes)	8.99	3.17-25.5	0.199	**<0.0001**	6.42	1.68-24.5	0.218	**0.0065**
HbA1c (%)	1.03	1.00-1.06	0.105	**0.0305**	1.02	0.99-1.05	0.218	0.3268
DPN (yes)	3.15	1.12-8.88	0.094	**0.0231**	1.37	0.51-5.36	0.218	0.6514
Retinopathy (yes)	3.30	1.08-10.1	0.088	**0.0360**	1.12	0.30-4.16	0.218	0.8652

OR.16 | NORMATIVE THRESHOLDS OF CARDIOVASCULAR AUTONOMIC FUNCTION: THE LOFUS STUDY

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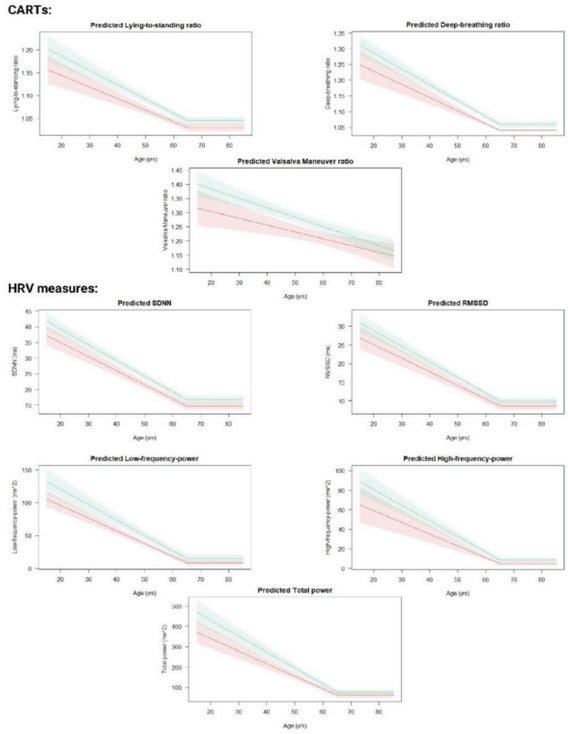
Objectives: Cardiovascular autonomic neuropathy (CAN) is a common diabetic complication associated with excess morbidity and mortality. Normative reference data of cardiovascular autonomic function used to differentiate between normal and abnormal function in subjects with diabetes. However, reference thresholds of both cardiovascular autonomic reflex tests (CARTs) and heart rate variability (HRV) are scarce. The aim of the study was to establish national normative reference thresholds based on a population without diabetes.

Methods: Cardiovascular autonomic function, including CARTs and short-term power spectral analysis of HRV, was assessed in subjects without diabetes and known cardiovascular disease from the Lolland-Falster Health Study (2018-2020) by applying the point-of-care device Vagus™. Because low values suggest poor cardiovascular autonomic function, age-specific normative reference thresholds were estimated by using piecewise linear quantile regression models at the 5th and 10th percentile. All models assessing the association between age and HRV-measures were adjusted for heart rate.

Results: We present normative reference thresholds for cardiovascular autonomic function including both CARTs and HRV for 882 subjects (47.9% females) aged 15-85 years. The thresholds are presented for both the 5th and 10th lower percentile. Median age was 50 years (IQR 32.6;65.0). Higher age was inversely associated with all outcomes. A linear reduction in cardiovascular autonomic function leveled off and plateaued beyond the age of 65 years for all outcomes except for Valsalva Maneuver-ratio which maintained the linear reduction across all ages (figure 1).

Conclusions: Age-related normative reference thresholds for both CARTs and HRV have been established. With this normative reference data, it is possible to assess CAN by applying both CARTs and HRV, which may facilitate improved quality of research and treatment for autonomic neuropathy in diabetes patients.

Figure 1: Visual presentation of the final models for each measure of cardiovascular autonomic function at the 5th (red) and 10th (green) lower percentile in subjects without diabetes and known cardiovascular disease.



CARTs: cardiovascular autonomic reflex tests, *HRV: heart rate variability, RMSSD:* 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 and HF power:* low-frequency power high-frequency power.

OR.17 | VALIDATION OF INDICATOR PLASTER NEUROPAD FOR THE DETECTION OF AUTONOMIC NEUROPATHY IN PATIENTS WITH DIABETES MELLITUS

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Objectives: To evaluate the specificity, sensitivity and accuracy of the Indicator Plaster Neuropad in detecting Diabetic Autonomic Neuropathy (DAN) in patients with Diabetes Mellitus (DM).

Methods: We studied 181 patients (82 with DM type 1, mean age 49.7+16.3 years). We performed the following Cardiovascular Reflex Tests (CRTs): R-R variation during deep breathing, Valsalva maneuver, R-R variability after a rapid change from lying to standing position and postural hypotension in all patients. The presence of DAN was established if 2 or more 4 CRTs were abnormal. According to the result the patients were divided in two groups: Group A (DAN) and Group B (no DAN). Examination of Neuropad was performed on all patients.

Results: Abnormal perspiration with Neuropad (uncompleted or no change in color) was detected in 94 patients. According to the number of abnormal tests, established DAN was detected in 82 patients. The sensitivity, specificity and accuracy of IP versus established DAN were 89%, 78% and 84% respectively, versus E/I index were 73%, 89% and 85% and finally versus Postural Hypotension were 95%, 77% and 85% respectively.

Conclusion: Neuropad has high sensitivity, specificity and accuracy in detecting established DAN versus CRTs.

Parameters	Total patients	T1DM	T2DM	p
n	**181**	82	99	
Sex m/f	**89/92**	40/42	49/50	NS
DM Duration (years)	17.3±7.7	18.7±8.4	16.1±6.8	**0.021**
Age (years)	49.7±16.3	36.2±12.2	61.1±8,4	**<0.005**
HbA1c (%)	7.4±1.3	7.5±1.3	7.3±1.3	NS
Alcohol (%)	**10.3**	8.9	11.6	NS
Smoking (%)	**16.1**	15.2	16.8	NS
Hypertension (%)	**28.2**	12.7	41.1	**<0.05**
Neuropad abnormal (n/ %)	**94/51.9**	30/36.5	64/64.6	**<0.05**
DAN present (n/ %)	**82/45.3**	**30/36.5**	**52/52.5**	**0.039**

OR.18 | SEX DIFFERENCES IN SEVERITY OF DIABETIC PERIPHERAL AND AUTONOMIC NEUROPATHY

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Aim: To investigate differences between men and women in the severity of Diabetic Neuropathy of the Peripheral (DPN) and Autonomic Nervous System (DAN) in patients with Diabetes Mellitus (DM).

Patients-Methods: The study included 179 patients with DM type 1 and 2 (79 DM type 1), mean age of 55.0 + 13.6 years and a mean duration of DM 19.7 + 8.0 years. All patients underwent the following tests to examine the peripheral and autonomic nervous system: Michigan Protocol, 10g monofilament test and determination of vibration perception threshold by biothesiometer, Cardiovascular Reflex Tests, Electrochemical Skin Conductance (SU), and electrophysiological tests (nerve conduction velocity, NCV, and amplitude AMP) with the use of sudoscan and neurometrix respectively. All patients had PDN and DAN and were classified into two groups: A (n = 85, male) and B (n = 94, women).

Results: Significant differences between the two groups (A vs. B) were observed in the E / I index (1.08 ± 0.03 vs. 1.06 ± 0.03, p = 0.016), MCR (13.43 ± 9.09 vs. 13,20 ± 7,17, p = 0,033), SD (23,94 ± 14,82 vs 21,84 ± 11,18, p = 0,013). In all other indices, we did not observe any significant difference (p> 0.05). SU, NCV, and AMP did not differ between the two groups: SU (74.9 ± 12.0 vs. 78.9 ± 10.8, p= 0,177), NCV (48.4 ± 14.0 vs. 50.2 ± 10.8 p= 0,572) AMP (5.9 ± 3.4 vs 6.7 ± 4. 2 p= 0.432). Men were smokers and alcohol users at a higher frequency (p <0.05).

Conclusions: Women showed a significantly greater severity of the parasympathetic DAN, as expressed by the E / I, MCR and SD indices. Therefore, women are likely to develop more severe parasympathetic DAN than men.

OR.19 | INVESTIGATING THE ROLE OF OBESITY AND METABOLIC MARKERS FOR THE PRESENCE AND SEVERITY OF PERIPHERAL NEUROPATHY IN TYPE 2 DIABETES, PRE-DIABETES (IGT) AND HEALTHY SUBJECTS

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Objectives: The prevalence of type 2 diabetes, metabolic syndrome and obesity is increasing worldwide. Obesity is the second leading risk factor for peripheral neuropathy (PN) after diabetes. The current study aimed to determine the effect of obesity on PN in subjects with diabetes, pre-diabetes (IGT) and healthy subjects.

Methods: 322 subjects, including 208 T2DM,24 IGT and 90 Healthy controls HC), were investigated in detail for medical, neurological and ophthalmological assessments. All participants underwent fasting lipid profile, HbA1c and participants without diabetes also underwent glucose tolerance testing. The study was in the Japanese population; the cut-off point for Obesity is BMI >25. Subjects were classified to BMI to ≤25.0 and BMI > 25. Table 1 presents a summary of demographic data for study groups.

Results: HC with(n=19) and without(n=71) obesity did not present any abnormal clinical findings. The small c nerve fibres measured with CCM(NFD, NBD, NFL) were within normal range. OCT parameters in some regions of the retina were increased more in obese HC, but no difference in the nerve layers.

For IGT, although metabolic markers were significantly different between obese(n=13) and non-obese(n=11) subjects, there was no significant difference in neuropathy markers that were assessed with NDS, NCS, QST and autonomic function tests. The Corneal nerve parameters(i.e.NFD, NBD, NFL) showed significant reduction compared to the HC, but no difference between the obese and non-obese IGT. OCT showed that GCL, OPL and NPL layers' thickness significantly increased in obese subjects.

T2DM subjects were presented with significant neuropathy compared to HC and IGT. T2DM with obesity (n=123) vs those without obesity (n= 85) showed significant abnormality for Lipid profile, kidney function and neurological markers. Both groups had similar duration of diabetes; however, the obese group was marginally younger(49 vs 51) and had higher HbA1C(8.1% vs 7.97%).

NDS was significantly higher in obese subjects(4.28 vs 3.41). There was no significant difference in other neuropathy markers. Corneal nerve parameters were significantly reduced in T2DM, but there was no difference between obese and non-obese subjects. There was no significant difference in OCT parameters between T2DM with and without obesity.

Conclusion: In this study, we investigated the role of obesity, metabolic and neurological markers in a large cohort of diabetes, pre-diabetes and healthy subjects. The outcome demonstrated T2DM with Obesity has the greatest level of peripheral neuropathy. A similar pattern was observed in IGT subjects. Although obesity plays an important role, the high glucose level is the main cause of nerve damage alongside lipid and metabolic parameters. Future studies need to investigate the follow-up of these subjects and subjects with more severe obesity.

Table 1: Summary of demographic figures for study subjects

	Controls		IGT		T2DM	
	BMI≦25	BMI > 25	BMI≦25	BMI > 25	BMI≦25	BMI > 25
Number (Male/Female, %)	71 (47.9/52.1)	19 (73.7/26.3)	11 (27.3/72.7)	13 (92.3/7.7)	85 (63.5/36.5)	123 (68.3/31.7)
Age (year)	49.3±1.1	53.8±1.9	55.3±3.4	49.3±2.8	53.1±0.8	48.8±0.76
Body mass index (kg/m²)	21.5±0.27	27.2±0.33	20.7±0.54	28.1±0.71	22.2±0.20	30.1±0.47
Duration of diabetes (year)	-	-	-	-	8.8±0.87	8.7±0.60
HbA1c (%)	5.54±0.038	5.72±0.068	6.00±0.085	5.99±0.061	7.97±0.22	8.18±0.17
eGFR (mL/min)	82.5±1.94	77.5±2.73	66.3±2.37	76.7±3.55	81.9±2.26	85.1±1.77
Urinary albumin to creatinine ratio (mg/gCr)	9.0±1.1	9.2±2.2	9.6±1.88	23.2±16.2	32.8±11.9	55.3±18.1
NDS	0.44±0.069	0.58±0.16	1.91±0.60	3.00±0.53	3.41±0.27	4.28±0.25

OR.20 | NEW NORMATIVE REFERENCE DATA FOR RYDEL-SEIFFER TUNING FORK VIBRATION THRESHOLDS AND DIAGNOSTIC PERFORMANCE OF NEUROPATHY DISABILITY SCORE TO DETECT DIABETIC POLYNEUROPATHY

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Objectives: The detection of distal sensorimotor polyneuropathy (DSPN) remains a challenge in clinical practice. Strategies to address this issue could include improvements in handling and interpretation of clinical screening instruments. Therefore, we aimed to provide normative reference data of the vibration thresholds (VT) at a standard examination site using the 64 Hz-Rydel-Seiffer tuning fork in a comprehensively phenotyped cohort of individuals with normal glucose tolerance (NGT) and to test the diagnostic performance of the Neuropathy Disability Score (NDS) including the newly generated VT normative data in individuals with type 1 or type 2 diabetes to detect DSPN characterised by large-fibre impairments.

Methods: VTs were assessed in a cohort of 236 NGT individuals (age [median (1st, 3rd quartile)]: 48.9 (34.5, 58.0) years, sex: 58.5% male) from the German Diabetes Study (GDS) at the dorsal interphalangeal joint of the hallux at both feet after exclusion of DSPN. NDS and DSPN were assessed in a cohort of 1210 participants (type 1/type 2 diabetes: n=405/805; sex: 59.0/69.2% male; age: 35.2 (26.6, 48.2)/56.0 (47.9, 64.0) years; DSPN: 8.1/19.0%) from the GDS and PROPANE study. DSPN was defined as the presence of abnormal nerve conduction indices in ≥2 peripheral nerves at the lower extremity.
Results: In NGT, multiple linear regression analyses revealed a negative association between VT and age which was considered in the generation of the equation (9.236-(0.055 × age [years]) - (1.645*1.2265)) to calculate the 5th percentile threshold. For clinical practice, approximate VT cut-offs in different age groups were 6.0 (≤20 years), 5.5 (21-30 years), 5.0 (31-40 years), 4.5 (41-50 years), 4.0 (51-60 years), 3.5 (61-70 years), and 3.0 (≥71 years). Including the new VT score in the NDS, the diagnostic performance of NDS ≥ 3 points to detect DSPN was [sensitivity/specificity/positive likelihood ratio/negative likelihood ratio] 63.0%/92.7%/8.68/0.40 and 75.7%/76.1%/3.16/0.32 in type 1 and type 2 diabetes, respectively. In participants with type 1 diabetes aged < 50 years, ROC and Youden index (J) analyses indicated a cut-point of NDS ≥ 2 points (J = 0.283), resulting in a diagnostic performance of 41.7%/86.6%/3.11/0.67.
Conclusion: This study provides new normative reference data for the interpretation of the tuning fork examination which is part of many DSPN screening instruments for neuropathic deficits. The NDS incorporating these data represents a useful screening tool for DSPN. However, further evaluation related to small-fibre innervation is needed to also support its application in younger individuals with type 1 diabetes.

OR. 21 | NATURAL COURSE OF DECLINING NERVE FUNCTION DURING THE FIRST 10 YEARS OF WELL-CONTROLLED RECENTLY DIAGNOSED TYPE 2 DIABETES

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Objectives: There is a lack of evidence on the long-term changes of nerve function in individuals with well-controlled type 2 diabetes compared to those with normal glucose tolerance (NGT). The aim of the present prospective study was to assess motor and sensory nerve conduction velocities (MNCV, SNCV), sensory nerve action potentials (SNAP), vibration perception threshold (VPT) and thermal detection threshold (TDT) of lower extremities in individuals with recently diagnosed type 2 diabetes and NGT.
Methods: The study included 52 pairwise matched individuals from the German Diabetes Study baseline cohort with recently diagnosed type 2 diabetes (known diabetes duration (median [1st, 3rd quartile]): 6 [4, 8] months) and NGT who had a five years follow-up. Individuals were matched pairwise for age (T2D/NGT: 51.4 [44.3, 59.1]/51.7 [44.3, 58.8] years) and sex (67/67% male). In addition, the study included 142 individuals with type 2 diabetes, who were followed over ten years. Functional tests included motor and sensory nerve conduction velocities, sensory nerve action potentials, vibration perception threshold and thermal detection threshold of lower extremities. All statistical tests ($\chi 2$ test, paired t-test, multivariate analyses of covariance) were two-sided, and the level of significance was set at α=0.05.
Results: At baseline, peroneal MNCV (45.0 [40.3, 48.1] vs 46.5 [43.3, 48.8]) and sural SNAP (6.9 [5.4, 9.8] vs 10.0 [7.5, 12.0]) were lower in the type 2 diabetes group compared to NGT group, while malleolar VPT (1.16 [0.55, 2.42] vs 0.83 [0.46, 1.61]) was higher (all $p < 0.05$). After five years, two out of six indices (peroneal MNCV and malleolar VPT) deteriorated in individuals with type 2 diabetes and two (malleolar VPT and foot TDT for cold) in individuals with NGT (all $p < 0.05$). Multivariate analyses of covariance (adjusted for baseline values, height, BMI, and matching) revealed that nerve function similarly declined over the first five years in both groups. For sural SNCV and foot TDT for cold the test for equal slopes revealed differences with respect to baseline values ($p < 0.05$). A comparable deterioration of all six indices was also observed in individuals with type 2 diabetes over ten years.
Conclusions: Parallel decline in small and large fiber function in both NGT and recently diagnosed type 2 diabetes indicates that the main events leading to impaired nerve function in well-controlled type 2 diabetes might occur earlier than previously assumed.

OR.22 | LONG-TERM ABNORMAL ORNEAL NERVE MORPHOLOGY PREDICTS PROGRESSION OF NEUROPATHIC DEFICITS IN TYPE 2 DIABETES

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Aim: This study investigated the association of prolonged abnormalities in corneal nerve morphology with progression of neuropathic symptoms and deficits in individuals with type 2 diabetes (T2D).
Methods: Participants with T2D underwent clinical, metabolic testing and assessment of neuropathic symptoms, vibration perception threshold, sudomotor function, and corneal confocal microscopy at baseline and at follow up at three visits on years 1, 2, and a final visit between 4-7 years. Healthy controls were enrolled only for the baseline visit to define the cut-off values (>1.5 SD) for abnormal corneal nerve morphology.
Results: 107 participants with T2D (aged 54.8±8.5 years) and 57 age-matched controls without diabetes (aged 50.6±16.9 years, P=0.11) were recruited. Follow-up assessments were conducted over a period of 1-7 years, with around 2/3rd of the cohort completing follow-up assessments within 4-5 years. Throughout the study, 51 (48%) had ≥50% abnormal corneal nerve fiber density (CNFD), 23 (22%) had ≥50% abnormal corneal nerve branch density (CNBD), and 63 (59%) had ≥50% abnormal corneal nerve fiber length (CNFL). A sustained abnormality in CNFD was associated with greater neuropathic symptoms at baseline and progression of impaired vibration perception (all P<0.05). Sustained abnormal CNBD was associated with a greater impairment in vibration perception at baseline (P<0.05) and a decline in sudomotor function (not significant, P=0.07). Sustained abnormal CNFL was associated with progression of impaired vibration perception (P=0.05) and a decline in sudomotor function (not significant, P=0.07).
Conclusions: This study suggests that patients with T2D and a sustained abnormality in corneal nerve morphology are at greater risk for progression of neuropathy.

OR.23 | ELEVATED DIABETIC KETOACIDOSIS RISK FOLLOWING ULCER OR AMPUTATION IN T1D: 34 YEAR FOLLOW-UP OF DCCT/EDIC

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Objectives: People with type 1 diabetes and advanced neuropathy complications have augmented risk of adverse outcomes including mortality and cardiovascular disease. We aimed to determine if advanced neuropathy independently increases risk of acute complications such as diabetic ketoacidosis (DKA).
Methods:. We accessed previously-collected data from the Diabetes Control and Complications Trial/Epidemiology of Diabetes Interventions and Complications (DCCT/EDIC) Study, an interval and open cohort study, through the NIH Public Repository. For advanced neuropathy as the exposure, occurrence of self-reported and verified ulcer or amputation, as well as first DKA from enrolment as the outcome, were evaluated annually

throughout follow-up. Multivariable Cox Proportional Hazard models with time-varying exposure and co-variates collected annually were used.

Results: 1441 people participated in the DCCT, 1375 of whom joined the EDIC phase, representing 95% of the surviving participants. At baseline of the DCCT, mean age was 26.8 (SD 7.1) years, diabetes duration was 5.6 (SD 4.2) years, HbA1c was 8.9 (SD 1.6) %, 47% were female, and 97% were white. There were 527 foot ulcers noted and 202 amputation events among 226 individuals, and 488 DKA events among 297 individuals. Ulcer/amputation was associated with increased risk of DKA (Univariable Hazard Ratio 1.8, 95% confidence interval 1.2 to 2.8, p = 0.004). In multivariable analysis, ulcer/amputation was independently associated with increased risk of DKA (Hazard Ratio 1.7, 95% confidence interval 1.1 to 2.5, p = 0.019). DKA risk was also associated with insulin pump use (HR 3.0, 2.2 to 3.9, p<0.001), higher insulin dose (HR for 1 unit/kg/day 2.4, 1.7 to 3.3, p<0.001), female sex (HR 2.0, 1.5 to 2.6, p<0.001), shorter duration of diabetes (HR for 10 years 1.4, 1.0 to 1.9, p = 0.025), and higher time-updated HbA1c (HR for 1 percent 1.4, 1.3 to 1.5, p<0.001). In this model, there was no association with age, baseline HbA1c, weight or time-updated retinopathy or nephropathy.

Conclusions: In addition to previously reported augmented mortality and cardiovascular disease risk, this analysis demonstrates a substantially higher risk of DKA independent of possible confounders and other complications in those with a history of foot ulcer or amputation. This implies a need for greater metabolic control, self-management skills and education in those with advanced neuropathy. The mechanism of such acute complications and the other adverse outcomes requires further study.

OR.24 | THE INFLUENCE OF CHRONIC KIDNEY DISEASE ON DIABETES NEUROPATHY – RESULTS OF THE 5-YEAR LONGITUDINAL IPSWICH NEURODIAB STUDY

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Objectives: The overlapping combination of diabetes and chronic kidney disease (CKD) is believed to increase the risk of progression to macroangiopathic complications. However, the influence of CKD and its progression in people with and without diabetes on neural structure and function has not been widely studied. This 5-year longitudinal study evaluated the effect of changes in renal function on small and large fibre neural indices in Type-1 (T1DM) and Type-2 (T2DM) diabetes subjects as well as matched healthy controls (HC)

Methods: At baseline, we examined 240 subjects (80 each T1Dm and T2DM and 80 HV) and compared their neural parameters with renal functions (creatinine and eGFR). Subjects were also grouped into CKD+ (eGFR<60) and CKD- (eGFR≥60). Similar comparisons were done at the end of 5 years for 150 remaining subjects (50 each T1DM, T2DM and HC). Small fibre function was assessed using the LDIFLARE method whilst small fibre structure was examined with Corneal confocal microscopy. Large fibre neural parameters were measured using Sural nerve conduction velocity (SNCV), amplitude (SNAP) and vibration perception threshold (VPT).

Results: ***At baseline,*** no significant correlation (p >0.05) was observed between eGFR and all neural parameters (small and large fibres) in T1DM (mean age ± SD=41.5yr±15.2), T2DM (54.1yr±9.1years) and HV (39.67±15.17 years). However, when divided into groups with and without CKD, T2DM CKD+ had significantly (p<0.05) smaller LDIFLARE, CCM, SNCV, SNAP and VPT values when compared to T2DM CKD-. No significance was observed within T1DM and HV groups.

After 5-year follow up (see table below), when the remaining 50 T1DM, T2DM and HV subjects were examined, the rate of fall of CKD (measured as mL/min/1.73m2/year) correlated significantly (p<0.05) with the decline of LDIFLARE, CNFD, CNBD and SNCV between CKD+ and CKD- group in T2DM but not in T1DM nor HC.

5-year follow up		Rate of decline of eGFR *mL/min/1.73m²/year*		
Rate of decline/year	**DM type**	**CKD +**	**CKD -**	**Significance**
LDI_{FLARE} *(cm² ± SD)*	T1DM	0.11 cm²/yr	0.09 cm²/yr	NS
	T2DM	0.22 cm²/yr	0.10 cm²/yr	p=0.01
Corneal nerve fibre density (CNFD) *(no/mm² ± SD)*	T1DM	0.22 fibres/mm²/yr	0.20 fibres/mm²/yr	NS
	T2DM	0.52 fibres/mm²/yr	0.29 fibres/mm2/yr	p=0.001
Corneal nerve branch density (CNBD) *(no/mm² ± SD)*	T1DM	0.19 fibres/mm²/yr	0.16 fibres/mm²/yr	NS
	T2DM	0.29 fibres/mm²/yr	0.15 fibres/mm²/yr	p=0.02
Corneal nerve fibre length (CNFL) *(mm/mm² ± SD)*	T1DM	0.10 mm/mm²/yr	0.08 mm/mm²/yr	NS
	T2DM	0.10 mm/mm²/yr	0.09 mm/mm²/yr	NS
SNCV *(m/s ± SD)*	T1DM	0.21 ms^{-1}/mm²/yr	0.20 ms^{-1}/mm²/yr	NS
	T2DM	0.41 ms^{-1}/mm²/yr	0.29 ms^{-1}/mm²/yr	p=0.009
SNAP *(μV ± SD)*	T1DM	0.09 μV mm²/yr	0.05 μV mm²/yr	NS
	T2DM	0.19 μV mm²/yr	0.15 μV mm²/yr	NS
VPT *(mV ± SD)*	T1DM	0.03 mV mm²/yr	0.03 mV mm²/yr	NS
	T2DM	0.11 mV mm²/yr	0.09 mV mm²/yr	NS

Conclusions: This study found that cross sectionally at baseline, the degree of neural damage is significantly greater in patients with CKD+ as compared to those without. Furthermore, this prospective study showed that at 5 years follow up, the rate of fall of CKD+ specifically in T2DM correlates significantly with the decline of small and large fibre indices indicating that the pathophysiology of neuropathy in T2DM might be further influenced by additional factors including the metabolic-renal syndrome. Further studies will be required in larger cohorts to support the above outcomes.

OR.25 | BIDIRECTIONAL ASSOCIATION BETWEEN DIABETIC PERIPHERAL NEUROPATHY AND VITAMIN B12 DEFICIENCY: TWO LONGITUDINAL 9-YEAR FOLLOW-UP STUDIES USING A NATIONAL SAMPLE COHORT

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Objectives: Vitamin B12 deficiency (vit B12) causes peripheral neuropathy and metformin reduces vit B12 level in diabetes, thus increases diabetic peripheral neuropathy (DPN) incidence. However, metformin may not be related to DPN occurrence due to its glucose lowering and neuroprotective effects in diabetes. Few studies have investigated vit B12 deficiency according to the presence/absence of DPN in diabetes. Therefore, we investigated the association among metformin use, vit B12 deficiency, and DPN occurrence in diabetes.

Methods: This retrospective, propensity-matched cohort study was performed using the National Health Insurance Service database - National Sample Cohort (NHIS-NSC), which includes 1,000,000 patients of the total 50 million people in South Korea. Study 1 analyzed DPN incidence according to vit B12 deficiency and study 2 analyzed vit B12 deficiency incidence according to the presence/absence of DPN. Moreover, we compared the results with respect to metformin use. The cohort selection period was 2002–2004, and outcome occurrence was evaluated until 2013.

Results: In study 1, DPN incidence per 10000 person-year (PY) was 179.7 and 76.6 in the vit B12 and non-vit B12 deficiency groups, respectively. The adjusted HR was 1.32 (95% CI; 1.21-1.44, P<0.05) and metformin use elicited a more significant effect of DPN occurrence in patients with vit B12 deficiency (HR: 5.76 (95% CI; 5.28-6.29). In study 2, vit B12 deficiency incidence per 10000 PY was 250.6 and 129.4 in the DPN and non-DPN groups, respectively. The adjusted HR was 2.44 (95% CI; 2.24-2.66, P<0.05), however, metformin prescription was associated with the reduced prevalence of vit B12 deficiency in DPN patients (HR 0.68 (95% CI; 0.62-0.74, P<0.05).
Conclusion: DPN occurrence increased in diabetes with vit B12 deficiency and the incidence of vit B12 deficiency was also high in DPN patients. However, metformin showed opposite effects in both cohorts. Further studies clarifying the causal relationship among DPN occurrence, vit B12 deficiency, and metformin use are warranted.

OR.26 | OPENING OF KV7 CHANNELS ACTIVATES AMPK AND MIMICS ASPECTS OF ANTIMUSCARINIC DRUG ACTION IN ADULT SENSORY NEURONS

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Background: Voltage-gated potassium channels, with particular reference to Kv7 sub-types, are regulators of cellular physiology and controlled, in part, by G protein-coupled receptors (GPCRs). The most abundant subunits of Kv7 in sensory neurons are Kv7.2/7.3 and remain closed under conditions where acetylcholine activates a GPCR, the muscarinic acetylcholine type 1 receptor (M1R). Consequently, these Kv7 subtypes have been termed M-channels (Brown and Passmore, British Journal of Pharmacology, 2009). Currents passing through M-channels are low-threshold, slowly activating potassium currents that maintain a negative resting membrane potential to prevent hyperexcitability. Thus, agonist action at M1R drives closing of Kv7 channels leading to increased excitability. Development of selective modulators for Kv7 channels represent a novel and exciting therapeutic target in the treatment of neurodegenerative diseases, including neuropathic pain. Selective or specific antagonism of the M1R using pirenzepine (PZ) or muscarinic toxin 7 (MT7), respectively, induced AMP-activated protein kinase (AMPK) activity and augmented mitochondrial function to enhance nerve repair in neuropathic disease (Calcutt et al, Journal of Clinical Investigation, 2017; Saleh et al, Molecular Neurobiology, 2020). This project aimed to determine mechanisms of action of antimuscarinic drugs, at the M1R, with a focus on modulation of Kv7. We hypothesized that M1R antagonism via activation of Kv7.2/7.3 enhanced mitochondrial function to suppress sensory neuron excitability and provide neuroprotective effects.
Methods: Dorsal root ganglia (DRG) sensory neuron cultures derived from adult control or streptozotocin (STZ)-induced diabetic rats were treated with PZ (1microM), MT7 (100nM), Kv7 opener retigabine (10microM) or Kv7 inhibitor XE991 (15microM). Cellular bioenergetic status was assessed using a Seahorse XF-24. Cultured DRG neurons were loaded with voltage sensor probe DiBAC4(3) to evaluate the plasma membrane potential. Expression analysis of AMPK was performed by Western blot and neurite outgrowth assessed using immunocytochemistry.
Results: PZ or retigabine treatment significantly increased AMPK phosphorylation and ATP production in cultures derived from control or diabetic rats. Both drugs similarly induced hyperpolarization of the plasma membrane. These positive effects of PZ and retigabine on membrane hyperpolarization were blocked by the selective Kv7 blocker, XE991 (15microM). DRG cultures from diabetic rats exhibited a significant 2-3-fold elevation in neurite outgrowth in response to PZ or retigabine (with no additive effect when combined).
Conclusions: These findings reveal that antagonism of M1R activates Kv7.2/7.3 to elevate mitochondrial function and support axonal sprouting and regeneration. Funding: MITACs # IT14860 and WinSanTor Inc.

OR.27 | RESPONDERS TO NEUROPATHIC PAIN TREATMENT HAVE GREATER TARGET ENGAGEMENT OF DOPAMINE RECEPTOR SYSTEMS: A RESTING-STATE FUNCTIONAL MAGNETIC RESONANCE IMAGING STUDY IN PAINFUL DIABETIC NEUROPATHY

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Importance: The best we can hope for with pharmacotherapy is 50% pain relief in only half of patients with painful diabetic peripheral neuropathy (DPN). The reason for this poor treatment response is poorly understood.
Objectives: To examine alterations in resting state functional magnetic resonance imaging (RS-fMRI) in brain regions involved in pain control/regulation in painful DPN and determine if differences in opioid and dopamine receptor enriched functional connectivity (FC) predicts analgesic treatment response.
Design and Participants: 208 subjects (No DPN, n=38; Painless DPN, 45; Painful DPN, 88; HV, 36) underwent detailed clinical/neurophysiological assessments and RS-fMRI from June 2017 and October 2021.
Interventions: Treatment response was assessed using intravenous lidocaine [5mg/kg dose over 60-minutes (maximum dose 300mg)] in 50 painful DPN subjects in an open labelled, single blind study. Responders reported at least a 30% reduction in an 11-point numeric rating pain scale (0=no pain and 10=worst pain imaginable) within a week after lidocaine treatment lasting for at least 3 weeks
Results: Compared to controls, Painful DPN subjects showed reduced FC in the postcentral (right, p-FDR=0.01) and precentral gyri (left, p-FDR=0.02; right, p-FDR<0.001). Subjects with painful DPN had increased FC between the orbital frontal cortex and the basal ganglia/corticolimbic system (p-FDR<0.001) compared to Painless DPN. There was significantly increased m-opioid (amygdala, p-FDR=0.006; anterior prefrontal cortex, p-FDR=0.01) and dopamine receptor enriched FC (anterior prefrontal cortex, p-FDR=0.04; orbital frontal cortex p-FDR=0.04; midbrain, p-FDR=0.009) in responders compared to non-responders.
Conclusions and relevance: In this, the largest RS-fMRI neuroimaging study in DPN to date, subjects with painful DPN present functional alterations in key brain regions, associated pain control and regulation, namely in the descending modulatory pathway – rich in opioid and dopamine neurotransmitters. We found that responders to neuropathic pain treatment demonstrated greater opioid and dopamine enriched FC compared to non-responders. Hence, pre-treatment inter-individual differences in opioid and dopamine enriched FC might underlie variability in their response to pharmacological treatment.

OR.29 | LX9211 IN INDIVIDUALS WITH PAINFUL DIABETIC PERIPHERAL NEUROPATHY: RESULTS FROM A RANDOMIZED, DOUBLE-BLIND, PLACEBO-CONTROLLED, PARALLEL-GROUP, MULTICENTER STUDY

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Objectives: Painful diabetic peripheral neuropathy (DPN) is a debilitating condition affecting millions of people. The currently available therapies

often provide inadequate pain relief in most individuals with painful DPN. LX9211 is a potent, novel, orally administered inhibitor of adaptor-associated protein kinase 1 (AAK1), a non-opioid target for neuropathic pain. The objective of this study was to demonstrate the efficacy and safety of LX9211 in people with painful DPN.

Methods: RELIEF-DPN 1 (NCT04455633) was a randomized, double-blind, placebo-controlled, parallel-group, multicenter clinical trial in which participants with painful DPN were randomized to receive placebo, LX9211 10 mg (with a 100 mg loading dose on Day 1), or LX9211 20 mg (with a 200 mg loading dose on Day 1), once daily for 6 weeks. The double-blind period was followed by a 5-week blinded safety follow-up period during which subjects received placebo once daily. The primary endpoint was the difference in change in average daily pain score (ADPS) between LX9211 and placebo at 6 weeks, as evaluated by mixed model repeated measures analysis.

Results: Among 319 adults randomized, baseline mean (SD) age was 62 (10) years, 41% were women, 76% White, 18% Black, mean HbA1C 7.7 (1.28) %, 61(14) mmol/mol, body mass index (BMI) 32.07 (4.45) kg/m2, and average daily pain score (ADPS) after placebo run-in period 6.55 (1.089). At Week 6, LX9211 was associated with achieving the primary endpoint (change from placebo in the ADPS) in the low dose arm (Low Dose: -1.39, p=0.007), and with significant improvement in: Neuropathic Pain Symptom Inventory (NPSI) total score (Low Dose: -5.18, p=0.064; High Dose: -7.22, p=0.008), burning pain (Low Dose: -1.40; p<0.001; High Dose: -0.89, p=0.017), pain interference on sleep (Low Dose: -0.96, p=0.005; High Dose: -1.04, p=0.002) and Patient Global Impression of Change score (Low Dose: -0.35, p=0.031; High Dose: -0.15, p=0.351) compared to placebo. LX9211 was safe (no treatment-related SAEs or deaths) and did not affect key cardiometabolic parameters (body weight, blood pressure, glucose control, cholesterol levels).

Conclusions: RELIEF-DPN 1 demonstrated significant improvements in validated neuropathic pain instruments and in other patient reported outcomes suggesting that LX9211 is a promising, opioid independent new avenue to treat people with painful DPN. Confirmation of these positive results are planned in future Phase 3 trials.

OR.30 | OLFACTORY FUNCTION AND MEASUREMENTS OF RHINENCEPHALON STRUCTURES UPON MAGNETIC RESONANCE IMAGING IN ADULTS WITH TYPE 1 DIABETES ARE RELATED TO DIABETIC PERIPHERAL NEUROPATHY

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Objectives: Rhinencephalon imaging in patients with diabetes and dysosmia may bring essential insights into the advancement of chronic complications of diabetes. The aim was to assess neurodegenerative changes of rhinencephalon in patients with Type 1 Diabetes Mellitus (T1DM) via magnetic resonance imaging (MRI) in relation to the presence of diabetic peripheral neuropathy (DPN).

Methods: We included T1DM patients aged 18-65 with disease duration >10 years. The control group included diabetes-free subjects. The study group was divided according to the presence of diabetic peripheral neuropathy. Complete otorhinolaryngological examination and olfactory assessment with Sniffin'Sticks were performed. To evaluate the morphology of the rhinencephalon, MRI of the head was performed. T1 and T2, 3D MPRANGE sequences were used to perform volumetric measurements of the olfactory bulbs and pyriform cortices thickness.

Results: The study group consisted of 32 subjects, 24 males, median age 43.5 years (IQR: 37.0-48.5), with disease duration of 24.5 years (IQR: 20.5-27.0), HbA1c 7.9% (IQR: 7.4-8.4); 63 mmol/l (IQR: 57-68). The control group consisted of 6 subjects, 4 males, median age 41.0 years (IQR: 36.0-48.0). Significantly lower olfactory test results in TDI (Threshold-Differentiation-Identification) [31.5 (IQR: 28.7-33.6) vs 34.1 (IQR: 33.2-37.2), p=0.02] and olfactory threshold [7.0 (IQR: 6.5-8.0) vs 8.5 (IQR: 8.0-9.0); p=0.049] were obtained in the study group as compared to the controls. Summarized olfactory bulbs volumes [65.8 mm3 (IQR: 57.9-71.7) vs 75.8 mm3 (IQR: 74.8-76.7); p=0.0005], as well as separately right [33.4 mm3 (IQR: 28.6-36.2) vs 37.5 mm3 (IQR: 36.9-38.8); p=0.001] and left [32.6 mm3 (IQR: 29.1-35.4) vs 37.9 mm3 (IQR: 37.2-38.8); p=0.0006] olfactory bulb volumes were significantly smaller in patients with T1DM than in the controls. A smaller thickness of the left pyriform cortex was found in the study group as compared to the controls [3.1mm (IQR: 2.7-3.4) vs 3.6mm (IQR: 3.5-4.1); p=0.02]. In patients with diabetes and DPN, significantly smaller olfactory bulb volumes were found as compared to patients without this complication [58.1 mm3 (IQR: 54.0-70.9) vs 69.8 mm3 (IQR: 65.0-72.2); p=0.02]. In the multiple linear regression model tobacco smoking (β:0.37; p=0.03) and the presence of diabetic peripheral neuropathy (β:0.45; p=0.02) proved to be independent predictors of olfactory bulb volume.

Conclusions: In adults with type 1 diabetes olfactory function is worse than in the healthy controls, and measurements of rhinencephalon structures are smaller. The volumetric parameters of rhinencephalon are determined by the presence of diabetic peripheral neuropathy and smoking status.

OR.31 | THE IMPACT OF AUTONOMIC AND PERIPHERAL DIABETIC NEUROPATHY ON COGNITIVE FUNCTION IN OLDER TYPE 2 DIABETIC PATIENTS

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Objective: Diabetic neuropathy (DN) cannot be considered a disease only of the peripheral nervous system anymore and different involvement of the brain are described according to different phenotypes of DN. This aspect became more relevant in older type 2 diabetic (T2D) patients. The aims of our study were to explore the impact of diabetic peripheral neuropathy (DPN) and cardiac autonomic neuropathy (CAN) on cognitive functions and the possible association among cognitive scores and clinical parameters.

Materials and methods: 69 T2D patients (65-90 years), without previous history of stroke or neurodegenerative diseases, were enrolled. All patients performed Michigan Neuropathy Screening Instruments, vibration perception threshold, thermal perception thresholds and cardiovascular autonomic reflex tests. Patients were divided in DPN+ or DPN- and, then, the DPN+ group was subdivided in CAN- and CAN+. Participants also performed the Montreal Cognitive Assessment Test (MoCA), to screen mild cognitive impairment (MCI), and cognitive domains were assessed using the Trail Making Test (TMT-A and B), the Rey–Osterrieth complex figure Test, the Rey- Auditory Verbal Learning Test (RAVLT), the Digit Symbol Substitution Test (DSST). Patients with dementia or depression were excluded according to the clinical dementia rating scale and the Geriatric depression scale, respectively.

Results: DSST was significantly lower in DPN+ group versus DPN- (27.68 vs 37.31 p=0.03). The prevalence of MCI was significantly higher in DPN+ and CAN+ group versus DPN+ and CAN- (100% vs 82.1%, p=0,04), Moreover, MoCA became smaller in CAN+ group versus CAN- (18.75 vs 22.04

p<0.01). Also RAVLT (5.36 vs 9.25 p<0.01), TMT A (68.55 vs 45.13 p<0.01) and DSST (20.0 vs 38.88 p<0.01) were significantly lower in CAN+ group versus CAN-. There was a negative correlation between systolic blood pressure delta and RAVLT (r=-0.49; p=0.01).it was observed a positive correlation between E/I and 30:15 ratio and RAVLT (r=0.49; p=0.01 and r=0.49; p=0.01) and between 30:15 ratio and DSST (r=0.54; p<0.01).

Conclusion: DN seems to have a high impact on cognitive function in T2D patients. Moreover, the association of DPN and CAN is linked with more serious phenotypes of cognitive decline. T2D patients, in presence of DN, have to be screened and monitored for progression of cognitive impairment.

OR.32 | SOLUBLE UROKINASE PLAMINOGEN ACTIVATOR RECEPTOR IS ASSOCIATED WITH CARDIOVASCULAR AUTONOMIC NEUROAPTHY IN TYPE 1 DIABETES

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Objectives: Cardiovascular autonomic neuropathy (CAN) and distal symmetric polyneuropathy (DSPN) are common and severe complications to diabetes associated with increased risk of morbidity and mortality with no current treatment. Inflammation is part of the pathogeneses causing neuropathy. Soluble urokinase plasminogen activator receptor (suPAR) is a marker of inflammation associated with diabetic complications. We investigated the associations between serum suPAR levels and the diagnosis of CAN and DSPN in people with type 1 diabetes (T1D).

Methods: In a cross-sectional study of people with T1D, serum suPAR was measured by ELISA analyses. CAN was assessed by cardiovascular reflex tests (CARTs): heart rate response to deep breathing (E/I ratio), to standing (30/15 ratio) and to the Valsalva manoeuvre (VM). Two or three pathological CARTs constituted CAN. Peripheral neuropathy was assessed by biothesiometry, where symmetrical vibration perception threshold (VPT) above 25 volts constituted DSPN.

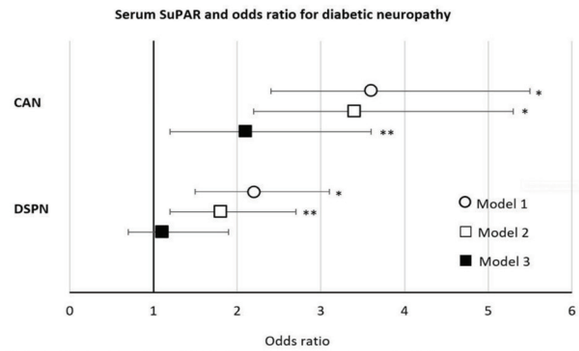
Results: A total of 298 persons with T1D were included. The mean (SD) age was 55.7 (9.3) years, 51% were male, diabetes duration was 40.1(8.9) years, HbA1c was 62.9(1.9) mmol/mol, estimated glomerular filtration ratio(eGFR) 78.1(24.9) ml/min/1.73m2 and median (IQR) serum suPAR was 3.6 (3.0;4.7) ng/ml.

Of 256 participants with CARTs available, 34% (n= 87) had CAN. DSPN was assessed in all participants and was present in 48% (n=143).

In models adjusted for age, sex and high-sensitive C-reactive protein (model 1) and additionally adjusted for diabetes duration, HbA1c, BMI, smoking, systolic blood pressure, serum LDL cholesterol and beta blocker use (only for CAN) (model 2), a doubling of suPAR, was significantly associated with odds ratios >3 for CAN and > 1 for DSPN, respectively. Significance was retained after additional adjustment for eGFR (model 3) for CAN (Odds ratio 2.1(95%CI: 1.2;3.6 p=0.007), but not for DSPN (Odds ratio 1.1(95%CI: 0.7;1.9 p=0.634) (Figure).

Conclusions: We demonstrated an association between serum suPAR levels, a biomarker of systemic inflammation, , and CAN and DSPN in T1D. The most pronounced association was seen for CAN, suggesting that suPAR may play a more significant role in pathogenesis leading to small fibre neuropathy as e.g. CAN, than to large fibre neuropathy as e.g. DSPN assessed by VBT.

Figure



Odds ratios (95% confidence intervals) of logistic regression analyses of associations between serum suPAR. Odds ratios are presented as a doubling of suPAR: model 1 adjusted for age, sex and high-sensitive C-reactive protein, model 2 further adjusted for diabetes duration, HbA1c, BMI, smoking, systolic blood pressure, serum LDL cholesterol and beta blocker use (only for CAN), model 3 additionally adjusted for eGFR. * = p < 0.001, ** = p<0.01.

OR.33 | CHANGES IN DIASTOLE DURATION DURING FIVE MINUTES OF DEEP BREATHING IN OVERWEIGHT OR DIABETIC PATIENTS WITH OBSTRUCTIVE SLEEP APNOEA SYNDROME

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Objectives: Patients with obstructive sleep apnoea syndrome (OSAS) exhibit an increased sympathetic activity which elevates heart rate (HR) and blood pressure. In healthy individuals the relative duration of diastole (%DD=DD/cardiac cycle duration) decreases when HR increases, which is critically important since the greatest proportion of coronary blood flow occurs in diastole. Some studies suggest that deep breathing (DB) may reduce blood pressure in hypertensive patients. This study aimed to assess the effects of DB on DD and its adaptation to HR in overweight patients with OSAS.

Methods: We included 90 overweight patients with or without type 2 diabetes, with OSAS (mild/moderate/severe according to nocturnal polygraphy: 26/13/51 patients). The patients performed DB (6 cycles/min) during 5 minutes. Using Nox-T3 polygrapher (Resmed®), respiration was monitored (thoracic and abdominal bands), HR and DD were measured continuously using the photoplethysmographic signals and analysed when breathing-in and breathing-out.

Results: During the first minute (min-1), HR was higher when breathing-in than when breathing-out (108 vs 103 bpm in means) and the difference disappeared during the 5th minute (min-5) (105 and 105 bpm) ; as a result the ratio of HR when breathing-in/ breathing-out decreased (from 1.04 to 1.01 in means). DD when breathing-in was shorter than when breathing-out and increased significantly from min-1 to min-5 (221 to 255 ms), but not DD when breathing-out (252 to 249 ms). %DD was low and increased slightly from min-1 to min-5 (41% to 44%), while the ratio of %DD when breathing-in/ breathing-out increased markedly (from 0.87 to 1.06), more in patients with moderate/severe than with mild OSAS (p<0.0001). During min-1, %DD when breathing-in and when breathing-out did not correlate with concomitant HR; the correlation became significant during min-5 (r=-0.371, p<0.001 and r=-0.206, p<0.05, respectively). During min-1, the ratio of %DD when breathing-in/breathing-out did not correlate significantly with concomitant HR changes; during min-5, the correlation became significant (r=-0.431, p<0.0001), and the changes in absolute DD values correlated more strongly with concomitant HR changes (r=-0.774, p<0.0001 vs r=-0.288 at min-1).

Conclusions: In overweight/diabetic patients with OSAS, HR variations are depressed (suggestive of low vagal activity) and %DD is low. Five minutes

of DB is able to lengthen the relative diastole duration, particularly when breathing-in, and to restore an adaptation of DD to HR. This improvement is likely to result from a reduction of sympathetic activity and to have implications for left ventricle filling and coronary perfusion.

OR.34 | NO CERTAIN ASSOCIATION BETWEEN AUTONOMIC NERVE DYSFUNCTION AND THE INCRETIN EFFECT

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Objectives: The incretin effect (i.e. the potentiation of glucose-stimulated insulin secretion exerted by the gut-derived incretin hormones released after nutrient ingestion) is reduced in type 2 diabetes, and has been shown to deteriorate with longer diabetes duration and worsening of glycaemic control. As the incretin effect in part may be mediated by vagal transmission, we investigated the association between diabetic autonomic neuropathy and the incretin effect.
Methods: We subjected individuals with longstanding type 2 diabetes (n=20), individuals with recent onset diabetes (n=15) and healthy controls matched for age, sex and body mass index to an oral glucose tolerance test and an intravenous isoglycaemic glucose infusion to calculate gastrointestinal-mediated glucose disposal (GIGD) and the incretin effect. Established neuropathy tests included cardiovascular reflex and heart rate variability, tests for sudomotor function, sural nerve conduction velocity and amplitude, and the monofilament test. We also performed rapid rectal balloon distention measuring evoked potential following earliest sensation and unpleasant threshold, as a proxy for gut visceral afferent nerve function.
Results: We detected no between-group differences regarding established neuropathy tests, but found significantly different values for glucose, HbA1c, GIGD and incretin effect, see table 1. The pressure needed to reach earliest sensation performing rapid rectal balloon distention was significantly higher in the groups with longstanding diabetes (3.7+1.1) and in early diabetes (4.0+1.3) compared to the control group (3.0+0.9), p=0.005. Rectal hyposensitivity for earliest sensation was weakly associated with GIGD (rho -0.341, p=0.005), but not with the incretin effect (rho=-0.204, p=0.106). Combining all groups, GIGD (mean+SD) was borderline significantly higher for people with rectal pressure for earliest sensation <3.0 kPa (47+25%), compared to >3.0 kPa (34+24%), p=0.051. This was not found for the incretin effect (36+24% and 29+25%, p=0.286). We found no other significant associations between GIGD or incretin effect and other neuropathy tests.
Conclusions: In the present cohort, no association between diabetic autonomic neuropathy and the reduced incretin effect was observed, but visceral sensitivity was associated with GIGD alluding to a potential link between autonomic neuropathy and gut-derived mechanisms governing glucose tolerance.

	Longstanding diabetes (n=20)	Early diabetes (n=15)	Controls (n=30)	p-value
Neuropathy:				
Cardiovascular autonomic neuropathy: No/borderline/definite, %	69/31/0	77/15/8	83/13/4	0.540
Peripheral neuropathy, sural nerve conduction: No/mild/moderate/serious, %	76/10/10/0	80/13/7/0	87/0/7/3	0.680
Peripheral neuropathy, monofilament: Unlikely/possibly/likely, %	71/24/5	87/13/0	90/0/10	0.060
Sudomotor function (hands-feet): Normal/moderately reduced /severely reduced, %	70/25/5-71/19/10	67/33/0-80/20/0	77/20/3 - 87/7/7	0.810-0.450
Glucose variables				
Fasting glucose OGTT, mmol/l	9.4±2.1	7.2±1.0	6.0±0.6	<0.001
2-hour glucose OGTT, mmol/l	18.7±3.9	13.1±4.2	7.9±1.5	<0.001
HbA1c, mmol/mol	53.5±11.2	43.3±4.9	37.1±3.0	<0.001
Gastrointestinal glucose disposal, %	17±22	36±15	59±14	<0.001
Incretin effect, %	12±22*	30±20*	48±17	<0.001

Table 1: Between-group differences for neuropathy tests, glucose variables, gastrointestinal-mediated glucose disposal and incretin effect. P-values for categorical data from chi-square, for continuous data from one-way ANOVA. Post hoc test for continuous data using Bonferroni test with *=significant only compared to controls, all others significant for each group compared to another.

OR.35 | DIETARY REVERSAL AND/OR EXERCISE CORRECT PERIPHERAL NEUROPATHY IN A MOUSE MODEL OF DIET-INDUCED OBESITY

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Objectives: Rate of obesity, prediabetes, and type 2 diabetes are on the rise. Increasing similarly are rates of diabetic complications, such as peripheral neuropathy (PN). PN is estimated to affect ~30% of patients with prediabetes and 60% of patients with type 2 diabetes. Currently, there are no effective treatments for PN, aside from tight glucose control. However, tight glucose control has little impact on PN in patients with prediabetes and type 2 diabetes. Rather, the new clinical guidelines for treating PN recommend diet and exercise. However, guidelines for the optimal regimen are lacking, as are studies to determine if one intervention generates superior PN outcomes. Therefore, the aim of the current study was to compare diet and exercise as interventions to treat PN, alone or combined in the high fat diet (HFD)-fed mouse model of obesity, prediabetes, and PN.
Methods: To this end, our study consisted of 5 animal groups: 1) control mice on standard diet (SD), 2) HFD mice, 3) HFD mice placed on a dietary reversal (DR) paradigm at 18 wk, 4) HFD mice maintained on HFD but provided access to a running wheel (EX) at 18 wk (HFD-EX), and 5) HFD mice placed on both a DR and EX paradigms at 18 wk (DR-EX). At 26 wk, terminal metabolic and neuropathy phenotyping were performed.
Results: HFD mice developed metabolic abnormalities, with significant increases in body weight 2 weeks after HFD, which persisted until study end. They also displayed impaired glucose tolerance at 26 wk. HFD mice developed PN at 26 wk, with thermal and mechanical hypoalgesia and slowed sensory and motor nerve conduction velocities (NCVs). DR and DR-EX attenuated the metabolic abnormalities, with improved body weight and glycemic control. However, EX alone did not impact these parameters. DR and DR-EX improved PN measures to a similar degree. Despite an abnormal metabolic profile, EX in HFD animals restored thermal and mechanical sensation, significantly increased sensory NCVs and improved motor NCVs (56±2.38 m/s) relative to HFD (45.96±1.42 m/s) mice but did not normalize (60.04±1.28 m/s) them completely.
Conclusion: Overall, these data suggest DR and particularly EX have beneficial effects beyond improving systemic metabolic profiles, that may be directly related to the nerve microenvironment and neurometabolic coupling.

OR.36 | IMEGLIMIN, A NEW ORAL HYPOGLYCEMIC AGENT, IMPROVES HYPERGLYCEMIA AND HYPOGLYCEMIA-INDUCED CELL DEATH AND MITOCHONDRIAL DYSFUNCTION IN SCHWANN CELLS

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Objectives: Hyperglycemia-induced oxidative stress is a major cause of the pathogenesis of diabetic neuropathy, and hyperglycemia-induced mitochondrial reactive oxygen species (ROS) production is considered as one important mechanism of increased oxidative stress. On the other hand, imeglimin is a new class of oral hypoglycemic agents called "glymines" containing tetrahydrotriazines, which targets mitochondrial dysfunction. We investigated the effects of imeglimin on cell death and mitochondrial dysfunction induced by high glucose and low glucose in Schwann cells.
Methods: 1) Immortalized adult mouse Schwann (IMS32) cells were cultured for 1 h in the medium with normal glucose of 5.5 mM (NG), low glucose of 2.5 mM (LG), and high glucose of 25 mM (HG). 2) Cells were pretreated with 100μM imeglimin for 24h. 3) Cell viability was evaluated by MTT assay. 4) Oxidative stress was measured by TBARS assay. 5) Mitochondrial oxidative stress was measured using MitoSOX. 6) Mitochondrial membrane potential was evaluated using JC-10. 7) The oxygen consumption rate (OCR) was analyzed using MitoXpress Xtra. 8) The activity of complex I was assessed by Colorimetric assay. 9) NAD+ were determined using the bioluminescent assay.
Results: Compared to NG, not only HG, but also LG decreased cell viability of IMS32 cells and increased mitochondrial oxidative stress. Mitochondrial membrane potential was also decreased by either HG or LG. In addition, OCR was increased by LG as well as HG. Mitochondria isolated from IMS32 cells exposed to HG and LG exhibited increased activity of complex I. Imeglimin ameliorated the decrease in cell viability and improved the mitochondrial dysfunctions via inhibiting the increase of mitochondrial oxidative stress, OCR and the activity of complex I caused by HG and LG. Imeglimin also increased NAD+ in HG and LG.
Conclusions: These findings suggest that hyperglycemia and hypoglycemia induce mitochondrial dysfunction in nerves, and that imeglimin may prevent against diabetic neuropathy by ameliorating mitochondrial dysfunction and cell death in Schwann cells.

OR.37 | IMPROVEMENT OF CARDIOVASCULAR AUTONOMIC FUNCTION IN PATIENTS WITH METABOLIC SYNDROME WITH AND WITHOUT DIABETES AFTER A PHYSICAL TRAINING PROGRAM

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Introduction: Vascular complications and neuropathy may develop in the presence of metabolic syndrome. The aim of our study was to measure the cardiovascular autonomic function following physical training in patients with metabolic syndrome with and without diabetes.
Subjects and Methods: 56 patients with metabolic syndrome (32 men/24 women, 40 non-diabetic patients (NDMetS)/ 16 diabetic patients (DMetS) [mean ± SD]: age: 50.35±8.03 vs. 56.8±9.30 years, p=0.023; baseline BMI: 32.2±7.03 vs. 32.8±5.94 kg/m2, p=0.739) were involved in our study. All tests and measurements were carried out before and following a 3-month physical training period. Autonomic function was assessed by means of five standard cardiovascular reflex tests. ECG repolarization parameters, including short-term QT variability and stress-ECG were also measured.
Results: In the whole population, Valsalva-ratio (VR) and the autonomic score (AS) improved following training (VR: 1.49±0.24 vs. 1.64±0.34, p=0.001; AS: 2.05±1.73 vs. 1.41±1.36, p=0.015) accompanied by the significant decrease of the systolic (150.3±16.12 vs. 134.1±16.67 mmHg, p<0.001) and diastolic (90.64±12.8 vs. 82.79±11.1 mmHg, p<0.001) blood pressure. An improvement in VR was detected in NDMetS patients following training (1.51±0.24 vs. 1.67±0.31, p= 0.002). No significant changes could be detected in autonomic tests' results in the DMetS patient group following training. The applied exercise training program did not lead to significant changes in ECG repolarization. The stress-ECG test in the whole study population yielded a significant increase in the test duration (12.9±3.76 vs. 15.1±2.96 min, p<0.001) and in the test load (10.5±2.78 vs. 11.6±2.39 MET, p<0.001). The load capability improved significantly in both subgroups: 11.1±2.04 vs. 12.1±1.82, (p<0.001) and 9.0±3.64 vs. 10.4±3.05, (p=0.033) in subpopulations of NDMetS and DMetS, respectively. The DMetS patients achieved a significantly lower MET score at baseline (p=0.039) and following training (p=0.044) in comparison to the NDMetS patients.
Conclusions: The three-month exercise program improved the Valsalva-ratio and the AN score in the MetS patients, which is potentially protective against cardiovascular events. The training had some beneficial effect on blood pressure and the results of the stress-ECG tests in both groups. The absence of the significant change in the reflex tests in the DMetS group reflects an impaired adaptation compared to the NDMestS group.

OR.38 | THE IMPACT OF OBSTRUCTIVE SLEEP APNOEA TREATMENT ON PERIPHERAL NEUROPATHY IN PATIENTS WITH TYPE 2 DIABETES: RESULTS FROM A 2-YEAR FEASIBILITY RCT

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Background: Obstructive Sleep Apnoea (OSA) is associated with an increased risk of Peripheral Neuropathy in patients with T2D (DPN). Hence, continuous positive airway pressure (CPAP) might be beneficial in reducing the burden of DPN in T2D.
Method: We conducted an open-label multicentre (13 centres) feasibility randomised control trial (RCT) of patients with T2D and OSA, where they were randomised to CPAP vs no CPAP over 2 years. The primary outcomes of this trial were related to feasibility. In this abstract, we report a secondary outcome of the trial, the impact of CPAP on DPN. Participants with resting Oxygen saturation <90%, central apnoea index >15/hrs or Epworth Sleepiness Score (ESS) >= 11 were excluded. DPN was assessed

using The Michigan Neuropathy Screening Instrument (MNSI) (MNSIe>2 or MNSIq>=7), Neuropad, Vibration perception threshold (VPT>25V), and 10g monofilament. The follow-up procedures were amended due to the COVID-19 pandemic.

Results: Eighty-three patients were randomised to CPAP vs no CPAP (43 vs 40) with a median [IQR] follow-up of 645 [545,861] days. The study population mean (SD) age was 62.5 (10.9) years, BMI was 35.4 (7.2), and diabetes duration was 12.2(7.9) years. 89.1 % (n=74) were white European ethnicity, 28.9% (n=24) were women, and 48.2% (n=40) were prescribed insulin. The prevalence of DPN at baseline was 52.6% (n=41) based on MNSI. Only 26/43 patients used CPAP, with a median (IQR) usage of 3:40 (hours: minutes) [0:06, 4:45] per night. The intention-to-treat analysis is summarised in Table 1. At the study end, being randomised to CPAP was associated with a possible favourable impact on DPN compared to no CPAP based on MNSI, the Neuropad, VPT and 10g monofilament.

Conclusion: CPAP might have a favourable impact on DPN in patients with T2D. However, this requires a to be tested in the fully dedicated RCT.

Table 1: Summary of the effects of CPAP and no CPAP on DPN assessments

	Baseline		Follow-up		Adjusted relative risk[1] (95% CI)	Unadjusted relative risk[2] (95% CI)
	CPAP N (%)	No CPAP N (%)	CPAP N (%)	No CPAP N (%)		
MNSI questionnaire						
Abnormal	5 (12.5%)	12 (27.9%)	0 (-)	7 (26.9%)	0.78 (0.4, 1.6)	0.73 (0.4, 1.4)
Missing	0	0	6	9		
MNSI examination						
Abnormal	18 (47.4%)	20 (50.0%)	7 (36.8%)	7 (50.0%)	0.83 (0.3, 2.7)	0.79 (0.4, 1.5)
Missing	2	3	5	21		
MNSI overall score						
Abnormal	19 (50.0%)	22 (55.0%)	7 (41.2%)	12 (80.0%)	0.51 (0.1, 2.3)	0.34 (0.1, 1.1)
Missing	2	3	7	20		
Neuropod/ Both feet[3]						
Incomplete/ abnormal	24 (63.2%)	31 (73.8%)	12 (57.1%)	11 (68.8%)	0.87 (0.3, 2.3)	0.83 (0.5, 1.4)
Missing	2	1	2	17		
Vibration perception/ Average both feet[4]						
Abnormal (>25V)	8 (33.3%)	17 (60.7%)	4 (36.4%)	3 (60.0%)	0.64 (0.04, 9.2)	0.61 (0.2, 1.9)
Missing	16	15	12	28		
10-gram Monofilament/ Both feet[5]						
Abnormal	15 (38.5%)	22 (52.4%)	6 (28.6%)	15 (88.2%)	0.49 (0.1, 1.5)	0.32 (0.2, 0.6)
Missing	1	1	2	16		

[1]Adjusted for ethnicity, gender, OSA severity, age, and baseline value. A relative risk <1 favours CPAP. Analysis
[2]A relative risk <1 favours CPAP. Only participants with both baseline and follow-up values are included in the analysis.

POSTER SESSIONS

P.01 | PREDICTORS OF DIABETIC PERIPHERAL NEUROPATHY: SYSTEMATIC REVIEW AND META-ANALYSIS

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Objectives: To identify significant predictors of Diabetic Peripheral Neuropathy (DPN).
Methods: The electronic databases PubMed and Embase were searched for longitudinal studies where the outcome was the development of DPN. Eligible studies were longitudinal, included participants with a clinical diagnosis of Diabetes Mellitus and explored the association of pre-defined characteristics with the development of DPN. The comparator population was individuals with diabetes who did not develop DPN. Articles which met these inclusion criteria were screened for risk of bias using the STrengthening the Reporting of OBservational studies in Epidemiology (STROBE) checklist, and only studies with a score of 15 and above were included.
Potential predictors were extracted from these studies and weighted mean differences (continuous variables) and odds ratios (dichotomous variables) of potential predictors between incident DPN and non-DPN groups were compared. A narrative synthesis was included to add insight to the conclusions of the meta-analysis.
Results: A total of 22 studies examining 19 predictors were included. The sample size ranged from 59 to 37375 (median: 344) and follow-up time ranged from 18 to 228 months. Extracted predictors included sociodemographic characteristics (age, gender, smoking status), anthropometric measurements (body mass index, waist circumference), comorbidities (cardiovascular disease, hypertension, retinopathy), diabetes-related parameters (diabetes duration, diabetes type) and clinical parameters (diastolic and systolic blood pressure, estimated glomerular filtration rate, fasting blood glucose, lipids and glycated haemoglobin)
The following predictors were significant in the meta-analyses.

Variable	Weighted Mean Difference (WMD) or Risk Ratio (RR), 95% Confidence Interval	Number of studies	Number of participants	I^2 statistic, p-value
Age (years)	WMD: 3.93 (2.44, 5.41)	13	42907	92.8%, 0.00
Sex (male as reference)	RR: 0.91 (0.88, 0.94)	14	60364	78.1%, 0.00
Diabetes Duration (years)	WMD: 1.92 (1.11, 2.73)	12	41300	82.6%, 0.00
Waist Circumference	WMD: 2.04 (0.58, 3.49)	5	2903	76.8%, 0.002
eGFR (mL/min/1.73m2)	WMD: -8.36 (-12.69, -4.04)	3	944	0.0%, 0.748
HbA1c (%)	WMD: 0.51 (0.25, 0.76)	13	5676	90.4%, 0.00
Fasting Plasma Glucose	WMD: 0.63 (0.50, 0.76)	6	4373	82.7%, 0.00

Discussion: Pooling the studies was challenging, due to the varying definitions of DPN and assessment tools, as well as the different effect measures used in individual studies. Sample

Discussion: Pooling the studies was challenging, due to the varying definitions of DPN and assessment tools, as well as the different effect measures used in individual studies. Sample size was smaller for some of the pooled variables, decreasing the certainty of the final conclusions. Despite these limitations, strong predictive effects were exhibited by age, sex, diabetes duration, waist circumference, eGFR and HbA1c, underlining their important role in the development of DPN.

P.02 | A HEAVY BURDEN OF AMPUTATION CAUSED BY DIABETIC NEUROPATHY FOR THE HEALTH CARE SYSTEM OF GEORGIA

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The aim: of the research was to study epidemiological data of the cases of diabetic neuropathy and as a result of foot amputation and the risk factors of this complication in Georgian patients with type1 and type 2 diabetes.
Methods: The research was based on data collected from questionnaire information, which was taken from patients with leg amputation as a result of diabetic neuropathy and National Center for Disease Control and Public Health (NCDC).
Results: There were 102874 patients in 2021 in Georgia registered diagnosed with diabetes. 0,59% (617pts) of them were diagnosed with diabetic neuropathy and 5,1% (32pts) of those were leg amputated. In cases of type 1 diabetes (14678pts) 0,88% (129pts) were with neuropathy and 5,4% (7pt) of them were amputated. The most frequent cases were in the age group of 60-64years, and all these cases were in women. Indicating type 2 diabetes, 488 had neuropathy, 5,1% (25 pts) of them had a leg amputation, 14 men and 11 women. Most of the interviewed patients were smokers (OR)= 4.9 95%CI (1.8-13.1), and 50-54 and 64-69 years old urban population.
Patients which were insurance beneficiaries were at less risk of developing neuropathy and as a result the risk of amputation was also low (OR)=9.9 95%CI (2.3-42.6),. Diabetic patients with neuropathy were more vulnerable to geographic, economic and psychological barriers. The number of amputations increased significantly in 2018-2019, which to some extent could be related to the social isolation of Covid-19 and the reduction of governmental (state) programs.
Conclusion: there is a very high risk of diabetic neuropathy complication in Georgia as in type 1 also in type 2 diabetes, which is a result of absence of type 2 diabetes registry, the existence of various barriers, very low level of awareness of the population about the complications of diabetes, the lack of access to screening programs and lack of availability of diagnostic variability of insurance packages.

P.03 | INVESTIGATING THE ASSOCIATION BETWEEN NEUROPATHY AND CARDIOVASCULAR DISEASE IN PATIENTS WITH DIABETES

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Objective: Diabetes mellitus (DM) is associated with a two-fold higher risk of cardiovascular disease (CVD), and results in an approximately seven-year reduction in life expectancy when compared to patients without DM. Peripheral and autonomic neuropathy are independent risk factors for CVD. We sought to establish the association between different measures of neuropathy and the CVD.
Methods: 114 patients with DM with no history of cardiovascular disease (No CVD) and 195 patients with DM and a history of CVD were recruited and underwent assessments of HbA1c, lipid profile, neuropathy symptom profile (NSP), neuropathy disability score (NDS), cardiac autonomic function testing, cold (CPT) and warm perception threshold (WPT), cold (CIP) and warm induced pain (WIP), intraepidermal nerve fibre density (IENFD), sural latency, sural amplitude, sural velocity, vibration perception threshold (VPT) and corneal confocal microscopy (CCM) to quantify corneal nerve fibre density (CNFD), branch density (CNBD) and fibre length (CNFL).
Results: Age(years) (48.52±15.32 vs 62.72±10.36, P=<.001) was higher, but there was no difference in duration of diabetes(years) (17.13±15.43 vs 19.75±16.31, P=0.1) and HbA1C (8.07±1.59 vs 7.84±1.34 P=.253) between No CVD vs CVD group. The percentage of patients taking statin in the groups 51.8% of patients in No CVD were taking a statin compared to 89.2% in the CVD group.
BMI(kg/m2) (28.01±5.31 vs 30.87±5.37, P=<.001) was higher, cholesterol(mmol/l) (4.33±0.92 vs 4.08±0.86, P=.024) and HDL(mmol/l) (1.44±0.45 vs 1.28±0.50, P=.008) were lower, triglycerides(mmol/l) (1.57±1.19 vs

1.88±1.11, P=.024) were higher and LDL(mmol/l) (2.17±0.82 vs 1.97±0.70, P=.026) was lower in no CVD vs CVD groups.
NSP(/38) (3.71±0.70 vs 6.00±0.50, P=.015), NDS(/10) (3.11±0.29 vs 3.89±0.21, P=.039) and WIP(Co) (46.52±0.28 vs 47.98±0.20, P=<.001) were higher, sural latency(m/s) (3.16±0.07 vs 3.41±0.06, P=.010), sural amplitude(uV) (10.76±0.69 vs 8.43±0.51, P=.010) and Valsalva Ratio(1.22±0.02 vs 1.15±0.02, P=.024) were significantly lower in No CVD vs CVD. There was no significant difference in CNFD(no./mm2) (24.22±0.84 vs 24.55±0.63, P=.76), CNBD (no./mm2) (55.27±3.83 vs 57.20±2.84, P=.70), CNFL(mm/mm2) (20.34±0.76 vs 20.28±0.56, P=.95) IENFD (5.64±0.68 vs 6.04±0.61, P=.686) in No CVD vs CVD.
In the CVD group, there were significant negative correlations between NDS and DB-HRV (r=-.319, P=.001) and Valsalva ratio (r=-.285, P=.047) and there was a significant positive correlation between LFA:RFA and HDL (r=.378, P=.013). There were no significant correlations between cardiac autonomic function testing and CCM parameters.
Conclusion: There were significant differences in neuropathy symptoms, disability and nerve conduction studies and autonomic function but no difference in small fibre abnormalities between diabetic patients with and without CVD.

P.04 | THE DIFFERENCE IN DIABETIC PERIPHERAL NEUROPATHY PREVALENCE IN TWO DISTINCT EDITIONS OF THE EUROPEAN FUTSAL CHAMPIONSHIP FOR PEOPLE WITH DIABETES

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Introduction: The importance of physical activity (PA) in diabetes (DM) management was recognized from ancient times, being an important therapeutic tool in the preinsulin era. The extensive use of continuous glucose monitoring systems (CGMS) and insulin pumps allowed more people with diabetes (PWD) to take part in competitive sports.
Objective: To compare the prevalence of diabetic peripheral neuropathy (DPN) among futsal players participating in the 2015 vs. 2017 edition of the European Futsal Championship for PWD (DiaEuro).
Methods: In this study, we included 139 amateur/professional futsal players (from 15 European and Central Asia countries) for the 2015 DiaEuro edition and 94 (from 9 European countries) for the 2017 edition. The evaluation was made based on the data extracted from the standard medical certificate completed by each player's diabetologist. The official participation criteria were: age ≥ 18 years old, a diagnosis of diabetes and no other severe comorbidities that could contraindicate this type of sport.
Results: Regarding type of DM, the percentages between 2015 and 2017 editions were: 92.8 vs. 95.74% for type 1 DM and 6.47 vs. 3.19% for type 2 DM. One subject from 2015 and respectively 2017 had latent autoimmune diabetes of adulthood and type 3c diabetes secondary to chronic pancreatitis. The differences in treatment regimen were among oral antidiabetics - 5.75% (2015) vs. 3.19% (2017) and insulin pump – 22.31% (2015) vs. 12.7% (2017). One player from 2015 and respectively 2017 was on mixed insulin and diet therapy. Comparing 2015 and 2017 editions in terms of microvascular complications, the following results were obtained: 9.35 vs. 2.12% for DPN, 8.75 vs. 3.19% for diabetic retinopathy and 4.31 vs. 6.38% for diabetic nephropathy.
Conclusions: This analysis revealed a more than 4 times lower prevalence of DPN in the 2017 vs. 2015 edition of the DiaEuro championship.

Parameter	Interval (min-max)		Mean		STDEV	
	2015	2017	2015	2017	2015	2017
Age (years)	18 - 52	18 - 55	26.69	27.74	±7.54	±8.23
Diabetes duration (years)	1 - 34*	1 - 39?	11.16	12.21	±7.25	±7.34
Last A_{1c} (%)	5.1 – 10.8**	5.3 – 10.5?	7.48	7.31	±1.07	±0.99

Table: The general characteristics of the study population; *Data were available for 138 subjects; **Data were available for 122 subjects; ?Data were available for 91 subjects; STDEV=standard deviation; A1c= glycated hemoglobin

P.05 | LONGITUDINAL CHANGES IN CORNEAL SMALL NERVE FIBRE MORPHOLOGY IN PARKINSON'S DISEASE: A CORNEAL CONFOCAL MICROSCOPY STUDY

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Objectives: Parkinson's disease (PD) is a central neurodegenerative condition affecting 2-3% of people over the age of 65 worldwide. Despite the large disease burden, PD diagnosis remains largely clinical. Corneal confocal microscopy (CCM) is a rapid non-invasive technique used in the assessment of corneal nerve changes in both peripheral and central neurodegenerative conditions. This longitudinal study assesses the utility of CCM in the identifying progressive neurodegeneration in patients with PD.
Methods: Fifty-one participants with PD and 21 healthy controls were enrolled. All patients underwent CCM, assessment of Movement Disorder Society Unified Parkinson's Disease Rating Scale, and Montreal Cognitive Assessment at baseline and 12 months follow up. CCM parameters were manually quantified and included corneal nerve fibre density (no/mm2) (CNFD), branch density (no./mm2) (CNBD), fibre length (mm/mm2) (CNFL), and inferior whorl length (mm/mm2) (IWL).
Results: CNFD (27.26± 5.77 vs. 34.69 ± 8.03, P<0.001), CNBD (52.56±28.82 vs. 83.05 ± 28.88, P<0.001), CNFL (17.66 ±4.83 vs. 25.20 ±6.09, P<0.001) and IWL (21.74±8.88 vs. 31.44±11.05, P<0.001) were significantly lower in patients with PD compared to controls at baseline. There was no significant change in motor or cognitive function except for the full MDS UPDRS score (P=0.002) over 12 months. There was no change in CNFD (27.26± 5.77 vs 27.58± 5.15, P=0.8), CNBD (52.56±28.82 vs 56.73±28.38, P=0.3), CNFL (17.66 ±4.83 vs 18.17±4.07, P=0.5) and IWL (21.74±8.88 vs 23.44±9.43, P=0.5) between baseline and follow up.
Conclusions: This study confirms previous findings of central corneal nerve loss in patients with PD and now also demonstrates more distal corneal nerve loss in the inferior whorl region. There was no significant progression of motor disability or cognitive function as well as corneal nerve loss over a period of 12 months in PD patients. This may be attributable to the slow progression of disease and underlying neurodegeneration in PD. Longer follow up studies are required to evaluate the potential of CCM as a marker to detect disease progression in PD.

P.06 | CHARACTERISING COGNITIVE DEFICITS AND TRANSCRIPTOMIC CHANGES IN THE HIPPOCAMPUS OF MALE WISTAR RATS WITH PREDIABETES

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Objectives: There is increasing evidence that diabetes mellitus (DM) and prediabetes increases the risk of developing cognitive deficits, both clinically and in preclinical rodent models. We have previously characterised diabetes-specific long-term recognition memory impairment and hippocampal changes in a streptozotocin-induced model of type 1 DM in rats. Here, we compare cognitive performance of rats with prediabetes with age-matched controls and characterise the impact of prediabetes on the hippocampal transcriptome.
Methods: Adult male Wistar rats were fed either standard chow diet (control group; 10% fat; n=12) or high-fat diet (HFD group; 45% fat; n=14) for

17 weeks. During week 16, behavioural testing for anxiety-type behaviours (elevated maze, and open field) and recognition memory (novel object recognition (NOR) with 1 hour inter-trial interval) was conducted. A glucose tolerance test and body composition analysis (Echo MRI) and sensory testing were performed prior to end of trial, with nerve conduction velocity measurement and tissue harvest in week 17. Bilateral hippocampi were dissected and prepared for RNA sequencing (Illumina NovaSeq6000), biochemical, or immunocytochemical analysis. Differentially expressed genes (DEGs) between control and HFD groups were identified using DESeq2 for subsequent bioinformatics analysis.
Results: Rats fed with HFD for 16 weeks developed significant obesity, impaired glucose handling, and hyperinsulinemia, but not hyperglycaemia or indices of peripheral neuropathy. However, the HFD rats displayed cognitive deficits compared to the control group fed with standard chow, with a significantly low discrimination index (DI) of the NOR test for HDF group compared to control group. Following the inter-trial-interval, control rats showed a significant preference to explore the novel object ($p<0.001$), while the rats from the HFD group showed no evidence of recognising the familiar, exploring both familiar and novel objects equally during the retention phase ($p>0.05$). RNA-seq analysis identified 1011 DEGs in the hippocampus (313 upregulated and 698 downregulated). Enrichment analysis using Ingenuity Pathway analysis (IPA) revealed significant over-represented canonical pathways related to EIF2 signalling, mitochondrial dysfunction, and synaptogenesis signalling pathways for characterisation.
Conclusions: The analysis of this hippocampal transcriptomic dataset provides further insight into the pathogenesis of cognitive dysfunction in prediabetes, and comparison with existing datasets in models of DM enables the development of further mechanistic and therapeutic studies to treat or reduced the impact of cognitive impairment.

P.07 | ACTIVATION AND REPROGRAMMING OF HUMAN MULLER CELL LINE MIO-M1 EXPOSED TO HIGH GLUCOSE AND GLUCOSE VARIABILITY: AN IN VITRO STUDY

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Objectives: In diabetic subjects, retinal neurodegeneration is associated with reactive gliosis which involves the activation of Muller cells (MCs), mainly characterized by increased expression of glial fibrillary acidic protein (GFAP). Recently, in lower vertebrates, it has been reported that, following reactive gliosis, MCs acquire characteristics of retinal stem cells and that Sonic Hedgehog (SHH) is a crucial regulator of this de-differentiation process. Although diabetic condition causes reactive gliosis in the retina, the effect of glycemic fluctuations on activation and reprogramming of human MCs is yet unknown. The aim of the study is to assess the activation and reprogramming of the human Muller cell line MIO-M1 exposed to high glucose (HG) and glucose variability (GV).
Methods: Human Muller cell line MIO-M1 was cultured in a medium containing either 5 mM (N cells) or 25 mM of glucose (H cells) and then incubated for 96 h in a medium with: basal glucose (5 or 25 mM), high glucose (25 or 45 mM), basal glucose and high glucose alternated every 24 hours (5/25 or 25/45 mM), basal glucose and single exposure to high glucose in the last 24h (5/s25 or 25/s45 mM), low glucose and high glucose alternated every 24 hours (3/25 or 5/45 mM). MCs activation and reprogramming was studied through the expression of GFAP and SHH respectively, evaluated by western blot analysis. In addition, a morphological analysis of MCs was performed by using GFAP and SHH immunolabelling on micrographs obtained with a fluorescence microscope.
Results: In N cells cultured with normal glucose (5mM), a significant upregulation of GFAP expression was observed in response to HG and GV conditions (p value = 0.0472 and p value = 0.0303 respectively). Moreover, this increase was associated with morphological changes and a higher number of hypertrophic cells (p value < 0.001). In H cells cultured with high glucose (25mM), there was no modulation of GFAP expression in response to either treatments. In N cells, an upregulation of SHH was also observed in response to HG and GV treatments, with a peculiar localization of the protein in multiple spots inside the cytoplasm. On the contrary, H cells showed a reduced expression of SHH in response to the treatments without morphological changes of intracellular SHH localization.
Conclusions: Our results highlight activation and reprogramming features of human Muller cell line MIO-M1 cultured in normal glucose and exposed to HG and GV conditions.

P.08 | THE IMPACT OF PCSK9 INHIBITION ON THE DEVELOPMENT OF PERIPHERAL NEUROPATHY

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Neuropathy is the most common chronic complication of diabetes. Diabetes and its associated metabolic syndrome can damage peripheral nerves in various ways, causing nerve dysfunction and loss. Dyslipidemia is recognized as an important risk factor for neuropathy and may play a direct and critical role in the development and progression of this pathology. Proprotein convertase subtilisin-kexin 9 (PCSK9) is a key regulator of lipid metabolism. It enhances the degradation of cell surface low-density lipoprotein family receptors and regulates extracellular and intracellular lipid homeostasis. Using in situ hybridization and immunohistochemistry analysis, we have been able to show PCSK9 mRNA and protein expression in schwann cells (SC) of mouse sciatic nerves along with the expression of the different PCSK9 target receptors (LDLR, VLDLR, APOER2, LRP1, and CD36). In a mouse model lacking PCSK9 (PCSK9 KO), we observed prominent neuropathic symptoms characterized by a significant loss of pain sensation with sensory tests (Von Frey and Pinprick test), a decrease in sensory nerve conduction velocity (SNCV), and signs of small nerve axonal swelling with electron miscopy (EM) analysis. A significant increase in lipid content was also observed in the nerves of PCSK9 KO mice compared to WT nerves. In parallel, using a double PCSK9/LDLR knockout (DKO) mice model (invalidated for both PCSK9 and LDLR), we investigated whether the consequences of PCSK9 loss on the reported neuropathic phenotype rely on its known target, the low-density lipoprotein receptor (LDLR). We observe a restoration of the normal phenotype in DKO mice with the different sensory tests performed as well as a normal nerve lipid content. In conclusion, this study suggests a role for PCSK9 and its target receptor LDLR in regulating nerve lipid levels and neuronal function. Future studies will focus on the analysis of lipoprotein receptors expression in control vs. PCSK9 KO and schwann cell conditional PCSK9 KO mice (PLP-CreERT2+; PCSK9 flox/flox).

P.09 | PERICYTE-ASTROCYTE CROSSTALK MEDIATING ALTERED MICROVASCULAR BLOOD FLOW IN DIABETIC NEUROPATHIC PAIN

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Objective: Neuropathic pain is a complication of diabetes experienced by 50% of patients, reducing quality of life significantly. Vascular degeneration is a key factor in the development of many neurological diseases. Accumulating evidence implies altered blood brain barrier (BBB) integrity is a risk factor in the onset of neurodegenerative disease. More recently, investigations exploring the spinal cord (SC) microvasculature have suggested reduced blood perfusion greatly influences pain perception. Pericytes, part of the BBB abluminally positioned on small capillaries, demon-

strate contractile abilities to modulate blood perfusion of nervous tissues. Our preliminary work supports angiotensin II (ANGII) type 1 receptor (AT1) activation acting as a fundamental modulatory component of vasoconstriction in spinal cord pericytes.
We hypothesise that SC astrocytes producing angiotensinogen act as key modulators of pericyte-mediated vessel constriction, inducing capillary breakdown and facilitating diabetic neuropathic pain.
Method: A high fat diet (HFD) induced mouse model of type 2 diabetes was established via a 60% (% of kcal) diet feed for 7 weeks in adult male C57BL/J mice, alongside an age-matched control group fed on standard chow. Nociceptive behavioural assessment was performed as well monitoring of body and blood glucose. Nanostring Geomx digital spatial profiling and immunohistochemistry was performed on lumbar spinal cord samples extracted at the termination of the study. Imaris image analysis was performed on acquired images. Astrocytes were isolated from mice using a miltenyi astrocyte isolation protocol. Angiotensinogen protein expression was measured via western blot in normoglycaemic and hyperglycaemia culture conditions for 24hrs.
Results: Heat hyperalgesia developed within the HFD group at week 7 vs. control diet group (HFD n=5 vs. control n=5, **p<0.001). SC tissue lysate from the HFD group indicated significantly elevated angiotensinogen compared to standard diet SC tissue (p<0.031*). SC tissues from HFD and standard diet were processed for GeoMx proteome spatial profiling. Astrocyte markers GFAP and S100B in HFD tissue were elevated in count compared to standard diet tissue. Confocal imaging and Imaris modelled SC microvessels indicated increased GFAP+astrocyte to CD31+vessel surface-to-surface interaction in HFD (70%) vs standard diet (43.33%) SC tissue (*p<0.04). In isolated mouse astrocytes AGT was upregulated in hyperglycaemic conditions.
Conclusion: Here we demonstrate that in a rodent model of HFD-induced neuropathic pain, increased angiotensinogen in the lumbar spinal cord is associated with increased astrocyte expression. This demonstrates the renin-angiotensin system is involved with the modulation of diabetic neuropathic pain.

P.10 | PERCEPTION THRESHOLD TRACKING REVEALS DIFFERENT SMALL NERVE FIBER FUNCTION IN SUBGROUPS OF PEOPLE WITH DIABETIC PERIPHERAL NEUROPATHY

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Objectives: Perception threshold tracking is a novel method for rapid assessment of large and small afferent nerve fiber function in diabetes. The method uses advanced electrical stimulation to assess nerve membrane excitability for large Aβ- and small Aδ-fibers selectively using unique surface stimulation electrodes. In this study, we aimed to investigate 1) whether perception threshold tracking can distinguish people with painful diabetic peripheral neuropathy (PDPN) from people with painless diabetic peripheral neuropathy (DPN) and 2) whether the method is sensitive to different phenotypes of PDPN.
Methods: A total of 65 individuals with diabetes and confirmed DPN according to the Toronto consensus were recruited from previous studies. Perception threshold tracking was performed using weak electrical currents with varying intensity using a special designed pin electrode for activation of small fibers. Nerve fiber activation was indicated by participants pressing a button. The minimal current needed to activate the nerve fibers was analyzed as the rheobase. Phenotyping of those with PDPN was performed using clustering based on the PainDETECT (Freyhoven et al. 2006) questionnaire as suggested by Baron et al. (2009), where cluster 1 is characterized by burning and prickling pain without numbness or thermal hypersensitivity, cluster 3 is characterized by diffuse pain without allodynia and only mild numbness, and cluster 5 is characterized by burning and pricking pain with pronounced numbness but without allodynia.
Results: People with PDPN had a median rheobase of 1.31 (IQR 0.76; 7.16) while those with painless DPN had a median rheobase of 0.89 (IQR 0.62; 1.19), with a difference between the two groups (p=0.01). When divided into clusters using the PainDETECT questionnaire, 15% ended in cluster 1, 20% ended in cluster 3, and 55% ended in cluster 5, while the remaining 10% ended in clusters 2 or 4. The median rheobase of the different clusters were 1.05 (IQR 0.44; 1.17), 0.60 (IQR 0.12; 1.13), and 16.1 (IQR 1.08; 25.0) for cluster 1, 3, and 5, respectively. There was an overall difference between the different clusters (p=0.02), and an individual difference between cluster 5 and both other clusters (both p<0.01).
Conclusions: The present data suggests that some phenotypes of people with PDPN have more pronounced small fiber dysfunction than people with painless DPN. The identification of subgroups of PDPN is important, as they might have different underlying pathophysiology, and therefore might respond differently to various treatments and have a different disease trajectory.

P.11 | ASSOCIATION BETWEEN GENERAL AND ABDOMINAL OBESITY IN TYPE 2 DIABETES WITH DIABETIC NEUROPATHY: RESULTS FROM A NATIONAL HEALTH INSURANCE SERVICE–NATIONAL SAMPLE COHORT, 2015

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Objectives: It remains unclear whether obesity increases the risk of diabetic neuropathy (DN). To investigate the association between general and abdominal obesity in type 2 diabetes with diabetic neuropathy .
Methods: From the target population a representative sample cohort of 1,021,208 participants was randomly selected, comprising 2.1% of the total eligible Korean population in 2006, and followed until 2015. Data source: NHIS-NSC: National Health Insurance Service–National Sample Cohort. We conducted a clinical analysis of 47,451 type 2 patients in 2015 among cohort subjects.
Results: According to the analysis, 21.2% were diagnosed with DN. Subjects with DN had low body mass index(24.8±3.4 vs 25.1±3.4 kg/m2) and high waist circumference(85.5±8.9 vs 85.3±8.9 cm) and abdominal obesity(40.5% vs 38.9%) than subjects without DN. DN patients with abdominal obesity showed that older age, being female, low physical activity, high body mass index, high fasting glucose, the presence of cardiovascular disease, a history of cerebrovascular accident, or peripheral arterial disease, the presence of hypertension or dyslipidemia, treatment with an oral hypoglycemic agent or insulin, a history of foot ulcers and amputation of foot and higher hospitalization than diabetic patients
Conclusions: Not general obesity but abdominal obesity was associated with DN. DN patients with abdominal obesity need attention in treating elderly people, poor lifestyle habits, high co-morbidities and complications, and high hospitalization rates.

P.12 | ASSOCIATION BETWEEN LIVER FIBROSIS AND COGNITIVE IMPAIRMENT IN ELDERLY PATIENTS WITH TYPE 2 DIABETES

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Objectives: Chronic liver diseases are increasingly being recognized as having an impact on brain health. The effect of liver fibrosis on the risk of mild cognitive impairment (MCI) and dementia remains unclear [1]. The main objective of this study was to evaluate the association between FIB-4 and MCI or dementia among elderly patients with type 2 diabetes (T2DM).
Methods: We performed a prospective cross-sectional study. Two-hundred consecutive patients with T2DM older than 60 years were recruited in Son Llatzer University Hospital (Balearic Islands, Spain). The Montreal Cognitive Assessment (MoCA) test was used as a screening tool for MCI or dementia using different cut-offs according to race, ethnicity, and years of education [2]. The degree of liver fibrosis was estimated using the no-invasive formula of Fibrosis-4 (FIB-4) liver fibrosis score. FIB-4 was categorized as moderate (FIB-4 between 1,45 and 3,25) and high (FIB-4> 3,25) risk of advanced fibrosis. We used binary logistic regression models to evaluate the association between liver fibrosis and MCI or dementia while adjusting for potential confounders.
Results: On all patients included in this study, the mean (SD) age was 71± 6 years and 47% were women. According to MoCA cut-off values, 110 (55%) and 34 (17%) patients had MCI and dementia respectively. Regarding FIB-4, 82 (41.0%) and 5 (2.5%) patients had a moderate and a high risk of advanced liver fibrosis, respectively. The percentage of patients with moderate or high risk of advanced fibrosis was significatively higher for patients with MCI or dementia compared to those with normal cognition (50.0% vs. 26.8%; p<0.001). After adjusting for age, gender, chronic kidney disease and BMI, liver fibrosis was associated to MCI or dementia (Odds Ratio 2.15, 95% CI 1.04-4.40; p=0.038).
Conclusions: Our study demonstrates that liver fibrosis is associated with MCI or dementia in older patients with T2DM. These findings have potentially important clinical implications because liver fibrosis might be an underestimated risk factor for cognitive impairment. Nevertheless, prospective studies are needed to establish the time sequence in this relationship and clinically relevant findings.

References

1. Moulton CD, Staite E, Winkley K, Heneghan MA, Ismail K. The association between liver fibrosis and cognitive impairment in type 2 diabetes. J Hepatol. 2023;78(1):e18-e20. doi: 10.1016/j.jhep.2022.08.040.
2. Milani SA, Marsiske M, Cottler LB, Chen X, Striley CW. Optimal cutoffs for the Montreal Cognitive Assessment vary by race and ethnicity. Alzheimers Dement (Amst). 2018;10:773-781. doi: 10.1016/j.dadm.2018.09.003.

P.13 | THE ROLE OF HYPERTRIGLYCERIDEMIA IN THE DEVELOPMENT OF DIABETIC NEUROPATHY (DPN) IN PATIENTS WITH TYPE 2 DIABETES IN GEORGIA BY SUDOSCAN

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Aim: Diabetic peripheral neuropathy (DPN) is a the common complication of type 2 diabetes and can lead to foot ulcer, gangrene or amputation. The risk of developing diabetic neuropathy increases with age, diabetes duration and poor control of blood glucose. About 60% to 70% of all people with diabetes will eventually develop DPN. Hypertriglyceridemia is a typical lipid disorder in patients with poorly controlled diabetes mellitus. The aim of this study was to assess the effect of hypertriglyceridemia on peripheral neuropathy in patients with type 2 diabetes (T2DM).
Methods: Totally 102 T2DM patients with peripheral neuropathy were enrolled in this study; among them, 54 men and 48 women (Study Group/ SG). Their mean age was 56±7 yrs and diabetes duration (DD) varied from 5 to 10 yrs. In all SG patients hypertriglyceridemia was diagnosed. 50 patients with the same age, sex (DD), with normal triglacerides (TG) but without DPN were used as controls (CG). HbA1c in SG was 8,1±1,2% and in CG - 7,7±1,1%. According to current Guidelines, to assess DPN, following neuropathy tests were performed in all patients: 10-g monofilament test, tip-term/temperature test, vibration test with the 128-Hz tuning fork, pick tests and neurological examination with Sudoscan (a non–invasive method for the assessment of the small fiber function, Impeto Medical, France). Results of all neurological tests in SG patients (monofilament test, tip-term/temperature test, vibration test) were positive, Sudoscan examination revealed presence of small fiber neuropathy. In CG patients all tests, except Sudoscan, were negative, while Sudoscan revealed small fiber damage. Association between hypertriglyceridemia and DPN was assessed. Serum triglyceride levels in SG patients were elevated (mean TG level 299± 100mg/dl, while in CG patients - 100±20mg/dl).
Results: According to neurological examinations prevalence of DPN in SG patients comprised 64,5% (66 cases).TG concentration was significantly elevated in T2DM patients with DPN when compared to patients without DPN and normal TG levels (P=0,005).Elevated serum triglyceride levels were associated with DPN (p<0,044).
Conclusions: This study shows that increased levels of serum triglycerides may play an important clinical role in development of DPN in T2DM patients in Georgia. The problem needs further investigation with other important parameters.

P.14 | LINK BETWEEN SMALL FIBER NEUROPATHY AND DEPRESSION IN PATIENTS WITH DIABETIC POLYNEUROPATHY: A CORNEAL CONFOCAL MICROSCOPY STUDY

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With the rising numbers of diabetics with neuropathy, this study assessed the association between small fibre neuropathy and depression using corneal confocal microscopy (CCM). Patients underwent CCM and then filled in the hospital anxiety and depression scale (HADS) which was used to categorise their depression. Certain parameters of CCM were shown to be significantly changed depending on their overall HADS score. Associations with age, duration, gender and ethnicity, BMI and HbA1c were examined in connection with HADS scoring.
Overall, the use of CCM greatly quantifies small fibre neuropathy which can be shown to play a role in the progression of depression in diabetic patients.
Introduction: Diabetic polyneuropathy (DPN) can affect ~50% of patients with diabetes and increases the risk of clinical depression by nearly 24%. Corneal confocal microscopy (CCM) can accurately assess small nerve fibre damage. The aim of this study was to evaluate the association between depression and small fibre neuropathy in patients with diabetes using corneal confocal microscopy.
Methods: 225 patients underwent assessment of the neuropathy disability score, thermal thresholds and CCM. Depression was assessed with the hospital anxiety and depression scale (HADS) and participants were divided based on the HADS score into those with (cut-off 15+) or without depression.
Results: Age (64.68± 1.04 vs 57.95± 1.80, p=0.02) was lower, but BMI (29.19± 0.94 vs 33.83± 1.25, p= 0.005) and HbA1c (53.65±1.69 vs 62.94± 2.31, p=0.002) were significantly higher in patients with compared to without depression. Patients with depression had a significantly lower corneal nerve fibre density (20.64± 1.07 vs. 23.38± 0.709, P=0.03), cold perception

threshold (22.02± 9.00 vs 26.28± 4.26, p<0.01) and higher warm perception thresholds (42.36± 5.03 vs 40.90± 4.07 , P=0.01), all suggestive of small fibre damage.
The HADS score correlated with age (r= -0.26, p=0.02), BMI (r= 0.35, p=0.01) and HbA1c (r= 0.36, p<0.01) However, type of diabetes, gender and ethnicity showed no association with the presence or absence of depression. There was no direct association between CCM parameters and HADS score.
Conclusion: This study shows that diabetic patients with depression have evidence of small fibre neuropathy which may be a factor in the development of depression in patients with diabetes.

P.15 | IS DIABETIC NEUROPATHY AFFECTED BY LIPOPROTEIN A? A RETROSPECTIVE EPIDEMIOLOGICAL STUDY IN AN EGYPTIAN COHORT

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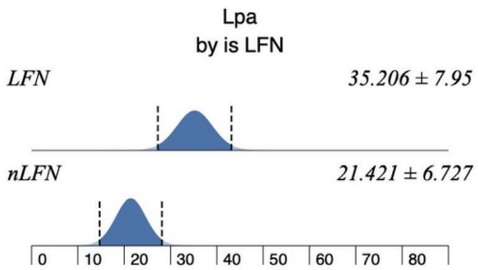
Objectives: Diabetic Neuropathy is a common complication of diabetes. Its presence is a marker of microvascular damage and a risk factor for atherosclerotic cardiovascular disease (ASCVD). Large fiber neuropathy can be assessed using vibratory perception threshold (VPT). Small Fiber Neuropathy can be assessed by electrochemical skin conductance. Both methods have been repeatedly validated in numerous trials and are good surrogates to nerve biopsy in diabetic neuropathy. Lipoprotein a (LPa) is currently being studied as a strong risk factor for ASCVD. Current guidelines recommend its measurement in all patients. But its effect on neuropathy has never been studied. We decided to retrospectively study our records to identify any correlation between LPa level and the presence of neuropathy.
Methods: We examined the records of 500 patients with diabetes. We checked their LPa level, the presence of Large Fiber Neuropathy (LFN) defined as vibratory perception threshold> 25V, Small fiber neuropathy (SFN) defined as electrochemical skin conductance (Sudoscan) <70. We also checked for BP, eGFR, and lipid profiles for any correlations.
Results: LPa was significantly higher in patients with LFN p=0.013 but not significantly higher with SFN. It did not correlate with BP, Chol, TG, HDL, LDL, or eGFR. LFN correlated with LPa, Age, BMI and duration of diabetes. SFN correlated with age, BMI, Triglycerides, eGFR and Duration of Diabetes.
Conclusion: In this small study, LPa positively correlated with LFN. This correlation needs to be validated in a larger cohort for causality. Additionally, the effect of LPa on diabetic microvascular disease needs to be studied.



P.16 | DIABETIC NEUROPATHY STATUS OF PATIENTS WITH OR WITHOUT ISCHEMIC HEART DISEASE, A RETROSPECTIVE EPIDEMIOLOGICAL STUDY IN AN EGYPTIAN COHORT

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Objective: We tried to find a threshold for Diabetic Peripheral Neuropathy (DPN) by quantitative sensory testing (QST) using Vibratory Perception Threshold (VPT) and Electrochemical Skin Conductance (ESC)- Sudoscan, after which there is an increased risk of IHD.
Method: We retrospectively studied 400 patient records which were divided into IHD or non-IHD. We then numerically correlated both groups with Large Fiber Neuropathy (LFN) by VPT and Small
Fiber Neuropathy (SFN) by ESC. We then correlated both groups categorically with the standard cut-off points for LFN>25 and SFN<70. Both groups were thereafter examined for better thresholds for IHD.
Results: 400 records were examined, Male/Female 201/199, IHD 84/316, HbA1c, Systolic Blood pressure was similar in both groups. Cholesterol, LDL and albuminuria were lower in the IHD group denoting treatment. The IHD group were older, had a longer duration of diabetes, and higher BMI.
VPT was higher in the IHD group (31.9/27) p<0.001, ESC was lower in the IHD group (60.3/65) p=0.021. But when LFN was categorized as present if VPT>25 and SFN if ESC<70, both markers lost their significance p=0.117, p=0.76 respectively.
A new categorical threshold was applied, VPT>30, ESC<50. After applying the new thresholds, both QST's became significantly correlated p=0.027 and p=0.024 respectively.
Conclusion: Categorizing VPT >30 and ESC<50 as severe neuropathy markers is more informative than the current thresholds regarding the risk for IHD. These numbers are to be validated in other populations.

P.17 | STATISTICS OF DIABETIC NEUROPATHY IN GEORGIA

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Aim: The abstract's subject is Georgia's statistics on diabetic neuropathy as of the year 2021. The goal of the study is to examine the epidemiology of diabetic neuropathy and the factors that affect it. The study of statistical data, both quantitatively and qualitatively, is the foundation of the research technique. The National Center for Disease Control and Public Health receives statistics data from hospitals and medical facilities (including primary care and hospital institutions) as well as from electronic health records.
Methods-Patients: 20,158 new cases of diabetes were identified in Georgia in 2021, and 617 of those cases (3.06%) progressed to diabetic neuropathy. Patients with type II diabetes, of whom 63% were women and 27% were men, were diagnosed with 79% (488 instances) of the new cases of diabetic neuropathy. Diabetes mellitus type I was identified in 21% (129 cases) of the new cases of diabetic neuropathy, mostly in females (52%).
Results: According to the age distribution of the data, diabetic neuropathy was most frequently identified in people with type I diabetes between the ages of 55 and 59, 65 to 69, and 70 to 74. The most cases of diabetes mellitus type I were seen in those aged 55–59, 60–64, 65-69, and 70–74. One in three cases of diabetes, according to the IDF (International Diabetes Federation), go undetected. It is reasonable to suppose that there are more people who have diabetic neuropathy than there are reported cases because of these limitations. The covid pandemic in 2021 decreased the number of referrals to medical facilities. It should be emphasized that the referral rate to a primary care physician for prevention purposes is quite low in the nation, which precludes early diabetes diagnosis. One of the challenges in identifying diabetes complications in people with private insurance is that the insurance provider does not or only partially reimburse policyholders for the diagnosis of these complications.
Conclusion: Diabetic neuropathy is fairly common in Georgia, especially in people with type II diabetes who are mostly female and between the ages of 55 and 74. This has a detrimental effect on citizens' ability to work and their level of health, which raises the burden of morbidity brought on by diabetic complications.It is challenging to register new cases of diabetes because there is no diabetesregistry in the nation. Referrals to primary care specialists and awareness of early disease identification and screening are both lacking.

P.18 | UNDERSTANDING THE MANAGEMENT OF DIABETIC NEUROPATHY: A NATIONAL SURVEY OF HEALTHCARE PROFESSIONALS IN THE UNITED KINGDOM

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Background and Objectives: In the United Kingdom (UK), the National Institute for Health and Care Excellence (NICE) has established clinical guidelines for the pharmacological management of neuropathic pain and prevention and management of diabetic foot problems. However, these guidelines do not provide specific recommendations for diabetic sensorimotor polyneuropathy (DSPN) and do not consider non-pharmacological interventions. Additionally, implementing these guidelines in clinical practice may be challenging. The objective of this study was to survey healthcare professionals (HCPs) on their current management practices for people with DSPN in the UK.

Methods: An iteratively developed and piloted survey was created using Qualtrics platform (Seattle, United States). The survey covered six domains of demographics, screening and diagnosis, therapeutic approaches, assessment and follow up, views on current guidelines and barriers faced when managing patients with DSPN. It was distributed to healthcare professionals, diabetes and footcare professional networks and on social media platforms. Quantitative analysis included frequencies and percentages, and thematic analysis was performed on qualitative data.

Results: To date, the survey has received 97 responses from HCPs across all regions of the UK. For diagnosis, the majority (85.1%) conducted a physical examination. Education was the most common management strategy (96.7%), followed by performing/recommending foot examinations and complications screening (79.7%), and then optimising glycaemic control (76.5%). In managing painful DSPN, the majority of respondents (31.4%) prescribed duloxetine as a first-line pharmacotherapy, but still 11.4% prescribed paracetamol. In addition, 43.2% prescribed pharmacotherapy combinations, with duloxetine and pregabalin (37.5%) being the most common, and 31.3% prescribed opioids as part of combination therapy. There was high variability in the order and combinations of pharmacotherapies prescribed. Furthermore, 31.5% referred patients with painful DSPN for non-pharmacotherapies including psychological therapy and neurostimulation. Many respondents (41.7%) considered current NICE guidance inadequate for managing DSPN and common barriers identified to managing DSPN included, patient non-compliance, HCPs lack of education, lack of resources and difficulty referring patients.

Conclusion: These findings suggest that the management of DSPN may vary across the UK. HCPs lack of education, as well as their views on the current NICE guidelines may lead to a lack of standardised management pathways. Despite the evidence base for optimising glycaemic control, it was not the most common management strategy. There may be a need for updated clinical guidelines for DSPN in the UK that make clear recommendations on pharmacological and nonpharmacological therapeutic options and address barriers such as inadequate resources and knowledge gaps.

P.19 | ASSESSING DIABETIC NEUROPATHY CLINICAL PRACTICE GUIDELINES USING THE AGREE II FRAMEWORK

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Objectives: Diabetic sensorimotor neuropathy (DSPN) is a significant and common complication of diabetes. Current treatment focuses on modifying lifestyle factors, improving glycaemic control, and managing neuropathic pain. DSPN is a leading risk factor for diabetic foot ulceration, which can cause lower limb amputations and mortality. Despite the substantial economic and clinical impacts of DSPN, there may be a lack of standardised management frameworks among practitioners caring for patients with DSPN. Guideline appraisal tools are available to evaluate the quality of clinical practice guidelines' (CPGs) development. The Appraisal of Guidelines for Research and Evaluation II (AGREE II) tool evaluates CPGs across six domains, including scope and purpose, stakeholder involvement, rigour of development, clarity of presentation, applicability, and editorial independence. The objective of this study is to evaluate the methodological quality of CPGs in DSPN using the AGREE II framework.

Methods: A systematic search of CPGs related to DSPN was conducted from January 2008 to January 2023. The databases Ovid Medline and Embase were searched, and grey literature sources were searched to identify additional CPGs. The search strategy identified 2533 references. All CPGs had to meet specific inclusion criteria, including being evidence-based and focused on DN diagnosis and/or management. Two reviewers independently screened and extracted the CPGs, resulting in 19 CPGs being included. Three independent reviewers assessed the methodological quality of each CPG using the AGREE II instrument. The three independent scores were synthesised and a percentage score was calculated for each domain as well as an overall guideline quality score.

Results: The 19 CPGs included guidelines focused on diabetic neuropathy/foot disease, general neuropathic pain, broad diabetes guidelines. Reasons for exclusion included lack of a detailed section on diabetic neuropathy, outdated versions and not qualifying as a guideline. The CPGs dated from 2009 to 2023, involved a wide range of healthcare professionals and originated from various regions (Europe n=5, America n=4, Asia n=9 and International Group n=1). Initial appraisal suggests there is some heterogeneity between CPGs for DSPN, particularly with respect to scores in methodology, recommendation level and topics included.

Conclusions: The authors suggest that the development of more comprehensive and standardized CPGs for DSPN is necessary to improve the management and quality of care. The importance of clinical practice guidelines for DSPN management is highlighted by this study, which could help reduce the economic and clinical impacts of DSPN.

P.20 | STUDY PROTOCOL FOR DEVELOPING A CORE OUTCOME SET FOR DIABETIC NEUROPATHY CLINICAL TRIALS (DECODE)

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Background and Objectives: Diabetic neuropathy is the most common complication of diabetes, affecting more than 50% of people with diabetes. It is characterised by peripheral nerve dysfunction, typically leading to sensorimotor symptoms such as unsteadiness, pain and/or numbness in the distal extremities. Diabetic neuropathy can lead to a reduced quality of life, and further complications include diabetic foot ulceration and Charcot neuropathic osteoarthropathy, which are associated with significant morbidity and mortality.

There have been several landmark diabetic neuropathy clinical trials, however, there has been heterogeneity in the outcomes measured leading to challenges in evidence synthesis. In addition, it has been proposed that promising novel therapies for diabetic neuropathy may have failed in clinical trials due to the outcomes measured. The objective of this study is to develop a core outcome set (COS) for diabetic neuropathy clinical trials.

Methods: The proposed methods will follow the Core Outcome Measures in Effectiveness Trials (COMET) Initiative Handbook. A systematic review of the literature will be conducted to identify and synthesise the outcomes measured in diabetic neuropathy clinical trials. Focus groups and semi-structured interviews with diabetic neuropathy patients, caregivers and patient support group representatives will be performed to identify which outcomes are most important to these stakeholders. A wide range of international stakeholders such as patients, healthcare professionals,

researchers and charities will be surveyed to identify their most important outcomes. A multi-round Delphi process will be undertaken to develop a COS for diabetic neuropathy clinical trials.
Results: The process for diabetic neuropathy COS development is underway, with the purpose of improving the quality of diabetic neuropathy research and inform future clinical trials, clinical practice guidelines and systematic reviews. Registration of the project in the COMET database has been approved (https://www.comet-initiative.org/Studies/Details/2461).
Conclusions: The project is ongoing, so conclusions cannot be drawn yet.

P.21 | THE ROLE OF THE PHARMACIST IN THE SCREENING FOR DIABETIC NEUROPATHY – PARTIALLY RESULTS FROM THE "SEE THE SWEET PART OF LIFE" CAMPAIGN

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Introduction: Despite current perception of "drug seller", the pharmacist might play a very important role in the diabetes (DM) management, especially in areas with deficit of diabetologists. Due to more frequent interaction with the patient, the pharmacist can provide essential information regarding diabetes care in order to improve glycemic control and prevent microvascular complications.
Objectives: The "See the sweet part of your life" campaign was design to train the pharmacists to detect the high risk people for developing diabetes and to offer proper advices in order to prevent it. In people with diabetes (PWD), they offered info regarding lifestyle optimization, proper monitoring and prevention of microvascular complications.
Methods: 85 pharmacists from 52 units were trained in 4 different regions of our country. The initial duration of the project (November 2019 – February 2020) was extended due to Covid-19 pandemic. During this campaign, the blood pressure, pulse and anthropometric measurements were systematically taken. The subjects completed different questionnaires (eg: Findrisk score), they received brochures about diabetes and prediabetes and a voucher for blood testing which included: glycated hemoglobin (A?c), glycemia, creatinine, lipid profile and liver enzymes. The Michigan Neuropathy Screening Instrument Questionnaire (MNSIQ) was used to detect people at risk for diabetic neuropathy. After the campaign was completed, each person received a report with all the collected data and was directed to the family physician or diabetologist.
Results: A total of 986 participants were enrolled. The majority were females 773 (78.95%), from urban areas (63%), with an age between 40 - 59 years old (43%) followed by those between 20 – 39 years old (36%). Of all participants, 53.24% were at high risk for diabetes, 0.6% had gestational diabetes, 12.47% had type 2 and 9.43% type 1 DM. Most of the participants (65%) declared they have eye problems followed by 15% with foot and kidney diseases and only 5% with heart conditions. Of the 216 PWD enrolled, 67% responded yes to the majority of the questions from the MNSIQ. Only 4.46% participants used the voucher for blood testing.
Conclusions: This campaign which involved pharmacists in screening, monitoring and education of the PWD or those with high risk for developing this disease is a premiere in our country. The percentage of PWD who responded yes to the majority of questions from MNSIQ resembles the data regarding diabetic neuropathy prevalence from clinical studies.

P.22 | PREDIABETES IMPAIRS SCHWANN CELL-AXON COMMUNICATION VIA THE LACTATE SHUTTLE

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Objectives: Prediabetes affects approximately 541 million individuals worldwide, of which 30% suffer from peripheral neuropathy (PN). Under normal conditions, Schwann cells (SCs) maintain peripheral nerve health by supplying axons with energy substrates, such as lactate through monocarboxylate transporters (MCTs). We propose that prediabetes compromises MCT-dependent lactate shuttling, leading to energy failure and PN.
Methods: Twelve-wk old male mice were fed standard diet (SD; 10% fat) or high fat diet (HFD; 60% fat) for 6 wks. At study termination, metabolic and neuropathy phenotyping as well as flux analysis were performed. Complimentary in vitro work in cultured rat primary SCs further characterized MCT-mediated lactate trafficking following palmitate treatment to mimic metabolic dysfunction.
Results: At study termination, we found that HFD mice were significantly heavier than their control littermates and had impaired glucose tolerance. They also developed nerve conduction velocity and intraepidermal nerve fiber density deficits. Flux analysis showed that these metabolic and neuropathic changes were associated with a significant reduction in lactate abundance in the sciatic nerves of HFD mice. In vitro, exposure of rat primary Schwann cells to increasing palmitate concentrations (31.25-250 μM) resulted in an early MCT1 upregulation coupled with increased lactate release. However, chronic palmitate exposure significantly reduced MCT4 gene expression, concomitant with SC oxidative stress and injury.
Conclusion: In summary, our results suggest that prediabetes impairs MCT-mediated lactate transport, which is likely to result in bioenergetics failure and neurodegeneration.

P.62 | TYPE 2 DIABETIC NEUROPATHIC PAIN IS DEPENDENT UPON HYPOXIA INDUCIBLE FACTOR 1 ALPHA MEDIATED ACTIVATION OF DORSAL HORN NEURONS

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Objectives: Neuropathic pain is a long-lasting inescapable condition common in people with diabetes, with symptoms including burning and shooting pains. Our research has demonstrated that diabetic neuropathic pain manifests due to a reduced blood perfusion of the spinal cord. Loss of vascular support results in dorsal horn neurons becoming hypoxic. The aim of this study is to identify a hypoxia responsive sensory neuronal ensemble that is fundamental to diabetic neuropathic pain manifestation.
Our hypothesis is that knockdown of hypoxia inducible factor 1 alpha expression in the spinal cord dorsal horn neurons will prevent type 2 diabetic neuropathic pain development.
Methods: All Experiments were designed in accordance with UK Home Office legislation, Animals (Scientific Procedures) Act 1986. C57bl6 HIF1alpha floxed (007561 Jax) mice (both males and females were used) were via tail vein intravenously injected with AAV PHP.eb syn cre eGFP (105540-PHP.eb ADDgene). Mice were given either experimental diet (high fat (60% cal fat)) or intrathecal injection of hypoxia mimetic, dimethyloaxallyl glycine (DMOG). Animals body weight, blood glucose and nociceptive behavioural withdrawals (including von Frey hair, Hargreaves test, Open field arena) were tested. Animals were terminally anaesthetised (intraperitoneal 60mg/kg Sodium Pentobarbital) and cardiac perfused with 4% paraformaldehyde. Lumbar spinal cords were extracted and processed (40μM thick sections) for confocal microscopy to identify neurons (NeuN), GFP labelled cells, transcription factor and marker neuronal activation Fos and hypoxia inducible factor 1 alpha (HIF1a). In addition, proteomic evaluation of hypoxia responsive spinal cord neurons was performed.
Results: Intrathecal DMOG treatment and high fat diet led to a pronounced induction of neuropathic pain behavioural phenotypes when compared to normal chow fed or vehicle treated mice. Lumbar spinal cord cryosections demonstrated increased abundance of neuronal HIF1a in DMOG and high fat fed mice when compared to lean or vehicle controls. In HIF1aKO mice, DMOG and high fat diet induced pain hypersensitivity was prevented. Western blotting and proteomic evaluation was performed on isolated spinal cord neurons demonstrating a reduction in HIF1a expression as well as cessation of HIFa dependent hypoxia signalling in HIF1aKO mouse spinal cord neurons.
Conclusions: Hypoxia signalling in the spinal cord is HIF1a dependent, and is fundamental to the manifestation of diabetic neuropathic pain.

P.23 | PERIPHERAL NERVOUS SYSTEM-SPECIFIC KCNJ11-DEFICIENT MICE DEVELOP DYSFUNCTION OF PERIPHERAL NERVES

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Objectives: The Kcnj11 gene encodes a protein called Kir6.2, which is a subunit of glucose-responsive ATP-sensitive potassium channels (KATP) found in the peripheral nervous system (PNS). KATP channels are formed by four pore-forming inward rectifier channel subunits, KIR6.1 (KCNJ8) or KIR6.2 (KCNJ11). KIR6.2 expresses in the peripheral nerve. Although the roles of KATP in the PNS remain unclear, our previous papers suggested that the physiological functions of the PNS in KATP-deficient (Kir6.2-deficient) mice were impaired. Here, we demonstrate the detailed roles of KATP in the PNS using peripheral nerve-specific Cre Recombinase mice.
Methods: Two strains of mice were used: C57BL/6J (BL6) mice and peripheral nerve-specific Kcnj 11 deficient mice (AdvCre: Kcnj11 fl/fl). We evaluated tactile perception by a monofilament test, thermal perception by a thermal plantar test, and nerve conduction velocity (NCV). The 50% hind paw withdrawal threshold was determined using von Frey filaments in the monofilament test. Casual blood glucose (CBG) levels and body weight (BW) were measured, and glucose tolerance was evaluated by an intraperitoneal glucose tolerance test (IPGTT) in 24-week-old mice.
Results: AdvCre: Kcnj11 fl/fl mice showed tactile allodynia and thermal hyperalgesia at 36 weeks old (thermal plantar test: BL6 7.4±1.9 s, Cre+ 9.4±0.7, $p < 0.05$; monofilament test: BL6 2.0±0.8 g, Cre+ 3.7±1.1, $p < 0.05$). Motor NCV (MNCV) was decreased in 24-week-old AdvCre: Kcnj11 fl/fl mice (BL6 43.2±3.5 m/s, Cre+ 36.7±4.7, $p < 0.01$). Sensory NCV (SNCV) was decreased in 30-36-week-old AdvCre: Kcnj11 fl/fl mice (30-week-old: BL6 36.8±3.1 m/s, Cre+ 31.7±5.8, $p < 0.05$; 36-week-old: Cre- 33.2±8.1, Cre+ 21.8±2.7, $p < 0.05$). There were no significant differences in BW and CBG levels in 30-week-old mice (BW: BL6 27.8±5.0 g, Cre+ 29.3±3.5, $p=0.58$; CBG: BL6 141.0±36.6, Cre+ 140.1±28.6 mg/dL, $p=0.97$). IPGTT in 24-week-old mice showed no significant difference.
Conclusions: AdvCre: Kcnj11 fl/fl mice showed dysfunction in the PNS. We suggest that physiological and pharmacological studies focusing on KATP channels should be considered to elucidate the roles of KATP in the PNS.

P.24 | DIMETHYL FUMARATE IMPROVES NRF-2 MEDIATED ANTI-OXIDANT RESPONSE TO AMELIORATE FUNCTIONAL AND MOLECULAR DEFICITS IN EXPERIMENTAL DIABETIC NEUROPATHY

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Objectives: Of the different pathological mechanisms of diabetic neuropathy (DN), oxidative stress and mitochondrial dysfunction play a significant role in altered metabolic indices of nerves that result in amplified pain response seen in DN. We assessed the pharmacological potential of dimethyl fumarate (DMF) on Nrf-2 mediated anti-oxidant defence, mitochondrial function and molecular chaperone activity in experimental diabetic neuropathy.
Methods: Diabetes was induced by streptozotocin (STZ; 55mg/kg, i.p) administration and DMF (25 and 50 mg/kg, p.o) treatment was started from 6th week and continued up to 14 days. Neurobehavioral and functional studies were conducted after the last dose of DMF, then molecular studies performed in isolated sciatic nerves and dorsal root ganglions (DRGs). For invitro studies, N2a cells were exposed to 35 mM glucose and treated with DMF (5 and 10 µM) then assessed for markers of oxidative stress, mitochondrial function and chaperone activity.
Results: DMF treatment significantly improved the motor (67 ± 4.04 Vs 38 ± 4.41 m/s; $p<0.001$), sensory (68.3 ± 3.18 Vs 49 ± 3.05 m/s ; $p<0.001$) nerve conduction velocities and nerve blood supply (101 ± 3.6 Vs 57.33 ± 4.63 PU ; $p<0.001$) in diabetic rats. Hyperalgesia and allodynia were reported in diabetic rats which is reversed up on DMF administration. At molecular level, DMF treatment markedly improved the expression of Nrf-2, NRF-1, PGC-1α and HSP70 levels in DRGs of diabetic rats which strengthened oxidative defence, mitochondrial function and chaperone activity otherwise compromised in diabetic control rats. In vitro results also showed potential of DMF in augmenting anti-oxidant defence and mitochondrial function.
Conclusion: DMF administration increased antioxidant defence by upregulating Nrf-2 levels. Additionally, DMF treatment restored mitochondrial function and augmented mitochondrial biogenesis via upregulation of NRF-1, PGC-1α and improved chaperone activity by increasing expression of heat shock proteins (HSP60and HSP 90) that may be responsible for the improved DN features in diabetic rats and high glucose induced toxicity in N2a cells.

P.25 | TRPM3 ACTIVATION MEDIATES STIMULATORY EFFECTS OF MUSCARINIC RECEPTOR ANTAGONISM ON MITOCHONDRIAL FUNCTION AND AXONAL OUTGROWTH IN DIABETIC PERIPHERAL NEUROPATHY

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Objectives: Diabetic peripheral neuropathy comprises a distal dying-back axonal degeneration that results in sensory loss and neuropathic pain. Our research has focused on promoting axon sprouting and regeneration of sensory neurons through inhibition of a G protein-coupled receptor (GPCR), the muscarinic acetylcholine type 1 receptor (M1R). In sensory neurons derived from diabetic rats M1R antagonism caused an influx and increase of intracellular Ca2+ in axons. This was associated with Ca2+/calmodulin-dependent protein kinase kinase II (CaMKKII) activation of AMP-activated protein kinase (AMPK) which promoted mitochondrial function and neurite outgrowth (Calcutt et al, Journal of Clinical Investigation, 2017; Saleh et al, Molecular Neurobiology, 2020). Transient receptor potential channel 3 (TRPM3) is a mediator of Ca2+ influx that binds calmodulin at its intracellular domain and is inactive at low phosphatidylinositol biphosphate (PIP2) levels (e.g. under conditions of GPCR agonist-mediated phosphoinositide hydrolysis). To test the mechanistic linkage between M1R receptor antagonism and TRPM3 channel activation we hypothesized that M1R antagonism induces a blockade of G protein signaling leading to increased PIP2 levels and subsequent TRPM3 activation and enhancement of Ca2+ influx.
Methods: Adult dorsal root ganglion (DRG) sensory neurons from age-matched or streptozotocin (STZ)-induced diabetic rats were cultured and treated with TRPM3 agonists, CIM0216 and pregnenolone sulphate (PS). We analyzed Ca2+ homeostasis, mitochondrial function and neurite outgrowth using fluorescence microscopy, Western blot and Seahorse XF24. Cellular metabolism was assessed through metabolomic profiling. Adeno-associated virus (AAV-PHP.s) delivered shRNA to specifically down-regulate TRPM3 expression.
Results: Selective TRPM3 inhibitors, primidone and isosakuranetin, blocked the Ca2+ influx induced by TRPM3 agonists. In cultures derived from M1R knockout mice, TRPM3 agonism caused a rise in intracellular Ca2+ that was suppressed compared with wild-type cultures. TRPM3 agonists activated AMPK, augmented mitochondrial function and elevated neurite outgrowth. AAV-PHP.s delivery of shRNA to TRPM3 hindered the stimulatory impact of CIM0216 or PS on AMPK phosphorylation. Piren-

zepine, a selective M1R antagonist, raised PIP2 levels and increased neurite outgrowth. TRPM3 knockdown suppressed the positive effect of pirenzepine on neurite outgrowth. ST0-609 (a selective CaMKKII inhibitor) inhibited CIM0216-induced AMPK phosphorylation revealing CaMKKII as an upstream regulator. Untargeted metabolomics analysis demonstrated enrichment in galactose and pyruvate metabolism induced by TRPM3 agonists, supporting stimulation of neuronal bioenergetics.
Conclusions: TRPM3 channels mediate positive effects of M1R antagonism on mitochondrial function and neurite outgrowth. This work supports ongoing clinical trials using M1R antagonists in individuals with diabetic peripheral neuropathy. Funded by CIHR grant # PJT-162172.

P.26 | BETA-ARRESTIN-BIASED AGONISM AT THE M1 MUSCARINIC RECEPTOR OF ADULT SENSORY NEURONS

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Objectives: We recently showed that application of selective (pirenzepine (PZ)) or specific (muscarinic toxin 7 (MT7)) antagonists of muscarinic acetylcholine type 1 receptor (M1R) reverse sensory nerve degeneration in different rodent models of peripheral neuropathy (Calcutt et al, Journal of Clinical Investigation, 2017; Saleh et al, Molecular Neurobiology, 2020; Jolivalt et al, Journal of Pharmacology and Experimental Therapeutics, 2020). In vitro studies have confirmed that beta-arrestin played a role in mediating these effects. To understand the mechanism of action of PZ and MT7, we investigated whether these drugs possess beta-arrestin-biased agonism at M1R of sensory neurons to drive neurite outgrowth.
Methods: Human embryonic kidney (HEK) 293 cells and cultured adult rat dorsal root ganglia (DRG) sensory neurons were used. The signaling and trafficking properties of muscarinic drugs were characterized using inositol-phosphate one (IP1) measurement, Nanobioluminescence resonance energy transfer (NanoBRET) and luminescence-based M1R internalization assay. Phospho-specific immunoblotting for serine and threonine residues was performed on M1R purified from HEK293 cells overexpressing Halo-tagged M1R. The role of Gαq-protein, G protein-coupled receptor kinases (GRKs), and beta-arrestins in PZ/MT7-induced ERK activation was investigated using specific inhibitors (for Gαq and GRK2/3) and beta-arrestin knock-out (KO) HEK293 cells, respectively.
Results: NanoBRET analysis revealed that M1R agonists and antagonists induced Halo-tagged beta-arrestin2 recruitment to M1R-Nluc in a dose-dependent manner in HEK293 cells. These results were replicated in primary adult DRG neurons. Unlike MT7 and PZ, muscarine increased IP1 levels, while both PZ and MT7 dose-dependently inhibited muscarine-induced IP1 generation. Also, MT7 and PZ increased ERK phosphorylation in both M1R-expressing HEK293 and DRG neurons in a time-dependent manner. This drug-induced activation of ERK was mechanistically linked to elevated neurite outgrowth in DRG neurons. These results suggest PZ/MT7 possess beta-arrestin-biased agonism. Beta-arrestins (and not Gαq protein) were necessary for PZ/MT7-induced ERK phosphorylation. Blockade of GRK2/3 significantly elevated P-ERK levels in the absence or presence of PZ/MT7. Further, both PZ/MT7 impacted serine/threonine phosphorylation status of M1R. Surprisingly, PZ/MT7 not only did not induce M1R internalization but increased surface expression of the receptor.
Conclusions: Overall, this study provides molecular evidence to support a role for selective/specific muscarinic receptor antagonists acting as biased agonists at the M1R to drive neurite outgrowth and prevent/reverse nerve degeneration in peripheral neuropathy. Funded by CIHR grant # PJT-162172.

P.27 | COULD BE METHYLGLYOXAL THE CULPRIT OF THE DIABETES-INDUCED PARKINSON'S DISEASE?

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Objectives: The hyperglycaemia resulting from the cellular inability to respond to insulin (known as type 2 diabetes mellitus (T2DM)) increases the risk of developing Parkinson's disease (PD) by ~40%. One of its signatures is the intraneuronal deposition of α-synuclein (αS) aggregates, known as Lewy bodies (LBs). The association between T2DM and PD led scientists to focus their efforts in unveiling the mechanisms underlying their connection. The answer might arise from the data obtained by Castellani et al., who detected the formation of Nε-(carboxyethyl)lysine (CEL) and the Lys-Lys crosslinked MOLD at the periphery of LBs and therefore, on aggregated αS. They arise from the reaction of the αS-Lys with methylglyoxal (MG), a toxic side product of the neuronal glycolysis overproduced under T2DM. The formation of CEL and MOLD led to the assumption that they stimulate the formation of LBs and therefore, the development of PD. Nevertheless, this has not been proved, and the mechanism throughwhich hyperglycaemia induces PD remains unclear. Here we have studied how MG affects the conformation of αS, but also to one of its main functions, that is to assemble synaptic vesicles (SVs).
Methods: Human αS was incubated with MG. MALDI-TOF mass spectrometry was used to identify the nature of the modifications induced by MG. NMR and SAXS spectroscopies were applied to determine how MG affected the conformational ensemble of αS. These techniques were also used to determine how MG affected the ability of αS to bind small unilamellar vesicles (SUVs) resembling SVs and to characterize the structure of the lipid-bound fraction MG-modified αS. Fluorescence, DLS and AFM were used to assess whether MG affected the aggregation of αS, the morphology of the aggregates and the ability of αS to fusion and cluster SUVs.
Results: MG breaks the transient N-/C-terminal contacts of αS that tie its conformational ensemble. It inhibits the αS aggregation, but it is not able to disassemble pre-existing fibrils, which proves that CEL/MOLD found on LBs must be formed in a later event after aggregation. MG completely abolishes the affinity of αS towards SUVs and consequently, it hampers its function as a catalyst of the clustering and the fusion of SVs.
Conclusions: Our data prove that MG does not stimulate the formation of LBs but the formation of toxic soluble αS oligomers. In addition, MG depletes αS of one of its main biological functions, that is bind and cluster SVs during the neurotransmission.

P.28 | EFFICACY OF PYRUVATE AND BENFOTIAMINE AGAINST MOUSE AND CELL CULTURE MODELS OF DIABETIC NEUROPATHY

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Objectives: Pyruvate functions as an antioxidant and a glycolysis accelerator, whereas a vitamin B1 derivative benfotiamine has been shown to suppress the collateral glycolysis pathway under diabetic conditions. These substances are suggested as potential remedies for diabetic complications, but the precise action mechanisms remain unclear. By using immortalized adult mouse Schwann (IMS32) cells under high glucose conditions and streptozotocin (STZ)-induced diabetic mice, we investigated the therapeutic efficacy of pyruvate and benfotiamine against diabetic neuropathy.
Methods: 1) IMS32 cells were exposed to normal (5 mM) and high glucose (10 mM, 25 mM, 50 mM) conditions in the presence or absence of sodium pyruvate (1 mM) for up to 24 h. The cell viability and glucose metabolism under each culture condition were evaluated using MTS assay, metabolome and the Extracellular Flux Analyzer. 2) STZ-diabetic mice received ad libitum access to drinking water in the presence or absence of pyruvate (10 mg/mL) and/or benfotiamine (0.1 mg/mL), and the mechanical nociception of each mouse was evaluated by Von Frey test at 3, 7, and 11 weeks after STZ injection.
Results: 1) Time (1 h < 3 h < 6 h < 24 h)- and glucose concentration (5 mM < 10 mM < 25 mM < 50 mM)-dependent cell death of IMS32 cells under pyruvate-deficient conditions was observed. Exposure of IMS32 cells to the high glucose (> 15 mM) and pyruvate-deficient conditions led to a significant decrease in glycolytic flux, mitochondrial respiration and ATP production, accompanied by enhanced collateral glycolysis pathways. Treat-

ment with benfotiamine (0.1 mM) prevented the cell death by restoring glycolytic flux but not mitochondrial respiration. 2) Pyruvate supplementation failed to normalize the blood glucose levels but restored the reduced mechanical nociception of STZ-diabetic mice, which effects were further enhanced by co-treatment with benfotiamine.
Conclusions: Exogenous pyruvate plays a major role in maintaining glycolysis-TCA cycle flux under high glucose conditions. Benfotiamine appears to prevent Schwann cell death by restoring ATP production through glycolysis. Because of the improvement of mechanical hypoalgesia in STZ-diabetic mice, supplementation of pyruvate and benfotiamine may be efficacious for the prevention and amelioration of diabetic neuropathy.

P.29 | TRANSPLANTATION OF DENTAL PULP STEM CELLS AMELIORATES HINDLIMB SKELETAL MUSCLE ATROPHY AND PERIPHERAL NERVE DYSFUNCTION IN DIABETIC RATS

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Objectives: Diabetic peripheral neuropathy (DPN) causes not only nerve damages but also muscle strength decrease in patients with diabetes. The development of successful therapies for nerve damage and muscle atrophy must be needed for patients with DPN. Here, we investigated the effects of dental pulp stem cell (DPSC) transplantation on diabetic skeletal muscles in streptozotocine (STZ)-induced diabetic rats.
Methods: DPSCs were isolated and expanded from dental pulp of 6-wk old Sprague-Dawley rats. DPSCs were transplanted into the unilateral hindlimb skeletal muscles of normal and streptozotocin-induced diabetic rats. Four weeks after DPSC transplantation, neurophysiological measurements, muscle strength and the assessments in gastrocnemius muscles were performed.
Results: DPSC transplantation significantly improved sciatic motor and sensory nerve conduction velocities in diabetic rats. Diabetic rats showed significant decreased hindlimb grip strength and blood flow, capillary number-to-muscle fiber ratio, and muscle fiber cross-sectional area in gastrocnemius muscle, all of which were ameliorated by DPSC transplantation. Pro-inflammatory cytokines mRNA expressions of TNF-α and IL-1β, the E3 ubiquitin ligases Atrogin-1 were increased in the skeletal muscle of the diabetic rats compared with normal rats. The transplantation of DPSCs significantly decreased TNF-α and Atrogin-1 mRNA expressions in the skeletal muscle of the diabetic rats. DPSC transplantation also increased expressions of growth factors such as FGF2 and transcription factors, PGC-1α and UCP-3.
Conclusions: We identified that DPSC transplantation into hindlimb skeletal muscle could improve nerve dysfunction as well as muscle atrophy in STZ-induced diabetic rats.

P.30 | THREE-DIMENSIONAL PATHOLOGICAL ANALYSIS OF DRG NEURONS IN EXPERIMENTAL DIABETIC POLYNEUROPATHY

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Objectives: In rodent diabetic model, atrophy of neuronal cell soma in dorsal root ganglia (DRG) is known to be one of the pathological hallmarks in diabetic polyneuropathy (DPN), while the reduction of cell number is not reported. In general, neuronal cell size is determined by measuring the cross-sectional area of each neuronal cell with nucleus on the sections in previous studies, but it has been pointed out that this may not accurately reflect the size of the cell body. In this study, we three-dimensionally quantified DRG in streptozotocin (STZ)-treated C57BL/6 mice and normal controls, and verified the changes in DRG neurons observed in the onset and progression of DPN.
Methods: STZ (160 mg/kg) was administered subperitoneally to 8-week-old male C57BL/6 mice. At 8 and 16 weeks after administration, body weight, blood glucose, tail flick latency, and motor and sensory nerve conduction velocities (MNCV, SNCV) were measured and DRG was collected. Dissected DRG was made transparent by the CUBIC method. Immunofluorescence was conducted with anti-neurofilament antibody and anti-CGRP antibody in whole mount DRG specimens, which were observed with a light sheet microscope. A part of the obtained three-dimensionally stacked images was extracted to create learning data, and the segmentation artificial intelligence (AI)(DeepLab3+) was trained. The three-dimensional image was segmented by trained AI and quantified by a separately created tool.
Results: SNCV and MNCV decreased in the STZ group at both 8 and 16 weeks compared to the control group, and Tail flick latency increased at 16 weeks ($p < 0.01$). Cell soma volume of DRG neurons in STZ group decreased at both 8 weeks ($p < 0.05$) and 16 weeks ($p < 0.05$) in three-dimensional analysis, while that was significantly reduced only at 16 weeks in two-dimensional analysis ($p < 0.05$). Two-dimensional measurements showed no change in the neuronal cell number, while three-dimensional measurements showed a decrease in cell number in both 8 and 16 weeks ($p<0.05$). Histograms of cell bodies showed a significant decrease in the size of 3000-6000 μm3 in both 8 and 16 weeks in the STZ group ($p < 0.05$).
Conclusions: Three-dimensional measurements clarified that the earlier atrophy of neuronal cell soma and the decrease in the number of neurons in the DRG of mouse DPN model. These findings may shed light on a new pathology of DPN.

P.31 | CO-CULTURE OF LINED DORSAL ROOT GANGLION NEURONS AND SCHWANN CELLS AS A USEFUL TOOL FOR THE STUDY OF DIABETIC NEUROPATHY

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Objectives: Co-culture models of neurons and Schwann cells have been utilized for the study of diabetic and other peripheral neuropathies. In most of the previous studies, however, these cells were obtained by primary culture that needs a time-consuming process to get good yields with high purity of the cells prior to each co-culture experiment. Our current investigation focuses on the establishment of a stable co-culture system with lined dorsal root ganglion neurons ND7/23 and lined Schwann cells IFRS1 as an in vitro model of diabetic neuropathy.
Methods: ND7/23 cells were seeded at a low density (2 ×103/cm2) and maintained for 5-7 days in Dulbecco's Modified Eagle's medium (DMEM) containing 5% fetal bovine serum (FBS), 1% non-essential amino acids, 10 ng/mL nerve growth factor (NGF), and 5 μM Rho kinase inhibitor Y27632. Upon observation of neurite outgrowth under a phase-contrast microscope, the cells were exposed to 1 μg/mL anti-mitotic agent mitomycin C (MMC) for 48 h, then co-cultured with IFRS1 cells (2 x 104/cm2) and maintained in DMEM/5%FBS supplemented with 50 μg/mL ascorbic acid, 10 ng/mL NGF, and 10 ng/mL ciliary neurotrophic factor (CNTF).
Results: MMC pretreatment suppressed the overgrowth of ND7/23 cells during the co-culture with IFRS1 cells, and CNTF could alleviate the MMC cytotoxicity. After 14 days of co-culture, some IFRS1 cells were closely attached to the neurites emerging from ND7/23 cells. Double-immunofluorescence staining carried out at day 21 of the co- culture showed peripheral myelin protein 22-immunoreactive IFRS1 cells surrounding the βIII tubulin-immunoreactive neurites emerging from ND7/23 cells.
Conclusions: This co-culture system can be a beneficial tool to study the pathogenesis of diabetic neuropathy and novel therapeutic approaches against them. We are about to investigate if the treatment with high-glucose (30 mM) or 0.5 mM glycolaldehyde induces axonal degeneration and demyelination-like changes in the co-culture.

P.32 | SYSTEMIC BIOMARKERS OF MICROVASCULAR ALTERATIONS IN TYPE 1 DIABETES ASSOCIATED NEUROPATHY & NEPHROPATHY

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Background and aims: Diabetic neuropathy and nephropathy are common complications in type 1 diabetes mellitus (T1D). This study explores the importance of circulating vascular factors for diabetic peripheral neuropathy (DPN) and nephropathy in T1D.

Materials and methods: This study was designed as a cross-sectional analysis of patients with childhood-onset T1D followed prospectively in a long-term longitudinal cohort study. A total of 49 patients (mean age± SD; 38,3±3,8 years; diabetes duration 30,6± 5,2 years), and 30 control subjects (37,9 ± 5,5 years) were enrolled. Clinical examination and electroneurography tests were performed on the T1D patients and the controls. DPN was defined as the presence of an abnormality in nerve conduction tests. Matrix Metalloproteinase-9 (MMP-9), its tissue inhibitor TIMP-1, Neutrophil Gelatinase-associated Lipocalin-2 (NGAL or Lipocalin-2), and soluble P-selectin (sP-selectin) were analyzed in plasma. Microalbuminuria was defined as an albumin/ creatinine ratio of 3-30 mg/mmol. Macroalbuminuria was defined as an albumin/creatinine ratio >30 mg/mmol.

Results: In the current cohort 51% (25/49) of patients had DPN; 4 of these patients (8%) had microalbuminuria, and 4 (8%) had macroalbuminuria. Patients with DPN had higher levels of TIMP-1 than patients without DPN (P= 0.035). Both patients with and without DPN had significantly higher TIMP-1 levels compared to healthy controls. sP-selectin was also significantly higher in patients with DPN in comparison to the controls (P=0.005). Additionally, patients with macroalbuminuria had significantly higher TIMP-1 (P=0.042) and MMP-9 was considerably higher for patients with microalbuminuria (P=0.020) in comparison to the other groups. Patients with macroalbuminuria had significantly lower eGFR (45±17 mL/min/1.73m², P<0.001) than the patients without albuminuria (eGFR=90.87±14 mL/min/1.73m²) or microalbuminuria (eGFR=91±13mL/min/1.73m²) Increased levels of NGAL were found in the macroalbuminuria group both in comparison to the T1D without albuminuria and the to control group.

Conclusion: Our findings indicate that TIMP-1 and MMP-9 as well as s P-selectin and NGAL are involved in microvascular complications in T1D, and monitoring and targeting these biomarkers may be a potential strategy for the treatment of diabetic nephropathy and neuropathy.

P.33 | BLOOD OXYGEN SATURATION AND ASSOCIATIONS WITH AUTONOMIC AND PERIPHERAL NEUROPATHY IN DIABETES

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Objectives: Blood oxygen saturation (SpO2) is lower in both people with type 1 diabetes (T1D) and type 2 diabetes (T2D) when compared to healthy individuals. Hypoxia is thought to play a role in the progression of diabetic complications, possibly also neuropathy. This study investigates the association between SpO2 and peripheral and autonomic neuropathy in a population of T1D and T2D patients.

Methods: The study involves participants with T1D and T2D from a cross-sectional study. SpO2 was measured in a supine position with pulse oximetry. Autonomic outcomes were: Cardiovascular autonomic neuropathy (CAN) and bilateral sudomotor dysfunction of hands or feet below age- and sex-stratified electrochemical skin conductance thresholds. CAN was assessed by cardiovascular reflex tests (CARTs): heart rate response to deep breathing, to standing, and to the Valsalva maneuver. Two or three pathological CARTs constituted CAN. Peripheral sensory outcomes were: symmetrical vibration perception threshold assessed by biothesiometry above 25 volts (VPT), loss of bilateral pain sensation by pinprick at the distal dorsal part of the 1st, 3rd and 5th toe, and sural nerve conduction velocity and amplitude assessed by DPNCheck. Odds ratios (OR) were adjusted for age and gender and calculated as a function of a 1% lower SpO2 for T1D and T2D respectively.

Results: We included 1192 patients with a mean age of 58±14 years (mean±SD). 446 (37%) were women, 630 (53%) had T1D, and 562 (47%) had T2D. In T1D and T2D respectively, 90 and 106 (14% vs. 19%) had CAN, and 161 and 267 (26% vs. 48%) had neuropathy by VPT.

Adjusted ORs for outcomes (95% CI, P-value) in T1D and T2D respectively, were 1.1 (0.9-1.3, p=0.54) and 1.1 (1.0-1.3, p=0.01) for CAN and 1.2 (1.0-1.4, p=0.02) and 1.0 (0.9-1.1, p=0.40) for VPT.

Unadjusted ORs for sudomotor function in the T1D group were significant (p<0.001) for both hands and feet, however, significance was lost after adjusting for age and gender in ORs for hands (p=0.07) and feet (p=0.16). ORs are shown in figure 1.

Conclusions: Lower blood oxygen saturation is associated with a higher risk of having cardiovascular autonomic neuropathy in T2D, and a higher risk of having a symmetrical vibration perception threshold above 25 volts in T1D. Whether these associations are causal remains to be determined.

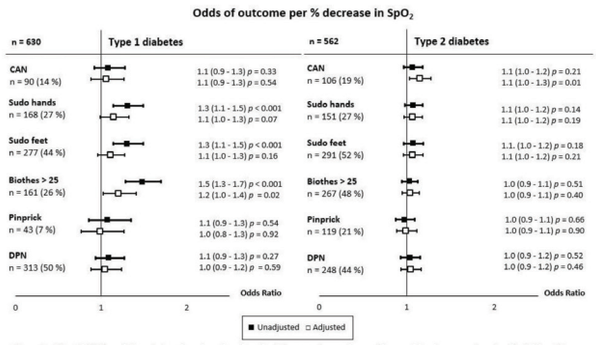

Figure 1 - ORs with 95% confidence intervals and *p*-values from logistic regression analyses with mean blood oxygen saturation (SpO_2) (per % decrease). The total number of events (and %) for each group is shown under each complication. White boxes are adjusted for age and gender.

P.34 | HYPERTRIGLYCERIDEMIA AND CARDIOVASCULAR AUTONOMIC FUNCTION IN PATIENTS WITHOUT DIABETES: A CROSS-SECTIONAL STUDY

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Background and Aims: Cardiac autonomic neuropathy (CAN) increases the risk for cardiovascular mortality. While the independent association of hypertriglyceridaemia with CAN in diabetes is well-known, the impact of hypertriglyceridemia on CAN in patients without diabetes remains unknown. Recent studies reported the effect of hypertriglyceridaemia on peripheral neuropathy in patients without dysglycaemia. The aim of this study was to investigate the effect of hypertriglyceridaemia (TG > 1.7 mmol/L) on cardiovascular autonomic function in patients without dysglycaemia.

Methods: A total of 21 patients with hypertriglyceridaemia, including 8 with mild to moderate hypertriglyceridaemia (TG 1.8 – 5.5 mmol/L) and 13 with severe hypertriglyceridaemia (TG >5.5 mmol/L), with no prior diagnosis of diabetes were recruited with 20 age and gender matched healthy controls. All participants underwent assessment for pulse, blood pressure, lipid profile, renal and liver functions, HbA1c and cardiac autonomic reflex testing (CART).

Results: There was no significant difference in age [48.4 (9.9) vs 40.5 (15.3), p = 0.06], HbA1c (mmol/mol) [37.4 (5.2) vs 35.0 (3.6), p=0.1] and gender distribution (p=0.26) between hypertriglyceridemia and controls. However, BMI (kg/m2) [28.7 (4.1) vs 23.8 (2.4), p=<0.001] and triglyceride concentration (mmol/L) [0.6 (0.3 -1.1) vs 8.1 (3.3-14.7), P<0.001] were higher in patients with hypertriglyceridaemia compared to controls.
Patients with hypertriglyceridaemia had significantly lower deep breathing heart rate variability (beats/minutes) (DB-HRV) [17.0 (10.5 – 23.0) vs 25.5 (19.0 – 31.7), p=0.007], reduced sympathetic balance (LFa/RFa ratio) [1.28 (0.62 – 2.07) vs 1.99 (1.24 – 3.09), p=0.037) and low expiration to inspiration (E-I) ratio [1.13 (1.08 – 1.19) vs 1.22 (1.12 – 1.41), p=0.028] compared to age and gender matched controls. Serum triglyceride concentration correlated negatively with DB-HRV (r= -0.315, p= 0.045) and E-I ratio (r=-0.330, p=0.035) but not with LFa/RFa ratio (r=-0.155, p=0.33). Patients with mild to moderate hypertriglyceridaemia had comparable DB-HRV (p=0.46) and E-I ratio (p=0.28) but lower LFa/RFa ratio [1.04 (0.61-1.69) vs 1.99 (1.24 – 3.09), p=0.021) as compared to controls. Patients with severe hypertriglyceridaemia had significantly lower DB-HRV [15.0 (10.0 – 19.0) vs 25.5 (19.0 – 31.7), p=0.001)] and E-I ratio [1.13 (1.07 – 1.18) vs 1.22 (1.12 – 1.41), p=0.02) but had comparable LFa/RFa ratio (p=0.207) as compared to controls.
Conclusion: Hypertriglyceridaemia is a risk factor for CAN in the absence of diabetes and may increase the risk of cardiovascular mortality. This may provide a potential therapeutic target to ameliorate cardiovascular risk in patients without diabetes.

P.35 | HEART FAILURE IN PATIENTS WITH TYPE 2 DIABETES MELLITUS AND CORONARY ARTERY DISEASE WITH AND WITHOUT CARDIOVASCULAR AUTONOMIC NEUROPATHY

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Objectives: Cardiovascular autonomic neuropathy (CAN) is an established risk factor for cardiovascular disease in patients with diabetes mellitus. However, an association between CAN and heart failure was not yet fully investigated. The aim of this study was to assess the association between CAN and echocardiographic signs of heart failure in the cohort of subjects with type 2 diabetes mellitus and coronary artery disease (CAD).
Methods: We studied 27 patients with type 2 diabetes mellitus and IHD aged 63.4±9.7 years (data are presented as mean±SD), BMI – 30.7±3.7 kg/m2, mean diabetes duration – 6.6±4.0 years, HbA1c – 6.9±1.04%. The patients were admitted to our clinical center with the clinical signs of IHD for the further evaluation and treatment. CAN was diagnosed by the standard battery of tests and the diagnosis was confirmed in the case of 2 abnormal tests found. Systolic and diastolic heart failure were diagnosed by echocardiography. The statistical analysis was performed with the Fisher test for relative values.
Results: CAN was diagnosed in 11 patients studied (40.7%). The age, duration of diabetes and levels of HbA1c did not differ significantly between patients with and without CAN. We found that diastolic dysfunction was more prevalent than systolic dysfunction in the studied cohort of subjects with type 2 diabetes mellitus and IHD. The prevalence of diastolic dysfunction was numerically higher in patients with CAN compared to those without CAN – 54.5 vs. 43.7% while the prevalence of systolic dysfunction was 18.2 vs. 12.5% in patients with and without CAN, respectively. However, the difference in the prevalence of systolic and diastolic dysfunction between groups of patients with and without CAN did not reach the levels of statistical significance, p>0.05, probably due to the small number of patients studied.
Conclusions: We found the high prevalence of CAN along with the myocardial dysfunction with the predominance of diastolic dysfunction in patients with type 2 diabetes mellitus and IHD. The association of diastolic dysfunction and CAN in this cohort of subjects requires further investigation.

P.36 | ASSESSMENT OF DIABETIC AUTONOMIC NEUROPATHY USING PUPILLOMETRY & CORNEAL CONFOCAL MICROSCOPY IN PATIENTS WITH DIABETES & CONCURRENT SEXUAL DYSFUNCTION

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Objective: The prevalence of cardiovascular autonomic neuropathy (CAN) is significantly underestimated and varied due to its insidious presentation, difficulty in accurate measurements and lack of standardised diagnostic criteria. Sexual dysfunction (SD) is another clinical manifestation of diabetic autonomic neuropathy (DAN) which is not commonly self-reported due to its sensitive nature. Pupillometry is a simple, non-invasive technique that can detect an impaired pupillary light reflex (PLR) in patients with CAN-indicative autonomic dysfunction. Corneal confocal microscopy (CCM) can detect small-fibre damage and diabetic peripheral neuropathy (DPN). We aim to assess the utility of pupillometry and CCM for the assessment of DAN in relation to SD in patients with type 1 diabetes (T1DM).
Methods: Thirty T1DM patients underwent detailed clinical assessment of DPN including Cardiac Autonomic Reflex Tests (CARTs), pupillometry, and CCM. Corneal nerve fibre density (CNFD), nerve branch density (CNBD), and nerve fibre length (CNFL) were measured using CCM. Patients have been divided based on 2 abnormal CARTs tests into two groups of CAN (n=15) and no CAN (n=14). The European Male Ageing Study sexual function and The Female Sexual Function Index questionnaires have been used to identify and quantify the presence of SD.
Results: Patients with CAN were significantly older (48.2±13.89vs33±10.13; P=0.002) and had longer duration of diabetes (29.44±14.16vs19.06±10.98;P=0.037) when compared to no CAN. Patients with CAN had a significantly reduced 30:15 ratio (1.15±0.61vs1.41±0.59;P=0.009), pupil diameter in response to scotopic (3.93±0.30vs4.94±0.30;P=0.035), and mesopic low light (3.45±0.20vs4.09±0.20; P=0.048), CNFD (14.95±1.45vs22.53±1.38 ;P=0.002), and CNFL (10.38±0.76vs14.08±0.73;P=0.004) compared to patients without CAN.
Deep-breathing heart rate variability was significantly associated with mesopic low (r=-0.823,P=0.002), mesopic high (r=-0.756,P=0.007), and alternate eyes 4 lux (r=-0.58,P=0.048). In patients with CAN, a 30:15 ratio was also significantly associated with alternate eyes 0 (r=0.626,P=0.039) and 0.04 lux pupil diameter (r=0.624,P=0.04).
The prevalence of patients with SD was 53.3% in CAN and 21.4% in no CAN. In female patients with SD, there were significant associations between LFA/RFA ratio (r=0.782,P=0.038), E/I ratio (r=0.76,P=0.048), 30:15 ratio (r=0.91,P=0.012) and Valsalva ratio (r=0.803,P=0.029) with sexual satisfaction. There was a significant association between alternate eyes 0.04 (r=0.771,P=0.025), 0.4 (r=0.821,P=0.025) and 4 lux pupil diameter (r=0.738,P=0.037) with sexual desire. In male patients with SD, there were no significant associations between sexual function domains and neuropathy assessments.
Conclusions: This study shows that CCM and pupillometry are promising techniques to assess small-fibre damage and detect impaired PLR, which can be used to identify patients at risk of DAN and developing CAN and SD.

P.37 | THE EFFECT OF GLOBAL NOX4 DELETION ON PERIPHERAL NERVE FUNCTION IN A MOUSE MODEL OF DIET-INDUCED OBESITY AND PREDIABETES

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Objectives: Prediabetes affects approximately 541 million individuals worldwide, of which 30% suffer from peripheral neuropathy (PN). Dyslipidemia is an important mediator of prediabetic PN. However, the mecha-

nisms by which dyslipidemia leads to injury are unknown. While dyslipidemia favors a highly oxidizing environment, how dyslipidemia intersects with specific sources of reactive oxygen species (ROS) to produce nerve damage is unclear. NADPH oxidase (Nox) enzymes are dedicated for ROS production, and of the 7 members (Nox1-5, Duox1 and 2), the Nox4 isoform is implicated in nerve degeneration and diabetic PN. Here, our aim was to evaluate whether Nox4 global deletion could improve metabolic parameters and nerve function in the high-fat diet (HFD)-fed mouse model of PN.

Methods: HFD-associated changes in PN were assessed in 12-week-old C57BL/6J male WT and Nox4 knockout (KO) mice. Body weights and pain behaviors were measured monthly. After 24 weeks of HFD, metabolic and PN phenotyping as well as western blotting were performed.

Results: Although KO mice gained weight at a slower pace compared to WT mice, both HFD and KO-HFD mice were significantly heavier than their respective controls at study termination. Both HFD and KO-HFD mice also had impaired glucose tolerance. While Nox4 deletion ameliorated thermal sensitivity after 12 weeks of HFD, this effect was abolished at study termination. Additionally, Nox4 deletion had no effect on large fiber function at early and later disease stages. We next determined whether Nox4 deletion triggered a compensatory induction of other Nox isoforms and found a significant increase in Nox2 protein expression in KO mice with or without HFD relative to WT mice on a standard diet.

Conclusion: These results suggest that increased Nox2 expression may mediate HFD-induced nerve dysfunction in the absence of Nox4. Thus, therapies aimed at normalizing Nox levels rather than completely silencing them may be promising therapeutic approaches for PN treatment.

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P.38 | EFFECT OF B VITAMINS ON NEURITE REGENERATION IN A 3D CO-CULTURE MODEL OF NEURODEGENERATION

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Objectives: Peripheral neuropathy (PN) is the most common disorder of the peripheral nervous system in adults caused by different aetiologies with diabetes as the most common cause [1,2]. Diabetic peripheral neuropathy (DPN), affecting 50% of adult diabetics, results in pain, paraesthesia, and sensory loss, negatively impacting quality of life [3]. There are currently no pharmacological treatments to reverse DPN [4]. The neurotropic B vitamins (B1, B6 and B12) play an essential role in the health of the nervous system and have therefore been suggested to have the potential to treat PN. The aim of our study was to determine the regenerative capacity of vitamin B1, B6 and B12 following neurite degeneration in vitro and explore the mechanisms through which these effects occur.

Methods: Following the development of a novel 3D-engineered co-culture degeneration model, we tested the regenerative capacity of vitamin B1 (thiamine hydrochloride), B6 (pyridoxal hydrochloride) and B12 (cyanocobalamin). This involved seeding NG108-15 cells on top of a collagen matrix containing SCL1.4/F7 Schwann cells which were then insulted with hydrogen peroxide to induce degeneration. Neurite length was analysed using βIII-Tubulin immunostaining.

Results: Treatment with B vitamins; B1, B6 and B12 individually or in combination were found to extend neurite length significantly in comparison to a no treatment control. This significantly beneficial effect on neurite extension was seen with both pre- and post-insult vitamin B treatment.

Conclusions: In conclusion, we have established a novel model of neurodegeneration which can be used to explore the neuromodulatory effects of compounds. This study provides evidence that the B vitamins have a beneficial neurite regenerative effect in vitro. Further in vitro assays exploring metabolism and cell phenotype are currently being conducted to decipher the mechanistic properties of these B vitamins.

References:

[1] Nold CS, Nozaki K. Peripheral neuropathy: clinical pearls for making the diagnosis. JAAPA. 2020;33(1):9-15.

[2] Callaghan BC, Price RS, Feldman EL. Distal symmetric polyneuropathy: a review. JAMA. 2015;314(20):2172-2181.

[3] Hicks, C.W. & Selvin, E. Epidemiology of Peripheral Neuropathy and Lower Extremity Disease in Diabetes. Curr Diab Rep 2019;19, 86.

[4] Gandhi M, Fargo E, Prasad-Reddy L, Mahoney KM, Isaacs D. Diabetes: how to manage diabetic peripheral neuropathy. Drugs Context. 2022; 14;11.

P.39 | THE ANTI-DIABETIC DRUG TROGLITAZONE ACTIVATES TRPA1 IN SENSORY NEURONS

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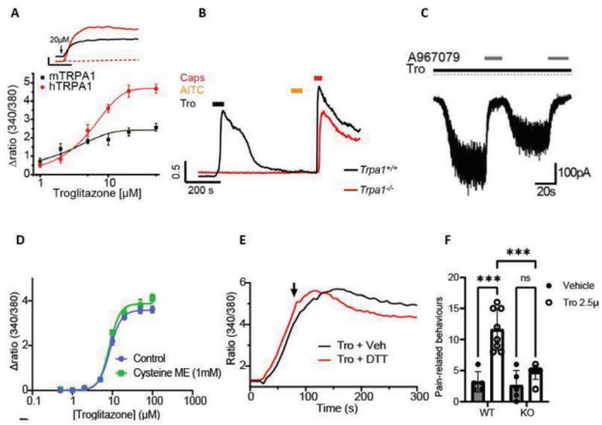
Objectives: Peroxisome proliferator-activated receptors (PPARs) are ligand-activated transcription factors that regulate glucose and lipid metabolism. Troglitazone, a synthetic thiazolidinedione (TZD) PPARγ agonist, has been used clinically in the treatment of type-2 diabetes to lower blood glucose levels by increasing insulin sensitivity. PPARγ is activated by the endogenous metabolites 15-deoxy-Δ12,14-PGJ2 (15d-PGJ2) and 4-hydroxynonenal, which are also electrophilic endogenous agonists of the transient receptor potential ankyrin-1 (TRPA1) nociceptive ion channel. Pharmacological inhibition and activation of TRPA1 effectively reduces mechanical and cold hypersensitivities in experimental models of neuropathic pain; consequently, TRPA1 has been widely pursued as a novel analgesic target. The structurally unrelated PPARγ agonists 15d-PGJ2 and the TZD pioglitazone were shown to act as analgesics in models of neuropathic pain. Hence, the effects of troglitazone on TRPA1 were investigated here.

Methods: The electrophysiological method of voltage clamp and measurements of intracellular Ca2+ concentration ([Ca2+]i) were used to elucidate troglitazone-dependent effects on TRPA1 in vitro. In vivo measurements included the assessment of nocifensive behaviour in mice upon intraplantar injections of troglitazone.

Results: Troglitazone evoked concentration-dependent Ca2+-influx responses in TRPA1-expressing Chinese hamster ovary (CHO) cells, but not in untransfected CHO cells. Furthermore, it evoked [Ca2+]i-responses in isolated mouse dorsal root ganglion (DRG) neurons natively expressing TRPA1, which were reversibly inhibited by the TRPA1 antagonist A967079, and were absent in DRG neurons from TRPA1-deficient mice. The presence of excess cysteine or cysteine-methylester did not inhibit the agonist effect of troglitazone. The evoked [Ca2+]i-responses were not affected by the cysteine reducing agent dithiothreitol either. These observations show that the agonist effect of troglitazone is independent of covalent modification or oxidation of cysteine residues. Intraplantar injections of troglitazone evoked pain-responses in wild-type mice, but not in Trpa1-/- mice.

Conclusions: Taken together, the results demonstrate that the TZD PPARγ agonist troglitazone is a non-covalent agonist of human and mouse TRPA1 in vitro, acting via a mechanism independent of cysteine modification. In contrast to the very potent effect on PPARγ in nanomolar range, activation of TRPA1 requires micromolar concentrations. Since the steady-state plasma concentration of troglitazone is in the micromolar range, it is likely that patients might have experienced TRPA1-dependent effects. In mice, topical administration of troglitazone provoked acute pronociceptive TRPA1-mediated responses.



P.40 | DIFFERENTIAL EFFECTS ON CORNEAL NERVE FIBER REGENERATION WITH DIFFERENT GLP-1 RECEPTOR AGONISTS IN CHILDREN AND ADULTS WITH OBESITY

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Aim: Glucagon-like peptide-1 receptor (GLP-1R) agonists are approved for the treatment of diabetes and obesity, but may also have a beneficial effect on the central and peripheral nervous system. Corneal Confocal Microscopy (CCM) has been used to show early nerve fiber regeneration in patients with diabetes and obesity after bariatric surgery.
Methods: Nineteen adults with obesity (102.35±23.21 kg) treated with s.c. Semaglutide 1.0mg weekly and 5 children with obesity (101.86±7.83 kg) treated with daily s.c. Liraglutide 3.0mg, underwent CCM to quantify corneal nerve fiber density (CNFD), branch density (CNBD) and length (CNFL) at baseline and after 3 months of Liraglutide and 6 months of Semaglutide.
Results: There was a significant reduction in body weight (-9.16±5.8 kg, P<0.0001) and a non-significant improvement in CNFD (1.041±5.116, P=0.39) and CNFL (MD 0.61±3.19, P=0.414) with no change in CNBD (MD -0.75±20.69, P=0.88), after 6 months of treatment with Semaglutide. Despite no change in weight (101.86±7.83 vs. 103.28±7.26, P=0.14) or body fat percent (51.32±4.43 vs. 48.46±2.5, P=0.31), CNFD (+5.92±3.39, P=0.017) and CNFL (+2.16±1.69, P=0.046) increased with no change in CNBD (-0.45±13.43, P=0.944) in children treated with Liraglutide.
Conclusion: Corneal confocal microscopy identifies early corneal nerve regeneration after 3 months of Liraglutide treatment in obese children, but minimal corneal nerve regeneration after 6 months of Semaglutide treatment, despite substantial weight loss in obese adults. This may represent differential effects of GLP-1 therapy or less benefit on nerve regeneration in adults.

P.41 | ALLEVIATION OF AUTONOMIC DYSFUNCTION MEASURED AS PRESSURE PAIN SENSITIVITY AT THE STERNUM IMPROVES EMPOWERMENT AND QUALITY OF LIFE IN TYPE 2 DIABETES: A RANDOMIZED TRIAL

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Objectives: Autonomic nervous system (ANS) regulates many bodily functions including glucose metabolism. Dysfunction of ANS (ANSD) disrupts glucose metabolism. An elevated pressure pain sensitivity (PPS) of the chest bone is linked to ANSD. A non-pharmacological PPS-biofeedback guided treatment based on: 1) daily PPS measurement for compliance enhancement and measurement of progression in the treatment, 2) daily non-noxious sensory nerve stimulation with the aim to reduce an elevated PPS, and 3) ongoing professional surveillance for proactive restoration of PPS, reduces PPS and HbA1c and with internal correlation between the two. ANSD, measured as an elevated PPS (i.e., ≥ 60 arbitrary units) is prevalent in 65% of people with type 2 diabetes (T2D).
Methods: In a single center randomized controlled trial we included individuals with T2D from general practice, with HbA1c ≤ 75 mmol/mol, PPS ≥ 60, BMI < 40, and age 18 to 75 years old. Participants were randomized to the non-pharmacological intervention or treatment as usual. The endpoints were evaluated with 8 validated questionnaires. Here we investigated if a reduction in PPS achieved by this self-managed intervention leads to improvement in empowerment (DES-SF), Diabetes Treatment Satisfaction (DTSQ), quality of life (QOL) (WHO-5), degree of depression (MDI), clinical stress signs (CSS), self-reported health (SF-36), and quality of sleep.
Results: We included 144 participants in the trial. Mean compliance rate for daily home PPS measurement was 90 %. Active intervention compared to control induced a reduction of PPS (p<0.0001), improved personal empowerment (p=0.004), DTSQ (p=0.001), QOL (p=0.056), SF-36 physical health (p=0.003), and quality of sleep (p=0.003). The remaining 3 questionnaires: CSS, MDI and SF-36 mental health improved significantly in both groups, but in-significantly between groups. Personal empowerment correlated significantly to DTSQ, QOL, MDI, CSS, SF-36 mental health, and PPS (all correlation coefficients > 0.2, all p<0.05), but not to HbA1c.
Conclusions: The non-pharmacological intervention including daily home measurements of PPS and sensory nerve stimulation was found to be associated with a high rate of compliance, to improve empowerment, treatment satisfaction, QOL, self-reported health and sleep. We conclude that the proposed intervention may be an important supplement to conventional therapy for T2D.

P.42 | NEUROMUSCULAR ELECTRICAL STIMULATION FOR THE TREATMENT OF DIABETIC SENSORIMOTOR POLYNEUROPATHY: A PROSPECTIVE, COHORT, PROOF-OF-CONCEPT STUDY

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Objectives: The objective of this single-centre, prospective, cohort, proof-of-concept study was to assess a potential efficacy signal, safety and feasibility of a neuromuscular electrical stimulation (NMES) device as an adjunct to standard of care in patients with diabetic sensorimotor polyneuropathy (DSPN).
Methods: Adults with DSPN (Michigan Neuropathy Screening Instrument (MNSI) questionnaire score of ≥7) were eligible. The target sample size was 20 participants, which was deemed realistic to achieve in the setting and to provide pilot data. The NMES device investigated was the Revitive (Actegy Ltd, England), which is a CE marked, class IIa medical device. The treatment protocol was at least one daily 30-minute session for 10 weeks. The primary outcome measure was lower limb nerve conductivity assessed using a nerve conduction study of the sural, superficial peroneal, common peroneal and tibial nerves at 10 weeks. Nerve conduction parameters measured included conduction velocity, sensory nerve action potential (SNAP) amplitude, compound muscle action potential ampli-

tude (CMAP) and minimum F wave latency. Secondary outcome measures included haemodynamics, quality of life, adverse events (AEs) and adherence. Paired parametric data were analysed using t-test statistics and paired non-parametric data were analysed using Wilcoxon-signed rank tests. Except for when multiple hypothesis tests were performed and a Bonferroni correction was used, statistical significance was p≤0.05.
Results: Twenty participants completed the trial. There were significant differences in the sural nerve SNAP amplitude and conduction velocity (both p<0.001), superficial peroneal nerve SNAP amplitude (p=0.001) and conduction velocity (p=0.002), common peroneal nerve conduction velocity (p=0.004) and tibial nerve CMAP amplitude (p=0.013) after 10 weeks. Time-averaged mean velocity and volume flow of the superficial femoral artery differed significantly during NMES device use compared to rest at Week 0 and Week 10 (p<0.001, except Week 10 volume flow where p=0.003). There were significant differences in foot flux during NMES device use compared to rest at Week 0 (p<0.001) and Week 10 (p=0.002). There was a significant difference in MNSI scores (p=0.028) at 10 weeks. Three AEs were reported, none of which were classified as related to the device and 15 participants (75%) adhered to the treatment protocol.
Conclusions: After 10 weeks, a NMES device as an adjunct to standard of care significantly increased lower limb nerve conductivity in people with DSPN. NMES is a potentially disease-modifying intervention for DSPN, but further high-quality research in the form of a randomised, sham-controlled trial is needed to better understand its effects.

P.43 | EARLY CORNEAL NERVE LOSS IN CHILDREN WITH MELANOCORTIN 4 RECEPTOR (MC4R) GENE MUTATION RELATED OBESITY

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Background: Obesity is highly prevalent worldwide, particularly in the MENA region. Whilst simple obesity has a variable genetic and environmental basis, syndromic and non-syndromic monogenic obesity has a strong genetic component. Melanocortin 4 receptor (MC4R) mutations are the commonest cause of monogenic obesity. MC4R also regulates neuropathic pain pathways via JNK signaling after nerve injury.
Methods: Five children with the rare MC4R gene mutation underwent corneal confocal microscopy (CCM) and were compared to healthy controls. Corneal nerve fiber density (CNFD), corneal nerve branch density (CNBD), and corneal nerve fiber length (CNFL) were quantified manually using CCMetrics software.
Results: Children with MC4R gene mutations compared to controls aged 8.43±1.5 vs. 11.6±1.14 years, weighing 76.32±20.54 vs. 44.44±12.09 kg, with 53.46±4.74 % body fat without neuropathic symptoms and normal VPT (3.94±2.22 V) had non-significantly lower CNBD (40.9±20.5 vs. 62.9±20.1, P= 0.344) and CNFL (20.37±2.01 vs. 22.63±4.5, P= 0.334), with no difference in CNFD (29.79±4.0 vs. 30.62±7.0, P= 0.822).
Conclusion: Young children without neuropathic pain and normal vibration perception have evidence of early corneal nerve loss, indicative of sub-clinical neuropathy. Further studies are required to understand how mutations in the MC4R lead to corneal nerve loss.

P.44 | EARLY CORNEAL NERVE LOSS IN CHILDREN WITH OBESITY AND TYPE 2 DIABETES

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Background: Childhood obesity is highly prevalent in the MENA region and may be associated with sub-clinical neuropathy.
Methods: Children with obesity with normal glucose tolerance (NGT), impaired glucose tolerance (IGT) and Type 2 diabetes Mellitus (T2DM) and healthy controls (HC) underwent body composition analysis, assessment of vibration perception threshold (VPT), monofilament sensitivity and corneal confocal microscopy (CCM) to quantify corneal nerve fiber density (CNFD), branch density (CNBD), and length (CNFL).
Results: Sixty-nine children with obesity (NGT (n=40), IGT (n=13) and T2DM (n=16)) aged 14.0±2.9 years were compared to 20 healthy controls (HC). There was no difference in VPT or monofilament sensitivity between groups. There was no difference in CNFD, CNBD or CNFL between obese children with NGT or obese children with IGT compared to HC and obese children with IGT compared to obese children with NGT. CNBD (34.4(32.3-43.8) vs. 48.9(43.8-66.3), P=0.04) was significantly lower in obese children compared to healthy controls. Children with hidden obesity had a significantly lower CNFD (27.8±7.4 vs. 32.8±5.6, P=0.05) with no change in CNBD and CNFL compared to solidly built children. CNFL was non-significantly lower (18.0±4.2 vs. 20.5±4.5, P=0.094) in obese children with T2DM compared to HC and obese children with T2DM had lower CNFD (26.8±6 vs. 30.4±7.5, P=0.067) and CNFL (18±4.2 vs. 21.3±5.8, P=0.027) compared to obese children with NGT.
Conclusion: Children with hidden obesity and especially obese children with T2DM have evidence of early corneal nerve loss, indicative of sub-clinical neuropathy.

P.45 | CORNEAL CONFOCAL MICROSCOPY AS A MARKER TO MONITOR THE PROGRESSION OF SMALL FIBRE NEUROPATHY IN PEOPLE WITH AND WITHOUT CARDIAC AUTONOMIC NEUROPATHY

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Objectives: Currently the diagnosis of CAN is made using cardiac autonomic reflex tests (CARTs), however these tests are shown to have low specificity and sensitivity, as well as limited availability. It is important to identify the measures that predict the development and progression of CAN. This study aims to assess the use of corneal confocal microscopy (CCM) as a tool to monitor both the development and progression of CAN.
Method: 105 patients with diabetes mellitus underwent assessment at baseline and follow up over a period of one to five years. Assessments included HbA1C, lipid profile and neuropathy assessments, including CARTS, neuropathy symptom profile, neuropathy disability score, Quantitative Sensory Testing, nerve conduction studies, vibration perception threshold and corneal confocal microscopy (CCM).
Patients were diagnosed with CAN if they had 2 or more abnormalities in CARTs.

Results: Patients without CAN at baseline who went on to develop CAN in the follow up period were significantly older (years) (49.16±16.22 vs 38.67±11.99, P=0.01) and had a higher HbA1c (mmol/mol) (65±15 vs 57±19.01, P=0.01), as well as lower E/I (1.28±0.13 vs 1.38±0.13, P=0.006) and Valsalva ratio (1.42±0.22 vs 1.53±0.23, P=0.03) at baseline compared to those who did not develop CAN.
There was no significant difference in CCM measures between those who did and did not develop CAN. Corneal nerve branch density (CNBD) was significantly lower at follow up in patients both with (71.51±32.57 vs 40.65±23.51, P=0.013) and without (84.49±38.3 vs 51.61±31.1, P=0.028) CAN at baseline. Corneal nerve fibre length (CNFL) deterioration was significantly higher in patients without baseline CAN (24.96±7.78 vs 18.39±6.06, P=0.003) compared to those with baseline CAN (22.27±5.71 vs 17.26±6.17, P= 0.083). Patients with neither baseline nor follow up CAN showed a significant deterioration of DB-HRV (30.56±7.73 vs 27.72±10.88, P= <0.001), E/I ratio (1.34±0.14 vs 1.29±0.16, P= <.001) and 30:15 ratio (1.46±1.01 vs 1.26±0.22, P= 0.002), but in patients with CAN at both baseline and follow up, only the Valsalva ratio (3.33±16.84 vs 1.32±0.49, P= 0.019) was lower. There was no significant change in the neuropathy symptom profile, neuropathy disability score, vibration perception threshold and thermal thresholds.
Conclusion: CCM measures do not predict the development of CAN, but patients without CAN at baseline have evidence of increased corneal nerve degeneration compared to those with CAN at baseline. Older age, higher HbA1c, lower E/I and Valsalva ratio predict the development of CAN.

P.46 | RELATION BETWEEN ADVANCED GLYCATED END PRODUCTS AND SYMPATHETIC ACTIVITY IN OVERWEIGHT PATIENTS WITH OBSTRUCTIVE SLEEP APNOEA SYNDROME

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Objectives: High blood levels of advanced glycation end products (AGE) were reported in patients with an obstructive sleep apnoea syndrome (OSAS). In these patients sympathetic activity was shown to be enhanced but the role of AGE in vago-sympathetic balance is not known. Skin autofluorescence (sAF) provides an estimate of AGE tissue accumulation. Artery stiffness (AS), an index for atherosclerosis, is a well-known marker for cardiovascular risk. Pulsatile stress (pulse pressure x heart rate), an index for sympathetic activity, is likely to contribute to macro and microvascular complications. The aims of this study were to examine the relation between sAF and AS and indexes of autonomic cardiovascular control in overweight patients with OSAS.
Methods: We included 112 overweight patients, aged 49.1±14.6 yrs, 80 women and 32 men, without cardiovascular disease and renal failure, 42 with type 2 diabetes. OSAS was confirmed in all the patients using nocturnal polygraphy, and was either mild, moderate or severe (14/25/73 patients, respectively). sAF was measured (AGE-Reader®). AS was evaluated using CAVI (cardiac-ankle vascular index, VaSera VS-1000®). Heart rate (HR) variations were measured during a one-minute deep-breathing test (cardiovagal control). Pulsatile stress was calculated at rest using SphygmoCor®, and before the deep-breathing test and before a night hypopneic episode using CAVI.
Results: Compared to non diabetic patients, patients with diabetes were older (p<0.0001) and had higher sAF (p=0.007) and AS (p<0.0001) but not significantly different pulsatile stress. In the total population, 29% had an elevated AS (>8), sAF and AS correlated strongly with age (r=0.407 and 0.360, p<0.0001 for both). sAF correlated weakly with AS (r=0.155; p=0.06 after adjustment for age) and the apnea-hypopnea index (r=0.165). sAF correlated with pulsatile stress measured at rest, before deep breathing and before an hypopnoea (r=0.267, p=0.055; r=0.241, p=0.04; 0.240, p<0.02, respectively), but not with HR variations during the deep-breathing test.
Conclusions: In overweight patients with OSAS, AGE augmentation, probably favored by the oxidative stress, is associated weakly with AS and more strongly with sympathetic activity, and might thus contribute to their increased cardiovascular risk. The role of AGE in sympathetic activation deserves being examined in further studies.

P.47 | CARDIAC AUTONOMIC NEUROPATHY AND PROGRESSIVE RENAL DECLINE IN PATIENTS WITH TYPE 1 DIABETES: A 15-YEAR FOLLOW UP STUDY

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Autonomic dysfunction may play a role in the pathogenesis of diabetic nephropathy through a relative increase in sympathetic tone, leading to proteinuria, nocturnal hypertension and declining renal function.
Aims: To examine the relationship between cardiac autonomic neuropathy (CAN) and progressive renal decline in patients with T1DM.
Methods: 36 subjects with T1DM (31 normoalbuminuria and 5 microalbuminuria) underwent assessment for CAN using cardiovascular reflex testing as per the O'Brien's criteria during baseline visits performed from 2007-2010. Cardiac autonomic neuropathy was defined as >3/5 abnormal reflex tests. Progressive renal decline was defined as decline in eGFR and/or incident advanced CKD (stage>3). Association with baseline CAN was assessed by logistic regression adjusted for baseline urine ACR, Hba1c and ACEi/ARBs use. Additional sensitivity analysis was performed by adjusting for all variables in the model as well as retinopathy separately.
Results: Among the 36 subjects [18 female, mean age 53.4(12.8)years and duration of diabetes 34.6(10.9)years] 12(33.3%) had baseline CAN, 13(36.1%) had progressive decline in eGFR up to 15 years follow-up. Renal decline occurred in 7(58.3%) of the 12 patients with CAN and 6(25.0%) in those without. Baseline CAN was strongly associated with the odds of renal decline [adjusted odds ratio 31.6(95%CI 1.3:796.0); p=0.01]. Results did not substantially change after additionally adjusting for retinopathy.
Conclusions: In this relatively small but carefully phenotyped study, CAN was a strong independent predictor of the long-term risk of renal decline in T1DM. Future larger studies are needed to confirm these findings and to explore the mechanisms by which CAN leads to renal decline.

P.48 | IS RECOVERY OF CARDIOVASCULAR AUTONOMIC NEUROPATHY POSSIBLE IN TYPE 1 DIABETES? A 5-YEAR FOLLOW-UP STUDY

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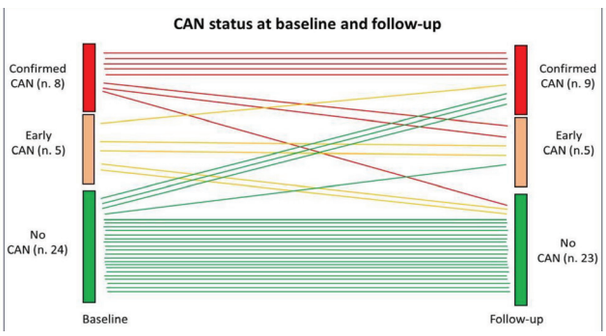
Objectives: This is a longitudinal retrospective study aimed at evaluating whether a diagnosis of cardiovascular autonomic neuropathy (CAN) in subjects with type 1 diabetes (T1D) is reversible and the factors associated with change of CAN status.
Methods: We retrospectively evaluated 37 participants with T1D (at baseline: age 39.1±12.9 years, diabetes duration 24.0±13.4 years, HbA1c 66.6±22.1 mmol/mol), followed for 4.74±1.8 years. We performed at baseline and follow-up four cardiovascular reflex tests (CARTs) and assessed symptoms and signs of diabetic polyneuropathy (DPN), clinical history and variables. We defined early and confirmed CAN in presence

of 1 or 2 abnormal cardiovascular reflex tests (CARTs), respectively. CAN regression was defined as an improvement in CAN stage (from early to normal or from confirmed to early or normal) and CAN progression as the change from normal to early or from early to confirmed CAN.
Results: At baseline 5 (14.7%), 8 (21.6%), and 24 participants (64.9%) had early CAN, confirmed CAN and no CAN, respectively; at follow-up, 5, 9, and 23 participants had early CAN, confirmed CAN and no CAN, respectively with one more participant with confirmed CAN (24.3%). In the whole population, among neuropathy measures, only deep breathing test (P<0.05) and vibration perception thresholds (P<0.001) deteriorated significantly from baseline to follow-up. At follow-up, CAN regression occurred in 5 (13.5%), CAN progression in 5 (13.5%), CAN status was unchanged in 27 participants (73%). CAN progression was associated with higher body mass index (BMI) at baseline compared to the other groups (P<0.05) and at follow-up compared to CAN regression (27.6±2.02 Vs. 21.9±1.4 Kg/m2, P<0.001), with higher cholesterol at baseline compared to CAN unchanged (P<0.05), with higher triglycerides at baseline and follow-up compared to CAN regression and CAN unchanged, respectively (P<0.05), and with lower eGFR at follow-up compared with CAN unchanged (P<0.01). The association of higher BMI with CAN progression persisted after ANOVA adjustment for age and sex (P<0.05). No differences were found between CAN progression and CAN unchanged.
Conclusions: In this well characterised population with T1D, we observed at 5 year follow-up an increase in overall CAN prevalence and a degree of CARTs deterioration lower than expected, with both progression and regression of CAN status. BMI seems to be the best predictor of CAN progression. The small dimensions of our population can have prevented the identification of clinical variables associated with CAN recovery.



P.49 | CARDIOVASCULAR AUTONOMIC NEUROPATHY IS A RISK FACTOR OF ARTERIAL STIFFNESS IN TYPE 2 DIABETES

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Aim: To test the hypothesis that cardiovascular autonomic neuropathy (CAN) in Type 2 diabetes is a risk factor of arterial stiffness.
Methods: In this cross-sectional study, 114 patients (57 males, 57 females) with type 2 diabetes mellitus were randomly selected from the diabetes clinic of Nazareth Hospital, Daegu, Korea, between January in 2022 and September in 2022, Subjects, whose mean age was 56.6±1.2 years, were tested for CAN using five non-invasive tests of autonomic function by Ewing`s method and brachial-ankle pulse wave velocity (baPWV) measurement as an index for arterial stiffness.
Results: CAN was found in 30/114 (26.3%) patients. In comparison with patients without CAN, patients with CAN had significantly higher age, triglyceride, hypertension, pulse pressure, fasting c-peptide, CAN score, and baPWV. CAN correlated positively with baPWV (r = 0.234; p = 0.012). After adjustment for age, patients with CAN still had significantly higher baPWV than without CAN (p = 0.03).
Conclusions: CAN is associated with baPWV. Our study suggests that CAN is a risk factor of arterial stiffness in patients with type 2 diabetes. This may help to explain the excess atherosclerosis seen in diabetic patients with CAN.
Key words: cardiovascular autonomic neuropathy; arterial stiffness; type 2 diabetes; pulse wave velocity.

P.50 | COMPARISON OF EACH TEST OF CARDIOVASCULAR REFLEX TESTS IN THE DIAGNOSIS OF DIABETIC CARDIOVASCULAR AUTONOMIC NEUROPATHY

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Objectives: Cardiovascular autonomic neuropathy(CAN) is associated with increased mortality and morbidity. Tests for diabetic cardiovascular autonomic neuropathy (DCAN), assessed by the five standard cardiovascular reflex tests(CART) according to Ewing's protocol. We investigated the sensitivity and specificity of CART in CAN in peoples with Type 2 diabetic mellitus.
Methods: Data of 884 diabetic patients undergoing CAN assessment was collected retrospectively from 8 hospitals in Korea. Patients' biodata were recorded, and electrocardiography (ECG) and autonomic nervous system function tests performed to aid in the diagnosis of CAN. The final CAN diagnosis was based on the ECG-cQT interval and Ewing's test in which heart rate variation (HRV) values were evaluated through deep-breathing, lying-to-standing, sustained handgrip test and Valsalva tests. We analyzed the sensitivity and specificity of CART and ECG-cQT interval in CAN in peoples with Type 2 diabetic mellitus.
Results: We included 884 patients, with a small proportion of T1DM patients (17). The number of the diabetes without CAN group (non-CAN group) was 106 (12%) while that of diabetes with CAN group (CAN group) was 778 (88%). The mean age of the non-CAN group was 56.77±10.78 years old and the CAN group was 62.38±9.90 years old (P<0.0001). The CAN group had a significantly longer DM duration (13.69±4.21 years vs 12.65±3.97 years, P=0.0161)
The analysis of the sensitivity of each test of CART were E:I_score(69.3%), Valsalva score(24.5%), Posture score(20.7%), BP score(12.2%), Handgrip score(56.0%). The analysis of area under the curve(AUC) of each test of CART were E:I_score(0.85), Valsalva score(0.62), Posture score(0.60), BP score(0.56), Handgrip score(0.78).
Conclusions: CARTs provide key information regarding the sympathetic and parasympathetic modulation of the cardiovascular system and a clinically relevant method for the diagnosis of CAN.

P.51 | TRANSCUTANEOUS VAGAL NERVE STIMULATION FOR TREATING GASTROINTESTINAL SYMPTOMS IN PEOPLE WITH DIABETES: A RANDOMIZED, DOUBLE-BLIND, SHAM-CONTROLLED, MULTICENTRE STUDY

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Objectives: Gastrointestinal autonomic neuropathy often causes debilitating symptoms in people with diabetes and available treatment options have limited efficacy and/or many side effects. Transcutaneous vagal

nerve stimulation has in preclinical experiments and healthy subjects been shown to increase gastric motility, and in two open-label studies in patients with gastroparesis it has shown promising reductions of gastrointestinal symptoms. We investigated the effect of transcutaneous vagal nerve stimulation on gastrointestinal symptoms in people with diabetes and symptomatic gastrointestinal autonomic neuropathy.

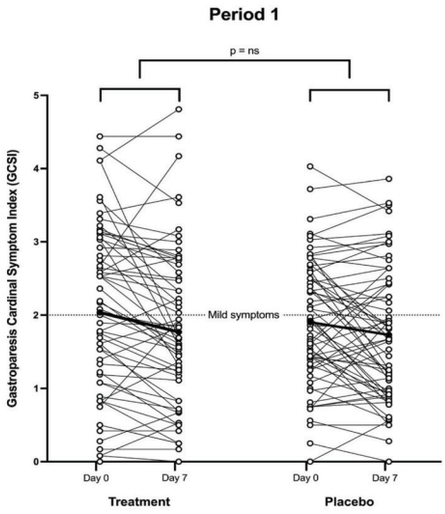
Methods: In a multi-centre, randomized, double-blind, sham-controlled study, adults with type 1 or type 2 diabetes and verified symptomatic gastrointestinal autonomic neuropathy were randomly assigned 1:1 to receive either self-administered bilateral cervical vagal nerve stimulation at a frequency of 5kHz or sham stimulations for two successive periods: One week stimulating 4 times daily followed by eight weeks with stimulation twice daily. Gastrointestinal symptoms were evaluated using the validated questionnaires Gastroparesis Cardinal Symptom Index and Gastrointestinal Symptoms Rating Scale before, during and after each period.

Results: Randomized participants were included in the modified intention-to-treat analysis, when at least one stimulation dose was administered. Of the 131 participants included in the analysis, 63 received active and 68 received sham stimulation. Both active and sham stimulation slightly decreased symptoms in both periods of stimulation, however there was no significant difference between treatments as seen in Table 1. The Gastroparesis Cardinal Symptom Index scores before and after stimulation in period 1 are shown for each participant in Figure 1.The vagal nerve stimulation was generally well-tolerated, and no serious adverse events were caused by the treatment.

Conclusion: Transcutaneous cervical vagal nerve stimulation, regardless of the duration and intensity, did not prove to be effective in reducing gastrointestinal symptoms in people with diabetes and symptomatic gastrointestinal autonomic neuropathy.

	Active stimulation	Sham stimulation	*p*-value
Period 1			
Gastroparesis Cardinal Symptom Index	-0.25 (-0.56 – 0.00)	-0.11 (-0.56 – 0.22)	0.38
Gastrointestinal Symptoms Rating Scale	-0.36 (-0.71 – 0.08)	-0.31 (-0.67 – 0.02)	0.89
Period 2			
Gastroparesis Cardinal Symptom Index	-0.39 (-0.88 – 0.07)	-0.25 (-0.61 – 0.03)	0.44
Gastrointestinal Symptoms Rating Scale	-0.26 (-0.70 – 0.05)	-0.32 (-0.66 – 0.19)	0.78

Data are presented as medians with interquartile ranges in parentheses



P.52 | CORNEAL NERVE SENSITIVITY: EARLY DETECTION OF DIABETIC PERIPHERAL NEUROPATHY (DPN)

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Objectives: Density of sub-epithelial corneal nerves have been promoted as a surrogate marker for early diagnosis of DPN. As an alternative, we developed an objective functional test of corneal sensitivity (Invest Ophthalmol Vis Sci. 2016, 57: 2412-9). In this study we sought to verify this methodology in human subjects with DPN.

Methods: Following verification of DPN, response to a drop of isotonic vs. 5% NaCl (hypertonic) solution was recorded (primary endpoint). Ratio of time that the eyelids were closed from 10s to 60s following application of each solution were quantified using an image analysis program.

Results: We examined 28 subjects with type 2 diabetes and 16 age-matched controls. The presence of DPN in diabetes vs. control subjects was verified by completing the Michigan Neuropathy Screening Instrument questionnaire and lower extremity examination including amplitude and conduction velocity of the sural nerve using DPNCheck. The presence of eye discomfort was examined for each subject by completing the DEQ5 and Ocular Surface Disease Index (OSDI) questionnaires. DPN was confirmed in all subjects with diabetes as well as presence of mild to moderate ocular surface disease. Two control subjects had mild ocular surface disease but no peripheral neuropathy. Cochet-Bonnet filament esthesiometer examination revealed significant corneal sensitivity impairment in subjects with diabetes vs. control subjects (5.64 ± 0.08 vs. 5.97 ± 0.03 cm, respectively). Corneas of subjects with diabetes were also significantly less sensitive vs. controls to application of hypertonic solution (0.18 ± 0.01 vs. 0.29 ± 0.04, (ratio of time eyelids were closed) respectively). Data is presented as mean ± S.E.M. There was no difference in sensitivity to the isotonic solution between diabetes and control subjects.

Conclusion: Corneal nerves that penetrate the epithelium and sprout near the surface of the eye and are the first to exhibit the "dying-back" phenomenon associated with DPN. Clinical evaluation of the sensitivity of these nerves could be a valuable method for early detection of DPN.

P.53 | PROPOSAL OF A NEW OBJECTIVE DIAGNOSTIC CRITERION WITH VERSATILITY FOR DIABETIC PERIPHERAL NEUROPATHY

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Objectives: According to the Toronto consensus, the confirmed diagnosis of diabetic polyneuropathy (DPN) requires a nerve conduction study (NCS) or authorized examinations for small fiber neuropathy. However, these tests are often complicated, require expensive equipment, and lack standard interpretation, resulting in poor versatility. An objective diagnostic method with versatility should be established. In this study, we propose a diagnostic criterion using the DPNCheck, a simple NCS device, and the coefficient of variation of RR intervals on electrocardiograms (CVR-R).

Methods: The study design was a single-center retrospective cross-sectional trial. The subjects were 174 patients with diabetes admitted for glycemic control: 102 males, mean body mass index of 25.5 ± 6.0, and mean HbA1c of 9.8 ± 2.3%. Each patient underwent both conventional NCS (CNCS) and NCS using DPNCheck. To calculate CVR-R, electrocardiograms were recorded for 1 minute during rest or deep breathing. Based on the CNCS, the severity of DPN was classified into five stages according to Baba's classification. The group with DPN severity stages 2 to 4 was defined as the DPN-positive group, and variables contributing to the diagnosis of the DPN-positive group were identified using a logistic regression analysis with the forced entry. The input variables were the values of the DPNCheck, age, and CVR-R. Subsequently, receiver operating characteristic curve (ROC) analysis was performed for the significant explanatory variables to obtain the optimal cutoff value using Youden's Index, followed by an analysis of diagnostic ability using the cutoff values. SPSS was used for the statistical analyses.

Results: The logistic regression analysis showed that the sensory nerve

action potentials (SNAP), sensory nerve conduction velocity (SCV) using DPNCheck, and CVR-R during deep breathing (DBCVR-R) were significant explanatory variables. Age and CVR-R at rest were not significant variables. The ROC analysis showed that SNAP had the highest area under the curve (AUROC): SNAP 0.815, SCV 0.736, DBCVR-R 0.672. The optimal cut-off values were SNAP 12.5 μV, SCV 49.5 m/s, and DVCVR-R 4.28%. These cutoff values were used to develop diagnostic criteria. When individuals with any two or more abnormalities were diagnosed with DPN, the ability to diagnose a DPN-positive group was excellent with a sensitivity of 0.822 and specificity of 0.691.

Conclusions: In conclusion, we proposed a diagnostic criterion for DPN using the DPNCheck and DVCVR-R, which could contribute to the establishment of a versatile diagnostic. This approach may offer a more practical and objective method for diagnosing DPN.

P.54 | THE MORPHOLOGICAL ANALYSIS OF LOWER LIMB NERVES USING ULTRASONOGRAPHY IS USEFUL TO EVALUATE DIABETIC POLYNEUROPATHY

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Objectives: Ultrasonography can assess nerve swelling and degeneration. The purpose of this study was to investigate whether ultrasonography of the tibial and sural nerves can be useful for evaluating diabetic polyneuropathy (DPN).

Methods: The study included 22 healthy individuals (Ctrl) (mean age 64.2 ± 11.8 years) and 50 patients with diabetes (DM) (mean age 65.5 ± 13.1 years). Ultrasound images were obtained using a CanonX aprio 200G, and the cross-sectional area (CSA) and brightness were quantified and analyzed using ImageJ. The severity of DPN was calculated using the estimated severity value (eMBC) in the modified Baba's classification, which is calculated using a conversion formula (eMBC = 2.046 + 0.509 × ln (age) - 0.033 × velocity in DPNCheck - 0.622 × ln (amplitude in DPNCheck)).

Results: The ultrasonography showed that the tibial nerve area was significantly larger in patients with diabetes than in healthy individuals, while the sural nerve area was significantly smaller in patients with diabetes than in healthy individuals: CSA of the tibial nerve: Ctrl 16.97±2.86 mm2, DM 18.87±3.50; CSA of the sural nerve: Ctrl 5.25±1.69, DM 4.37±1.31). The sural/tibial nerve area ratio was significantly larger in healthy individuals than in patients with diabetes: Ctrl 0.31±0.11, DM 0.23±0.08. There was no significant difference in nerve brightness between the two groups. The nerve conduction study showed that sensory nerve conduction velocity (SCV) and sensory nerve action potential (SNAP) were significantly higher in healthy individuals than in patients with diabetes: Ctrl SCV 54.00±4.73 m/s, SNAP 17.95±7.44 μV; DM: SCV 49.78±6.28, SNAP 11.34±7.8. The eMBC was significantly higher in patients with diabetes than in healthy individuals: Ctrl 0.64±0.42, DM 1.73±1.37. When DM was divided into two groups with an optimal cutoff value of 1.306 for eMBC and analyzed in three groups together with Ctrl, there was a significant trend in eMBC and sural/tibial nerve area ratio.

Conclusions: The ultrasonography of the tibial and sural nerves may be useful for evaluating DPN.

P.55 | A RANDOMIZED, DOUBLE-BLIND, PLACEBO-CONTROLLED 52-WEEK STUDY TO ASSESS THE EFFECTS OF LIRAGLUTIDE ON SOMATIC AND AUTONOMIC NERVE FUNCTION IN SUBJECTS WITH TYPE 2 DIABETES MELLITUS

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Objectives: Preclinical data has shown that GLP-1 receptor agonists play a role in nerve regeneration and repair. However, few studies have investigated the effects of these compounds on nerve function in humans. The aim of this study was to examine the effect of Liraglutide on somatic and autonomic nerve function in patients with type 2 diabetes.

Methods: Randomized, double-blind, placebo-controlled study of Liraglutide 1.8 mg daily or placebo equivalent for 52 weeks on subjects with Type 2 diabetes, with and without peripheral neuropathy. All participants were evaluated with the following tests at baseline, 26 & 52 weeks: Utah Early Neuropathy Scale (UENS), quantitative sensory testing for cold and warm perception thresholds (Q-Sense v6.0.13.1; Medoc - Minneapolis, MN), in vivo corneal confocal microscopy (CCM) to measure corneal nerve fiber density, branching and length (Tomograph III; Heidelberg Engineering - Smithfield, Rhode Island), sudomotor function testing (SudoscanTM, Impeto Medical - Paris, France), cardiac autonomic function testing (ANSAR,ANX 3.0; ANSAR Group, Inc. Philadelphia) and Norfolk Quality of Life for Diabetic Neuropathy questionnaires.

Results: We randomized 44 subjects (21 to Liraglutide and 23 to placebo). Baseline characteristics were similar between the groups (mean age of 57.9 years, 75% female, 61% African American, mean BMI of 36, mean duration of diabetes 8.5 years, mean glycated hemoglobin of 7.4%). Main results are shown in Table 1. In both groups, there was no significant within-subject or between subject changes on any of the autonomic or somatic nerve testing at 26 and 52 weeks. Glucose control improved significantly on the Liraglutide group and weight improved on both arms but only reaching significance on the placebo group. Twelve out of the 44 participants (27%) were lost to follow-up due in part to study being conducted during the COVID-19 pandemic.

Conclusions: This study did not show significant improvements in either autonomic or somatic nerve function measures after 52 weeks of treatment with Liraglutide. The small sample size, higher than expected drop-out rates and equivalent improvements in weight in both treatment groups may have contributed to the negative results. These results are similar to other small pilot studies. However, in the authors' opinion, further studies with increased sample size are needed to confirm or reject these findings.

Table 1. Changes in primary and secondary outcomes after 52 weeks of intervention with Liraglutide or placebo

	Liraglutide (n=21)				Placebo (n=23)				p**
	Baseline	W-52	p*	Change#	Baseline	W-52	p*	Change#	
Feet ESC *(μS)*	59.62±4.63	61.87±4.88	0.642	1.467	58.22±4.71	52.17±5.31	0.905	0.294	0.186
SDNN	39.05±5.32	38.80±4.27	0.712	-0.81	27.05±3.51	29.44±5.13	0.641	2.01	0.135
RMSSD	28.81±3.53	25.07±2.80	0.061	-4.87	19.48±3.29	22.56±5.03	0.793	1.29	0.081
UENS	7.34±1.67	8.73±2.37	0.216	2.13	6.85±1.44	7.75±2.30	0.943	-0.09	0.125
Warm DT GT *(δ)*	8.33±0.62	8.54±0.68	0.968	-1.63	8.08±0.57	8.90±0.62	0.596	-1.25	0.352
Weight *(lbs)*	225.9±11.2	210.6±12.6	0.079	-4.401	221.9±11.1	206.4±9.8	**0.046**	-5.73	0.716
HbA1C *(%)*	7.18±0.21	6.58±0.19	**0.002**	-0.44	7.50±0.25	7.42±0.33	0.577	0.18	**0.038**
CNFD *(fibers/mm²)*	17.26±1.20	19.03±1.49	0.356	1.07	18.09±1.64	18.56±2.57	0.872	1.72	0.771
CNFL *(mm/mm²)*	16.83±1.12	18.92±1.98	0.328	0.63	15.76±1.32	16.76±2.57	0.705	2.02	0.584

*Data is presented as mean ± SEM *Within group change from baseline to 52 weeks (repeated measures MANOVA), **Between group differences on mean change from baseline to 52 weeks (Paired T test), # change from baseline to 52 weeks. CNFD=corneal nerve fiber density; CNFL=corneal nerve fiber length, DT=detection threshold; GT=great toes; HbA1C=glycated hemoglobin; lbs=pounds; rmsSD=root mean square of the difference of successive R-R intervals; sdNN=sample difference of the beat to beat (NN) variability; UENS=Utah Early Neuropathy Scale; δ=delta from baseline 32°C temp*

P.56 | ID:17108 | ASSOCIATION OF NEUROPATHIC DEFICITS WITH PHARMACOLOGICAL INTERVENTIONS INDUCING WEIGHT CHANGE IN TYPE 2 DIABETES

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Aim: Obesity is a major risk factor for diabetic neuropathy in type 2 diabetes (T2D). This study investigated whether the use of medications which lead to weight gain are associated with worsening neuropathy in T2D.

Methods: Participants with T2D underwent clinical, metabolic testing and

assessment of neuropathic symptoms, vibration perception threshold, sudomotor function, and corneal confocal microscopy (CCM) at baseline and followed up for three visits at years 1, 2, and a final visit between 4 to 7 years.
Results: Of 76 participants, 72.4% were taking glucose or blood pressure lowering medications associated with weight gain, and 27.6% were taking medication associated with weight loss. Follow-up assessments were done over an average of 56 months. Participants taking medications associated with weight gain had more severe neuropathic symptoms at baseline (P<0.01) and a greater decline in small nerve fibers (All 3 CCM measures P<0.0001), with a lower percentage of participants with normal vibration perception threshold (P<0.01) and absence of neuropathic pain (P<0.01) compared to those taking medications associated with weight loss.
Conclusions: These findings suggest that the use of glucose or blood pressure lowering medications associated with weight gain may have a detrimental effect on the progression of neuropathy in patients with T2D, whereas medications associated with weight loss may confer a significant benefit.

P.57 | GLUCAGON-LIKE PEPTIDE 1 AGONISTS AND DIABETIC NEUROPATHY: A LITERATURE REVIEW

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Aim: Glucagon Like Peptide - 1 (GLP-1) receptor agonists represent a novel class of effective glucose-lowering agents with beneficial effects on both macrovascular complications of Diabetes and Diabetic Nephropathy. However, there is not enough evidence regarding their effect on emergence and prognosis of Diabetic Neuropathy. The purpose of this study is to review and critically appraise all relevant data.
Methods and Results: We searched MEDLINE (via PubMed) and the Cochrane Central Register of Controlled Trials for clinical trials reporting the effect of GLP-1 receptor agonists on Diabetic Neuropathy (Diabetic Peripheral Neuropathy and Diabetic Autonomic Neuropathy) up to February 2021. We included all human studies as well as animal studies. In addition, we included trials which investigate the influence of GLP-1 receptor agonists on heart rate variability (HRV), a modality that is affected by Diabetic Autonomic Neuropathy. Animal studies indicate favourable outcomes regarding emergence and prognosis of Diabetic Neuropathy. We found three non-comparable, small sample sized, human trials which show neutral results.
Conclusion: Although there is data indicating possible benefits of GLP-1 receptor agonists from animal studies showing promising results, unfortunately available evidence of human studies is scarce and does not demonstrate this observation.

P.58 | GLYCEMIC CHANGES AFTER TREATMENT WITH MOXONIDINE OR RAMIPRIL IN OVERWEIGHT PATIENTS WITH DYSGLYCEMIA AND MILD-TO-MODERATE HYPERTENSION

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[2.] International, multicenter study

Objectives: The antagonists of the renin-angiotensin system improve insulin sensitivity. Sympathetic activity is enhanced in patients with diabetes or prediabetes. The aim of this study was to evaluate the effects of moxonidine (Mox, a central sympatholytic agent) and ramipril (Ram, an ACE-inhibitor) on glycemic status and insulin sensitivity in overweight patients with dysglycemia and mild-to-moderate hypertension naïve for antihypertensive and glucose-lowering treatments.
Methods: In this prospective, randomized, double-blind, active-controlled, parallel-group, international, multicenter study, the patients were randomized to 12 weeks of double-blind moxonidine 0.4 mg (n=105) or ramipril 5 mg (n=102) once daily treatment, followed by a further 12 weeks of double-blind similar monotherapy, or combination of both agents in non-responders for blood pressure. Glycemic status was evaluated by an OGTT at inclusion, week 12 and week 24 (W12 and W24).
Results: At W12, on Mox and Ram, fasting plasma glucose (−0.38±0.97 mmol/L, p=0.009 and −0.30±0.94mmol/L, p=0.0164, respectively) and HbA1c (−0.13%, p=0.0028 and −0.11%, p=0.0042) decreased, without significant change at W24. Glycemic and insulin responses to OGTT and Matsuda index were similar on Mox, Ram and Mox/Ram combination therapy at W12 and W24. According to OGTT at inclusion, the proportions of patients with diabetes (56.7% and 55.4%, respectively) and prediabetes (impaired fasting glucose and/or impaired glucose tolerance) (43.3% and 44.6%) were very close in Mox and Ram arms. The proportion of non responders at W12 was also close (47.3% and 41.9%). From inclusion to W24, 36% improved their glycemic status (from diabetes to prediabetes or normoglycemia, or from prediabetes to normoglycemia); this improvement occurred more frequently among the patients on Mox or Ram monotherapy or who switched from Mox to combination therapy (38.8/42.6/43.2%) than among those who switched from Ram to combination therapy (15.4%) (p=0.03). The proportion of patients who converted from prediabetes to diabetes was close in the 4 situations (overall 8.6%). Moxonidine reduced significantly heart rate (HR) (average -3.5 bpm) in monotherapy (p=0.017) and similarly reduced HR when added to Ram (p=0.027 compared to HR changes when Ram was added to Mox).
Conclusions: In dysglycemic patients naive for antihypertensive and glucose-lowering treatments, moxonidine and ramipril improve comparably glycemic levels and glycemic status. This study supports the metabolic benefit of reducing sympathetic activity in these patients.

P.59 | THE IMPACT OF OBSTRUCTIVE SLEEP APNOEA TREATMENT ON PAIN IN PATIENTS WITH TYPE 2 DIABETES: RESULTS FROM A 2-YEAR FEASIBILITY RCT

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Background: Obstructive Sleep Apnoea (OSA) is associated with chronic pain in adults. We aimed to assess whether continuous positive airway pressure (CPAP) might impact pain in patients with T2D.
Method: We conducted an open-label multi-centre (13 centres) feasibility randomised control trial (RCT) in which patients with T2D and OSA (apnoea hypopnea index AHI ≥ 10 events/hour) were randomised to CPAP vs no CPAP over 2 years. Participants with resting oxygen saturation <90%, central apnoea index >15/hrs or Epworth Sleepiness Score (ESS) >= 11 were excluded. The primary outcomes of this trial were related to feasibility. In this abstract, we report on the secondary outcome related to pain which was assessed using the short form Mcgail pain questionnaire (SF-MPQ) and visual analogue scale (VAS).
Results: Eighty-three patients were randomised to CPAP vs no CPAP (43 vs 40) with a median [IQR] follow-up of 645 [545,861] days. The study population mean (SD) age was 62.5 (10.9) years, and diabetes duration was 12.2(7.9) years. 89.1 % (n=74) were white European ethnicity, 71.1% (n=59) were men, 77.7% (n=59) had obesity, and 48.2% (n=40) were prescribed insulin. Only 26/43 patients used CPAP, with a median (IQR) usage of 3:40 (hours: minutes) [0:06, 4:45] per night. Based on intention-to-treat analysis, CPAP numerically had a favourable impact on pain severity (overall, sensory, affective, VAS) (Table 1).
Conclusion: CPAP might have a favourable impact on reducing pain in patients with T2D. Full RCT is needed.

Table 1: SF-MPQ score – pain rating index and visual analogue scale

	Baseline		Follow-up		Adjusted mean difference[1] (95% CI)	Unadjusted mean difference[2] (95% CI)
	CPAP Mean (SD, N)	No CPAP Mean (SD, N)	CPAP Mean (SD, N)	No CPAP Mean (SD, N)		
Pain rating index – overall	6.0 (8.1, 36)	10.0 (9.3, 40)	8.5 (10.0, 17)	12.5 (10.2, 22)	-0.52 (-7.9, 6.8)	-4.0 (-10.6, 2.6)
Pain rating index – sensory	4.5 (6.1, 37)	7.9 (6.8, 41)	6.7 (6.8, 17)	9.8 (7.7, 23)	-0.89 (-6.0, 4.2)	-3.1 (-7.9, 1.6)
Pain rating index – affective	1.6 (2.6, 38)	2.3 (3.1, 41)	1.7 (3.3, 18)	2.9 (3.1, 22)	0.26 (-2.1, 2.6)	-1.1 (-3.2, 0.9)
Visual analogue scale	20.1 (23.6, 36)	21.7 (26.6, 31)	6.7 (14.3, 12)	25.4 (28.0, 22)	-14.7 (-32.2, 2.9)	-18.7 (-36.4, -1.1)

Note: SF-MPQ pain rating index sensory sub-score has a range from 0 to 33 where 0 is the best and 33 is the worst. SF-MPQ pain rating index affective sub-score has a range from 0 to 12 where a 0 is the best and 12 is the worst. SF-MPQ visual analogue scale has a range from 0 to 100 where 0 is the best and 100 is the worst.
[1]Adjusted for ethnicity, gender, OSA severity, age and baseline value. A negative mean difference favours CPAP.
[2]A negative mean difference favours CPAP.

P.60 | A RANDOMIZED, DOUBLE-BLIND, PLACEBO-CONTROLLED, PARALLEL, 12-WEEK, PHASE 2A STUDY OF TOPICAL PIRENZEPINE (WST-057) OR PLACEBO IN TYPE 2 DIABETES MELLITUS PATIENTS WITH PAINFUL DIABETIC NEUROPATHY

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Objectives: Muscarinic receptor antagonists have shown to be effective in improving structural and functional indices of established neuropathy in preclinical and clinical studies of patients with type 2 diabetes (T2DM). The main objectives of this study were to determine the safety, tolerability and efficacy of topical pirenzepine (WST-057) after daily administration in T2DM patients with painful peripheral neuropathy (DPN).
Methods: This was a randomized, double-blind, placebo-controlled, single site 12-week, Phase 2a study of WST-057 (4% pirenzepine free base monohydrate) or matching placebo in 55 subjects with established T2DM and DPN. Subjects were randomized to WST-057 or placebo in a 2:1 ratio (38 to WST-057 and 17 to placebo). Efficacy assessments at baseline, 6 and 12 weeks included: Visual Analogue Scale for pain in feet and legs; neuropathy scores including Utah Early Neuropathy Scale (UENS) and modified Toronto Clinical Neuropathy Score (mTCNS); skin biopsies to measure intra-epidermal nerve fiber density (IENFD); thermal and vibration perception thresholds; sural and peroneal nerve conduction studies; and pain and quality of life questionnaires.
Results: Baseline demographic characteristics were similar between the groups (51% female, 40% African American, mean age 63 years, BMI 32, HbA1C 7.5%, and duration of diabetes of 16 years). A mixed model with repeated measures (MMRM) analysis of both intention-to-treat (mITT) and per-protocol (PP) populations were conducted. At 12 weeks, pirenzepine improved UENS scores significantly vs placebo. Pirenzepine also showed a clinically relevant trend towards improvement in mTCNS scores and sural sensory nerve conduction velocities in comparison to placebo. No significant change versus placebo was detected in any of the other measures evaluated at 12 weeks (Table 1). WST-057 was safe and well tolerated after 12 weeks of exposure.
Conclusions: The data from this Phase 2a study suggest that WST-057 treatment has the potential to improve nerve function and signs and symptoms of DPN which limit mobility and impact well-being in patients with neuropathy. A parallel phase 2a, longer duration (24-week) clinical trial showed similar results with the additional improvement in intra-epidermal nerve fiber density in distal leg, suggesting nerve regeneration. Multicenter studies of longer duration are needed to confirm these encouraging results.

Table 1. Change from baseline to 12 weeks in different neuropathy measures in pirenzepine and placebo groups

	WST-057 (n=38)	Placebo (n=17)	WST-057 Difference from Placebo	p-value*
UENS Total Score^	-3.13 (-4.92, -1.34)	-0.17 (-2.57, 2.24)	-2.96	**0.0381**
mTCNS Total Score#	-1.97 (-3.55-0.40)	0.66 (-1.66, 2.99)	-2.64	0.0651
Sural nerve CV# *(m/s)*	3.03 (-3.0-20.0)	0.83 (-5.0-7.0)	2.21	0.099
IENFD^ *(n/mm)*	0.08 (-0.62-0.78)	0.40 (-0.66-1.47)	-0.32	0.620
Warm DT# *(°Celsius)*	-0.61 (-9.7-7.45)	-0.70 (-4.7-3.15)	0.09	0.875
Vibration DT# *(volts)*	-2.6 (-21.9-17.6)	-0.83 (-45.17-48.08)	-1.77	0.216
VAS pain# *(mm)*	-5.4 (-12.10-1.27)	-10.7 (-21.51-0.08)	5.3	0.418
BPI-DN#	-3.7 (-54-32)	-15.9 (-43-1)	12.2	0.127
Norfolk QOL-DN Total Score#	-4.31 (-8.42-0.19)	-7.12 (-13.23- -1.0)	12.81	0.452

*a. Data presented as mean (95% CI) *Mixed model with repeated measures (MMRM), including fixed effects for treatment, visit, and treatment-by-visit interaction and baseline score as a covariate. #mITT, ^pp. BPI-DN= Brief Pain Inventory-Diabetic Neuropathy; CV= conduction velocity; DT= detection threshold, IENFD= intraepidermal nerve fiber density; m/s= meters per second; mITT= modified intention to treat; mm= millimeters; mTCNS= modified Toronto Clinical Neuropathy Score, n/mm= number of nerve fibers per millimeter; pp= per protocol; QOL-DN= quality of life-diabetic neuropathy, UENS= Utah Early Neuropathy Scale, VAS= Visual Analogue Scale, WST-057=4% pirenzepine free base monohydrate.*

P.61 | REAL-WORLD EVALUATION OF OPSITE TOPICAL DRESSING IN PAINFUL DIABETIC NEUROPATHY

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Aims: Real-world evaluation of the use of topical non-medicated, vapour-permeable adhesive film dressing as adjuvant therapy in patients with painful diabetic neuropathy (DPN) attending a podiatry led clinic.
Methods: Open-labelled study of application of topical OpSite Plus dressing (6.5x5cm, Smith&Nephew Healthcare ltd) on the dorsal surface of both feet in patients with painful diabetic neuropathy. Pain was assessed using a validated Numeric rating scale (0=no pain and 10=most severe pain) at Week 0 and Week 4. The presence of painful DPN was confirmed using the Douleur Neuropathique 4 (DN-4) questionnaire. The presence of allodynia was assessed using a cotton-wool ball.
Results: 106 patients (males 58.5%, T2DM 92.5%) with painful DPN were included in this study with a mean age of 68.4(11.5) years and duration of diabetes 13.6(9.6) years. 35(33.0%) subjects had allodynia and the majority had pain for more than 12 months (<6 months 1, 0.9%; <12 months 5, 4.7%; >12 months 100, 94.2%). 10 patients were lost to follow-up. NRS improved from 8.2(1.6) pre-treatment to 4.7(2.5) post-treatment. Improvements in NRS were significantly greater in patients with allodynia compared to those without [4.1(2.9) vs 3.0(2.1), p=0.04; 95%CI 0.05:2.2]. 78(81.3%) of subjects reported subjective benefit from the intervention at 4 weeks
Conclusions: Topical OpSite dressing appeared to alleviate the pain and maybe a useful adjunctive treatment for painful DPN. Patients with allodynia reported greater benefit compared to those without. Further 8- and 12-week follow up is planned in this cohort.