NEURODIAB 2020

30TH ANNUAL MEETING OF THE DIABETIC NEUROPATHY STUDY GROUP OF THE EASD

18-20 SEPTEMBER 2020 - BUDAPEST (HUNGARY)

DAILY PROGRAMME

DAY 1

Friday 18/9/2020

13.45 – 14.00 OPENING REMARKS – Peter Kempler

14.00 – 14.30 **INVITED LECTURE 1 –** Solomon Tesfaye, United Kingdom: Optimal Pathway for TreatIng neurOpathic paiN in Diabetes Mellitus (OPTION-DM) trial

Chair: Peter Kempler

14.30 – 15.45 **ORAL SESSION:** Young Investigators Oral Presentations - [15min for each presentation]

Chairs: Solomon Tesfaye, Fabiana Picconi, ***Zsuzsanna Putz***

1. **CORNEAL CONFOCAL MICROSCOPY DETECTS SMALL FIBER NEUROPATHY IN PATIENTS WITH SEVERE HYPERTRIGLYCERIDAEMIA AND TYPE 1 DIABETES**
   Luca D'Onofrio[1,2], Alise Kalteniece[2], Maryam Ferdousi[2], Ioannis Petropoulos[3], Georgios Ponirakis[3], Raffaella Buzzetti[1], Rayaz A Malik[2,3] and Handrean Soran[2]
   [1]Department of Experimental Medicine, "Sapienza" University of Rome, Italy, [2]Institute of Cardiovascular Sciences, Cardiac Centre, Faculty of Medical and Human Sciences, University of Manchester and NIHR/Wellcome Trust Clinical Research Facility, Manchester, UK, [3]Department of Medicine, Weill-Cornell Medicine-Qatar, Doha, Qatar

2. **POST-EXERCISE HEART RATE VARIABILITY IN TYPE 2 DIABETES WITH AND WITHOUT CARDIAC AUTONOMIC NEUROPATHY: A STATISTICAL PARAMETRIC MAPPING**
   Jean-Baptiste Beaume[1,2], Cécile Reynes[2], Maximilien Bowen[1], Lisa Chatel[2], Françoise Latil-Plat[3], Houda Ennaifer[3], Laure Rocher[3], Yannick Knapp[2], Agnès Vinet[2]
   [1]Université Savoie Mont Blanc, Chambéry, France, [2]Avignon Université, Avignon, France, [3]Service Endocrinologie-Maladies Métaboliques, Centre hospitalier Henri Duffaut, Avignon, France

3. **SPECTRAL ANALYSIS OF THE VENOARTERIOLAR REFLEX IN TYPE 2 DIABETIC WITH AND WITHOUT PERIPHERAL NEUROPATHY**
   Cécile Reynès[1], Jean-Baptiste Beaume[1], Antonia Perez-Martin[2], Françoise Latil-Plat[3], Houda Ennaifer[3], Laure Rocher[3], Yannick Knapp[1], Agnès Vinet[1]
   [1]University of Avignon, Avignon, France, [2]Department of Vascular Investigations and Vascular Medicine, Nîmes University Hospital, University of Montpellier, France, [3]Department of Metabolic diseases and Endocrinology, Henri Duffaut Hospital, Avignon, France

4. **EFFICACY OF AN ORAL DISPERSIBLE TABLET CONTAINING VIT. B12 AFTER 12 MONTHS OF ADMINISTRATION IN PATIENTS WITH DIABETIC NEUROPATHY**
Eleni Karlafti[1], Eleni Margariti[1], Parthena Giannulaki[2], Zisis Kontoninas[1], Charalampos Margaritidis[1], Solomon Tesfaye[3], Apostolos Hatzitolios[1], Triantafyllos Didangelos[1]
[1]Diabetes Center, 1st Propeudetic Department of Internal Medicine, Medical School; "AHEPA" Hospital, Aristotle University of Thessaloniki, Greece, [2]Department of Nutrition and Dietetics, University General Hospital of Thessaloniki ''AHEPA'', Greece, [3]Diabetes Research Unit, Royal Hallamshire Hospital, Sheffield Teaching Hospitals NHS Foundation Trust, Sheffield, UK

5. **CARDIOVASCULAR AUTONOMIC DYSFUNCTION IS ASSOCIATED WITH DECLINE IN KIDNEY FUNCTION IN TYPE 2 DIABETES AND HEALTHY CONTROLS**
Jens Christian Laursen[1], Ida Kirstine B Rasmussen[1], Christian S Hansen[1], Bernt Johan von Scholten[2], Emilie H Zobel[1], Marie Frimodt-Møller[1], Tine W Hansen[1], Peter Rossing[1,3]
[1]Steno Diabetes Center Copenhagen, Gentofte, Denmark, [2]Novo Nordisk, [3]University of Copenhagen

15.45 – 16.15 COFFEE BREAK

16.15 – 16.45 **INVITED LECTURE 2** – Simona Frontoni, Italy: Diabetic neuropathy: a new vision

Chair: Vincenza Spallone, ***Tamás Várkonyi***

16.45 – 18.15 **ORAL SESSION:** Autonomic 1 [15min each]

Chairs: Simona Frontoni, Dan Ziegler, ***Anna Körei***

1. **PERIPHERAL POLYNEUROPATHY AFTER BARIATRIC SURGERY IN SEVERELY OBESE PATIENTS WITH PREDIABETES AND WITHOUT DIABETES: A COHORT STUDY**
Helena Schmid[1,2], Otto Henrique Nienov[1], Fernanda Dapper Machado[1]
[1]Programa de Pós-Graduação em Ciências da Saúde: Ginecologia e Obstetrícia, UFRGS, Porto Alegre, Brazil, [2]Centro de Tratamento da Obesidade, Hospital Santa Rita do Complexo Hospitalar Santa Casa de Misericórdia de Porto Alegre, Porto Alegre, Brazil

2. **DAPAGLIFLOZIN AND MEASURES OF CARDIOVASCUALR AUTONOMIC FUNCTION IN PATIENTS WITH TYPE 2 DIABETES**
Lynn Ang[1], Kelley Kidwell[2], Brendan Dillon[1], Jacob Reiss[1], Virginia Leone[1], Kara Mizokami-Stout[1], Rodica Pop-Busui[1]
[1]Metabolism, Endocrinology and Diabetes Division, University of Michigan, Ann Arbor, Michigan, [2]School of Public Health, University of Michigan, Ann Arbor, Michigan

3. **RELATIONSHIP BETWEEN CARDIAC AUTONOMIC NEUROPATHY AND STRUCTURAL AND FUNCTIONAL ALTERATIONS OF THE LEFT VENTRICLE IN ASYMPTOMATIC PATIENTS WITH TYPE 2 DIABETES**
Paul Valensi[1], Emanuel Cosson[1], Sara Pinto[1]
[1]Hôpital Jean Verdier, APHP, Université Paris Nord, CINFO, CRNH-IdF

4. **RELATIONSHIP BETWEEN HYPOGLYCAEMIA UNAWARENESS AND CARDIOVASCULAR AUTONONIC NEUROPATHY IN DISABLED PATIENTS WITH T1DM**
Olga Svetlova[1], Irina Gurieva[1]
[1]Federal Bureau of Medical and Social Expertise, Moscow, Russia

5. **POOR ORAL HEALTH PREDICTS PROGRESSION OF DIABETIC PERIPHERAL NEUROPATHY**
Anca Jivanescu[1], Cosmina Bondor[2], Diana Sima[2], Camelia Vonica[2], Daniel Cosma[2], Ioan Veresiu[2], Norina Gavan[3], Rodica Pop-Busui[4]
[1]University of Medicine and Pharmacy Victor Babes Timisoara Victor Babes, [2]Iuliu Haţieganu University of Medicine and Pharmacy Cluj-Napoca, Romania, [3]Worwag Pharma Romania SRL, Cluj-Napoca, Romania, [4]University of Michigan, Ann Arbor, MI USA

6. **FALLS IN INDIVIDUALS WITH TYPE 2 DIABETES; A CROSS-SECTIONAL STUDY ON THE IMPACT OF MOTOR DYSFUNCTION, POSTURAL INSTABILITY AND DIABETIC POLYNEUROPATHY**
Karolina S. Khan[1,2], Rodica Pop-Busui[6], Louise Devantier[3], Alexander G. Kristensen[2,4], Hatice Tankisi[2,4], Ulrik Dalgas[5], Kristian Overgaard[5], Henning Andersen[1,2]
[1]Department of Neurology, Aarhus University Hospital, Aarhus, Denmark, [2]Faculty of Health, Aarhus University, Aarhus, Denmark, [3]Department of Oto-Rhino-Laryngology, Regional Hospital West Jutland, Denmark, [4]Department of Clinical Neurophysiology, Aarhus University, Aarhus, Denmark, [5]Sport Biological Research, Department of Public Health, Aarhus University, Denmark, [6]Division of Metabolism, Endocrinology and Diabetes, Department of Internal Medicine, University of Michigan, Ann Arbor, MI

18.15 – 19.00 **INVITED LECTURE 3** – Mark Yorek, USA: Can a Case be Made to Advance Fish Oil and Salsalate to a Clinical Trial for Diabetic Peripheral Neuropathy?

Chair: Solomon Tesfaye, ***Tamás Várkonyi***

DAY 2

Saturday 19/9/2020

08.30 – 09.00 **Trigocare Symposium**

Chair: Peter Kempler

The indicator test for sudomotor dysfunction Neuropad. New prospective observational study: Dryness of foot skin assessed by the visual indicator plaster test and risk of diabetic foot ulceration

Lecturer: Nikos Papanas, Greece

09.00 – 10.00 **ORAL SESSION:** Treatment [15min each]

Chairs: Dinesh Selvarajah, Paul Valensi, ***Szabolcs Nyiraty***

1. **INCIDENCE AND RISK FACTORS FOR DIABETIC POLYNEUROPATHY AFTER BARIATRIC SURGERY**
   Helena Schmid[1,2], Otto Henrique Nienov[1], Fernanda Dapper Machado[1]
   [1]Programa de Pós-Graduação em Ciências da Saúde: Ginecologia e Obstetrícia, UFRGS, Hospital de Clínicas de Porto Alegre, Brazil, [2]Centro de Tratamento da Obesidade, Hospital Santa Rita do Complexo Hospitalar Santa Casa de Misericórdia de Porto Alegre, Porto Alegre, Brazil

2. **LONG-TERM TREATMENT AND PREDICTORS OF OUTCOME IN PAINFUL DIABETIC POLYNEUROPATHY: AN OBSERVATIONAL STUDY**
   Giuseppe Seminara[1], Cinzia D'Amato[1], Carla Greco[1], Valentina Izzo[1], Mariateresa Staltari[1], Martina Leoni[1], Marika Menduni[1], Davide Lauro[1], Girolama Alessandra Marfia[2], Vincenza Spallone[1]
   [1]Department of Systems Medicine, Endocrinology Section; University of Rome Tor Vergata, Rome, Italy, [2]Department of Systems Medicine, Neurology Section; University of Rome Tor Vergata, Rome, Italy

3. **TREATMENT OF PAINFUL DIABETIC NEUROPATHY USING FREQUENCY RHYTHMIC ELECTRO MAGNETIC NEURAL STIMULATION (FREMS); EFFECTIVENESS IN DAILY PRACTICE**
   Abd A. Tahrani[1,2], Jack Heijster[1], Ben P. M. Imholz[1], Adriaan Kooy[1,3]
   [1]ETZ, Waalwijk, Netherlands, [2]Institute Met and System Res, Birmingham, UK, [3]Bethesda Diabetes Research, Hoogeveen, Netherlands

4. **PROGRESSION OF THE CARDIAC AND THE MICROVASCULAR COMPLICATIONS IN YOUNG TYPE 1 DIABETIC PATIENTS DURING 10 YEARS**
   Bettina Tóth[1], Fruzsina Pesei[1], Kálmán Havasi[2], Szabolcs Nyiraty[1], Árpád Kormányos[2], Andrea Orosz[3], Csaba Lengyel[1], Attila Nemes[2], Péter Kempler[4], Tamás Várkonyi[11]*First Dept of Internal Medicine, University of Szeged, Szeged, Hungary, [2]Second Dept. of Medicine, University of*

Szeged, Szeged, Hungary, [3]Department of Pharmacology and Pharmacotherapy, University of Szeged, Szeged, Hungary, [4]Department of Internal Medicine and Oncology, Semmelweis University, Budapest, Hungary

10.00 – 10.30 COFFEE BREAK

10.30 – 11.00 **INVITED LECTURE 4 –** Angelo Avogaro, Italy: Are microvascular complications the main risk factor of cardiovascular disease in diabetes?

Chair: Peter Kempler

11.00 – 12.30 **ORAL SESSION:** Diagnosis [15min each]

Chairs: Angelo Avogaro, Gerry Rayman, ***Szabolcs Nyiraty***

1. **IN OBESE PATIENTS AT HIGH RISK OF DIABETES CARDIAC AUTONOMIC DYSFUNCTION IS ASSOCIATED WITH HIGHER BLOOD GLUCOSE LEVELS AND EARLY INSULIN RESISTANCE MARKERS**
   Isabela Banu[1], Eliane Hamo-Tchatchouang[1], Sabrina Chiheb[1], Soumeya Chetouane[1], Emmanuel Cosson[1], Paul Valensi[1]
   [1]Department of Endocrinology-Diabetology-Nutrition, Jean Verdier hospital, AP-HP, CRNH-IdF, CINFO, Paris-Nord University, Bondy, France

2. **EFFECT OF EARLY INTERVENTION WITH A LONG LASTING INSULIN ANALOGUE ON PERIPHERAL NEUROPATHY IN TYPE 2 DIABETIC SPRAGUE-DAWLEY RATS**
   Thorbjorn Akerstrom[1], Mark Yorek[2,3]
   [1]Novo Nordisk, Maaloev, Denmark, [2]University of Iowa, Iowa City, Iowa, USA, [3]Iowa City VA Medical Center, Iowa City, Iowa, USA

3. **ASSOCIATION OF CARDIAC AUTONOMIC DYSFUNCTION WITH PLASMA BIOMARKERS OF LIPID METABOLISM IN RECENT-ONSET TYPE 2 DIABETES**
   Gidon J Bönhof[1,2,3], Alexander Strom[1,3], Klaus Straßburger[4,3], Birgit Knebel[5,3], Jörg Kotzka[5,3], Julia Szendroedi[1,3,2], Michael Roden[1,2,3], Dan Ziegler[1,2,3]
   [1]Institute for Clinical Diabetology, German Diabetes Center (DDZ), Leibniz Center for Diabetes Research at Heinrich Heine University, Düsseldorf, Germany, [2]Division of Endocrinology and Diabetology, Medical Faculty, Heinrich Heine University, Düsseldorf, Germany, [3]German Center for Diabetes Research (DZD), Munich-Neuherberg, Germany, [4]Institute for Biometrics and Epidemiology, German Diabetes Center (DDZ), Leibniz Center for Diabetes Research at Heinrich Heine University, Düsseldorf, Germany, [5]Institute for Clinical Biochemistry and Pathobiochemistry, German Diabetes Center (DDZ), Leibniz Center for Diabetes Research at Heinrich Heine University, Düsseldorf, Germany

4. **ARE THERE ECG PARAMETERS REPRESENTING CARDIAC REPOLARIZATION INFLUENCED BY THE PRESENCE CARDIOVASCULAR AUTONOMIC NEUROPATHY IN TYPE 1 DIABETES DURING EXERCISE?**
Viktor Horváth[1], Gergely Szabó[1], Emese Szelke[1], Péter Szelke[1], Anna Erzsébet Körei[1], Magdolna Békeffy[1], Ádám Tabák[1], Péter Kempler[1]
[1]Semmelweis University, Department of Internal Medicine and Oncology, Hungary

5. **CLASSIFYING PAINFUL DIABETIC NEUROPATHY INTO CLINICAL SENSORY PHENOTYPES: A NOVEL, MULTIMODAL MAGNETIC RESONANCE IMAGING AND A MACHINE LEARNING APPROACH**
Kevin Teh[2], Ian D Wilkinson[2], Francesa Heiberg-Gibbons[1], Mohammed Awadh[1], Alan Kelsall[3], Shillo Pallai[3], Gordon Sloan[3], Solomon Tesfaye[3], Dinesh Selvarajah[1]
[1]Department of Human Metabolism, University of Sheffield, Sheffield, UK, [2]Academic Department of Magnetic Resonance Imaging, University of Sheffield, Sheffield, UK, [3]Diabetes Research Department, Sheffield Teaching Hospitals NHS Foundation Trust, Sheffield, UK

6. **THE IPSWICH NEURODIAB STUDY: A 5-YEAR LONGITUDINAL STUDY EXAMINING THE PATHOPHYSIOLOGY AND NATURAL HISTORY OF DIABETES POLYNEUROPATHY (DPN)**
Sanjeev Sharma[1], Jenna Cross[1], Prashanth Vas[2], Gerry Rayman[1]
[1]Diabetes Research unit, Ipswich Hospital, Ipswich, UK, [2]Department of Diabetes, Kings College Hospital NHS Foundation Trust, London, UK

12.30 – 13.30 **Wörwag Pharma Symposium**

DIABETIC NEUROPATHY – FOCUS ON GENETICS AND OXIDATIVE STRESS

Chairman: Peter Kempler

Introduction

Peter Kempler, Hungary (10 min)

Do genetics play a role in the development of diabetic neuropathy?

Vincenza Spallone, Italy (20 min)

Relevance of oxidative stress in diabetic complications

Dan Ziegler, Germany (20 min)

Q&A Session (10 min)

13.30 – 14.30 LUNCH

14.30 – 16.00 **ORAL SESSION:** Pathogenesis [15min each]

Chairs: Rodica Pop-Busui, Mark Yorek, ***Zsuzsanna Putz***

1. **TRANSGENIC MICE UBIQUITOUSLY OVEREXPRESSING HUMAN 15-LIPOXYGENASE-1: CHARACTERIZATION OF DIABETIC PERIPHERAL NEUROPATHY AND EFFECT OF ENRICHING THE DIET WITH MENHADEON OIL**

   Mark Yorek[1, 2]

   [1]University of Iowa, United States of America, [2]Iowa City VA Medical Center, United States of America

2. **EFFECTS OF INTENSIVE RISK FACTOR MANAGEMENT ON CARDIOVASCULAR AUTONOMIC NEUROPATHY IN TYPE 2 DIABETES: FINDINGS FROM THE ACCORD CLINICAL TRIAL**

   Yaling Tang[1,2], Hetal Shah[1,2], Xiuqin Sun[1,3], Joanna Mitri[1,2], Maria Sambataro[4], Luisa Sambado[4], Hertzel Gerstein[5], Alessandro Doria[1,2], Rodica Pop-Busui[6]

   [1]Research Division, Joslin Diabetes Center, Boston, Massachusetts, [2]Department of Medicine, Harvard Medical School, Boston, Massachusetts, [3]Anzhen Hospital Affiliated to Capital Medical University, Beijing, China, [4]Endocrine, Metabolism and Nutrition Disease Unit, Internal Medicine Department, Santa Maria of Ca' Foncello Hospital, Treviso, Italy, [5]McMaster University and the Population Health Research Institute, Hamilton, Ontario, Canada, [6]Department of Internal Medicine, Division of Metabolism, Endocrinology and Diabetes, University of Michigan, Ann Arbor, Michigan

3. **DIFFUSION TENSOR IMAGING OF THE SCIATIC NERVE DETECTS A LOSS OF SENSORIMOTOR FUNCTION IN PATIENTS WITH TYPE 2 DIABETES**

   Zoltan Kender[1,2], Johann Jende[3], Felix Kurz[3], Peter Nawroth[1,2], Martin Bendszus[3], Stefan Kopf[1, 2]

   [1]Department of Endocrinology, Diabetology and Clinical Chemistry, University Hospital Heidelberg, Heidelberg, [2]German Center of Diabetes Research (DZD), associated Partner in the DZD; München-Neuherberg, [3]Department of Neuroradiology, University Hospital Heidelberg, Heidelberg

4. **RELATION BETWEEN HAPTICS AND STANDARD NEUROLOGICAL ASSESSMENT FOR THE EVALUATION OF TACTILE SENSITIVITY IN TYPE 1 DIABETES MELLITUS**

   Fabiana Picconi[1], Alessandro Moscatelli[2,3], Alessio Pepe[4], Colleen Ryan[2,3], Simone Ciotti[3], Benedetta Russo[1], Lacquaniti Francesco[2,3], Simona Frontoni[1]

   [1]Unit of Endocrinology, Diabetes and Metabolism, S. Giovanni Calibita Fatebenefratelli Hospital, Department of Systems Medicine, University of Rome Tor Vergata, Italy, [2]Department of Systems Medicine and Centre of Space Bio-medicine, University of Rome "Tor Vergata", Rome, Italy, [3]Laboratory of Neuromotor Physiology, IRCCS Santa Lucia Foundation, Rome, Italy, [4]Department of Neuroscience and Neurorehabilitation, IRCCS San Raffaele Pisana, Rome, Italy

5. **CEREBRAL MORPHOMETRIC ABNORMALITIES IN PAINLESS AND PAINFUL DIABETIC PERIPHERAL NEUROPATHY**

Gordon Sloan[1], Dinesh Selvarajah[1,2], Kevin Teh[3], Shillo Pallai[1,4], Marni Greig[1], Ian D. Wilkinson[2], Solomon Tesfaye[1]

[1]Diabetes Research Unit, Royal Hallamshire Hospital, Sheffield Teaching Hospitals NHS Foundation Trust, UK, [2]Department of Oncology and Human Metabolism, University of Sheffield, Sheffield, UK, [3]Academic Unit of Radiology, University of Sheffield, Sheffield, UK, [4]Department of Diabetes, Chesterfield Royal Hospital, Chesterfield UK

6. **STRUCTURAL GREY MATTER ALTERATIONS AND COGNITIVE FUNCTION IN DIABETES: A UK BIOBANK STUDY**

Jamie Burgess[1], Ioannis, N Petropoulos[2], Jonathan Z Lim[3], Bernhard Frank[4], Marta-Garcia Finana[5], Daniel J Cuthbertson[6], Simon Keller[7,8], Dinesh Selvarajah[9], Solomon Tesfaye[10], Uazman Alam[1, 11]

[1]Department of Eye & Vision Sciences, Institute of Ageing and Chronic Disease, University of Liverpool, UK., [2]Department of Medicine, Weill Cornell Medicine-Qatar, Doha, Qatar, [3]Diabetes and Endocrinology Research, Department of Eye and Vision Sciences and Pain Research Institute, Institute of Ageing and Chronic Disease, University of Liverpool and Aintree University Hospital NHS Foundation Trust, Liverpool, UK, [4]The Walton Centre, Department of Pain Medicine, Liverpool, UK. , [5]Department of Biostatistics, University of Liverpool, UK, [6]Metabolism and Nutrition Research Group, Institute of Ageing and Chronic Disease, University of Liverpool, Liverpool L69 7ZX, UK, [7]Department of Molecular and Clinical Pharmacology, Institute of Translational Medicine, University of Liverpool, Liverpool, UK,, [8]The Department of Neuroradiology, The Walton Centre NHS Foundation Trust, Liverpool, UK, [9]Department of Oncology and Human Metabolism, University of Sheffield, UK , [10]Academic Unit of Diabetes and Endocrinology, Sheffield Teaching Hospitals NHS Foundation Trust, Sheffield, UK , [11]Division of Diabetes, Endocrinology and Gastroenterology, Institute of Human Development, University of Manchester, UK

16.00 – 16.30 COFFEE BREAK

16.30 – 17.00 **INVITED LECTURE 5** – Rodica Pop-Busui, United States of America: The epidemiology of diabetic neuropathy

Chair: Dan Ziegler, ***Peter Kempler***

17.00 – 17.30 **ORAL SESSION:** Case Reports [10 min each]

Chairs: Eirik Softeland, Vincenza Spallone, ***Ferenc Sztanek***

1. **MAXIMAL DEGREE OF SENSORY HYPAESTHESIA AND ASYMPTOMATIC SEVERE OBLITERATIVE ARTERIAL DISEASE IN THE BACKGROUND OF A PAINLESS TOE GANGRENE**
   Orsolya Erzsébet Vági[1], Zsuzsanna Putz[1], Ildikó Istenes[1], Anna Erzsébet Körei[1], Noémi Hajdú[1], Magdolna Békeffy[1], Péter Kempler[1]
   [1]Department of Internal Medicine and Oncology, Semmelweis University, Budapest, Hungary
2. **IS THERE ANY INDICATION FOR PLASMAPHERESIS AND OPIOID THERAPY IN THE TREATMENT OF DIABETIC NEUROPATHY? – A CASE REPORT**
   Anna Erzsébet Körei [1], Karolina Kornélia Schnabel [1], Dóra Tordai [1], Magdolna Zsófia Békeffy [1], Erika Gulyásné Gáspár [1], Zsuzsanna Putz[1], Ildikó Istenes[1], Noémi Hajdú[1], Péter Kempler[1]
   [1]Department of Internal Medicine and Oncology, Semmelweis University, Budapest, Hungary

3. **SEVERE ORTHOSTATIC HYPOTENSION WITH HYPORENINISM AND HYPOALDOSTERONISM IN A YOUNG DIABETIC PATIENT**
   Sara Pinto[1], Léa Carlier[2], Raffaele Galiero[1], Paul Valensi[1]
   [1]Hopital Jean Verdier, Bondy, France, [2]Sorbonne Université, Paris, France

17.30 – 18.00 GENERAL ASSEMBLY

DAY 3

Sunday 20/9/2020

08.30 – 10.00 **ORAL SESSION:** Autonomic Neuropathy 2 [15min each]

Chairs: Tamás Várkonyi, Ferenc Sztanek

1. **CARDIOVASCULAR AUTONOMIC NEUROPATHY IN TYPE 1 DIABETES IS ASSOCIATED WITH SEVERAL METABOLIC PATHWAYS – NEW RISK MARKERS ON THE HORIZON?**
   Christian S Hansen[1], Tommi Suvitaival[1], Simone Theilade[1], Ismo Mattila[1], Maria Lajer[1], Kajetan Trošt[1], Linda Ahonen[1], Tine W Hansen [1], Cristina Legido-Quigley[1], Peter Rossing[1,2], Tarunveer S Ahluwalia[1]
   [1]Steno Diabetes Center Copenhagen, Gentofte, Denmark, [2]Department of Clinical Medicine, University of Copenhagen, Copenhagen, Denmark

2. **A CLINICAL SCORING SYSTEM FOR THE RISK OF CARDIOVASCULAR AUTONOMIC NEUROPATHY IN TYPE 1 DIABETES**
   Marika Menduni[1], Cinzia D'Amato[1], Martina Leoni[1], Carla Greco[1], Andrea Abbatepassero[1], Giuseppe Seminara[1], Davide Lauro[1], Vincenza Spallone[1]
   [1]Department of Systems Medicine, Endocrinology Section; University of Rome Tor Vergata, Rome, Italy

3. **CARDIAC AUTONOMIC FUNCTION IN DIABETIC GASTROPARESIS**
   Eirik Søfteland[1,2], Dag A. Sangnes[1,3], Georg Dimcevski[3]
   [1]Haukeland University Hospital, Department of Medicine, Bergen, Norway, [2]Haukeland University Hospital, Hormone Laboratory, Bergen, Norway, [3]University of Bergen, Faculty of Medicine, Bergen, Norway

4. **AUTONOMIC NEUROPATHY AND GLUCOSE VARIABILITY IN PATIENTS WITH TYPE 1 DIABETES. A POTENTIAL ROLE OF IMPAIRED GASTRIC EMPTYING?**
   Fruzsina Pesei[1], Szabolcs Nyiraty[1], Bettina Tóth[1], Andrea Orosz[2], Csaba Lengyel[1], László Pávics[3], György Ábrahám[1], Péter Kempler[4], Tamás Várkonyi[1]
   [1]First Department of Internal Medicine, University of Szeged, Szeged, Hungary, [2]Department of Pharmacology and Pharmacotherapy, University of Szeged, Szeged, Hungary, [3]Department of Nuclear Medicine, University of Szeged, Szeged, Hungary, [4]Department of Internal Medicine and Oncology, Semmelweis University, Budapest, Hungary

5. **AUTONOMIC NEUROPATHY AND THE FREQUENCY OF HYPOGLYCAEMIA IN PATENTS WITH TYPE 1 AND INSULIN-TREATED TYPE 2 DIABETES. IS THERE A RELATIONSHIP?**
   Szabolcs Nyiraty[1], Bettina Tóth[1], Andrea Orosz[2], Csaba Lengyel[1], Péter Kempler[3], Tamás Várkonyi[1]
   [1]First Dept of Internal Medicine, University of Szeged, Szeged, Hungary, [2]Department of Pharmacology and Pharmacotherapy, University of Szeged, Szeged, Hungary, [3]Department of Internal Medicine and Oncology, Semmelweis University, Budapest, Hungary

6. **CARDIOVASCULAR AUTONOMIC AND PERIPHERAL SENSORY FUNCTION IN TOP ATHLETES AT CONDITIONED AND DECONDITIONED STATES**
Anna Vágvölgyi[1], Attila Farkas[2], Julianna Bernadett Tóth[1], Mónika Szűcs[3], Andrea Orosz[4], András Varró[4], Tamás Várkonyi[1], Péter Kempler[5], Csaba Lengyel[1]
[1]University of Szeged, Faculty of Medicine, I. Department of Medicine, Szeged, Hungary, [2]University of Szeged, Faculty of Medicine, 2nd Department of Medicine, Szeged, Hungary, [3]University of Szeged, Faculty of Medicine, Department of Medical Physics and Informatics, Szeged, Hungary, [4]University of Szeged, Faculty of Medicine, Department of Pharmacology and Pharmacotherapy, Szeged, Hungary, [5]Semmelweis University, Department of Oncology and Internal Medicine, Budapest, Hungary

10.00 – 10.30 **INVITED LECTURE 6 –** Tamás Várkonyi, Hungary: Erectile dysfunction

Chair: Simona Frontoni, ***Szabolcs Nyiraty***

10.30 – 11.00 COFFEE BREAK

11.00 – 12.00 SMALL FIBRE AND PATHOGENESIS [15min each]

Chair: Anna Körei

1. **ALTERED MICROVASCULAR PERFUSION OF THE PAIN PROCESSING AREAS OF THE BRAIN DURING THE EXPERIENCE SPONTANEOUS NEUROPATHIC PAIN**
Marni Greig[1], Gordon Sloan[1], Sharon Caunt[1], Pallai Shillo[2], Dinesh Selvarajah[3], Iain D. Wilkinson[4], Solomon Tesfaye[1]
[1]Diabetes Research Unit, Royal Hallamshire Hospital, Sheffield Teaching Hospitals NHS Foundation Trust, Glossop Road, Sheffield S10 2JF, UK, [2]Department of Diabetes, Chesterfield Royal Hospital, Chesterfield UK, [3]Department of Oncology and Human Metabolism, University of Sheffield, Sheffield UK, [4]Academic Unit of Radiology, University of Sheffield, Sheffield, UK

2. **FOLLOW-UP OF PERIPHERAL POLYNEUROPATHY IN SEVERELY OBESE PATIENTS WITH METABOLIC SYNDROME (WITHOUT DIABETES) SUBMITTED TO BARIATRIC**
Helena Schmid[1,2], Otto Henrique Nienov[1], Fernanda Dapper Machado[1]
[1]Programa de Pós-Graduação em Ciências da Saúde: Ginecologia e Obstetrícia, UFRGS, Hospital de Clínicas de Porto Alegre, Brazil, [2]Centro de Tratamento da Obesidade, Hospital Santa Rita do Complexo Hospitalar Santa Casa de Misericórdia de Porto Alegre, Porto Alegre, Brazil

3. **ROLE OF MECHANOINSENSITIVE NOCICEPTORS IN PAINFUL DIABETIC PERIPHERAL NEUROPATHY**

Mikhail I. Nemenov[1], Louis S. Premkumar[2]

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4. **SOCIAL DEPRIVATION AND INCIDENT DIABETES-RELATED FOOT DISEASE IN PATIENTS WITH TYPE 2 DIABETES - A POPULATION-BASED COHORT STUDY**

Jenny Riley[1], Christina Antza[2,3], Punith Kempegowda[2], Anuradhaa Subramanian[1], Joht Singh Chandan[1], Krishna Gokhale[1], Neil Thomas[1], Christopher Sainsbury[1], Abd A Tahrani[2,3,4], Krishnarajah Nirantharakumar[1]

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12.00 – 12.15 CLOSING REMARKS - Peter Kempler

POST-EXERCISE HEART RATE VARIABILITY IN TYPE 2 DIABETES WITH AND WITHOUT CARDIAC AUTONOMIC NEUROPATHY: A STATISTICAL PARAMETRIC MAPPING ANALYSIS

Jean-Baptiste Beaume[1,2], Cécile Reynes[2], Maximilien Bowen[1], Lisa Chatel[2], Françoise Latil-Plat[3], Houda Ennaifer[3], Laure Rocher[3], Yannick Knapp[2], Agnès Vinet[2]
[1]Université Savoie Mont Blanc, Chambéry, France , [2]Avignon Université, Avignon, France, [3]Service Endocrinologie-Maladies Métaboliques, Centre hospitalier Henri Duffaut, Avignon, France

Objectives: Cardiac Autonomic Neuropathy (CAN) is a common underdiagnosed complication of type 2 diabetes (DT2). Heart Rate Variability (HRV) at rest was impaired in DT2 with and without CAN. Whether the magnitude of that impairment is worsened during post-exercise recovery phase was unknown. Thus the aim was to compare resting and post-exercise recovery kinetics of HRV frequency variables in DT2 patients with and without CAN and control participants.
Methods: Thirty-two DT2 patients and 14 nondiabetics obese (NDO) were included. DT2 were divided in DT2 with CAN (CAN+; n=11) and without CAN (CAN-, n=21) based on cardiovascular autonomic reflex tests. Short-term resting and post-exercise HRV after a six-minutes walking test (6MWT) were analysed in time and frequency domain (Total Power Spectrum (TP), Low-Frequency (LF), High Frequency (HF), LF/HF ratio). After preprocessing, signals have been processed on MATLAB 2019 to get Time-Frequency maps of the RR signal (Fig1). Statistical Parametric Mapping (SPM) was used to identify statistical group differences in HRV that occur over time and at which frequency a group effect occurred.
Results: At rest, TP was lower in CAN+ and CAN- than NDO (111±79; 415±293 and 1573±1172ms², respectively $p<0.001$) and decreased only at recovery in NDO ($p<0.001$). with the same trends in LF and HF. From rest to recovery, mean normalized LF increased and mean normalized HF decreased with no difference between groups. However, post-exercise recovery kinetics showed different trends between groups. 6MWT induced little change in CAN- with low value of normalised LF and HF. Whereas LF increased and HF decreased to return to resting value in NDO after 5-min recovery, CAN +, tended to maintain high sympathetic and low parasympathic activities compared to NDO at the end of recovery, even if kinetics were similar.
Conclusion: While mean normalized LF and HF were not significantly different between groups from rest to recovery, SPM analysis of the post-exercise LF and HF kinetics underlined dysfunctions of the autonomic nervous system during exercise recovery in DT2.

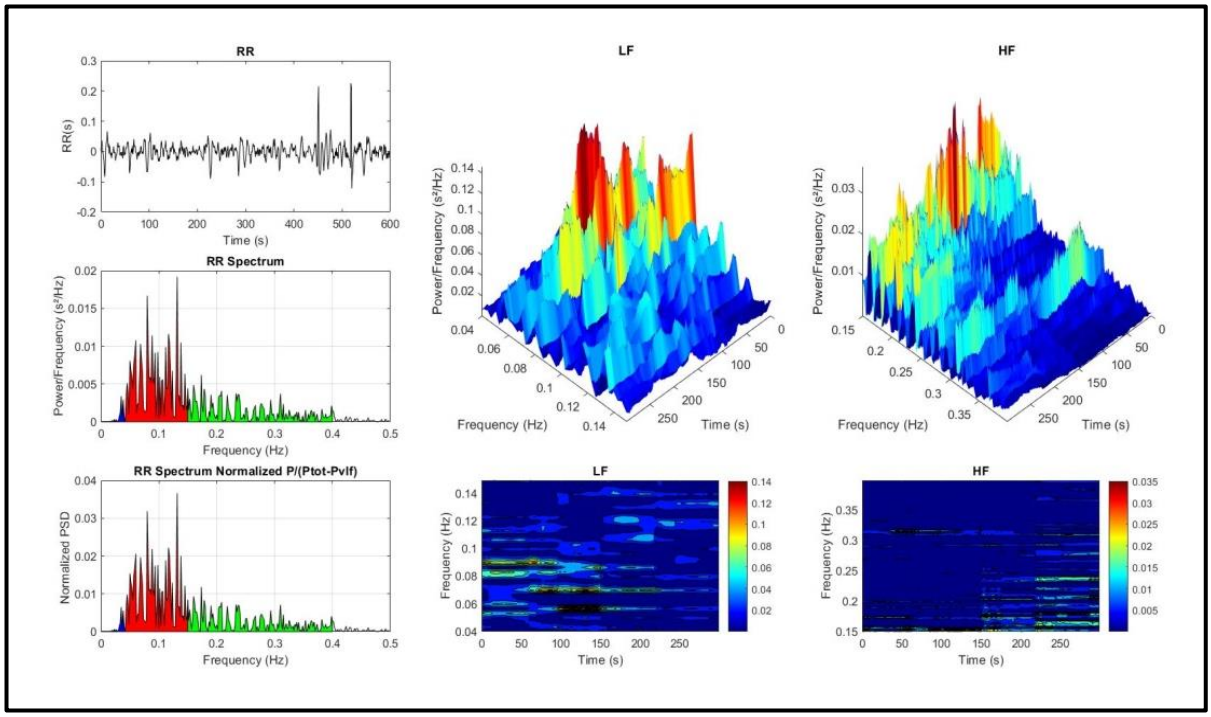

Fig.1 Data analyse on MATLAB 2019, to get Time-Frequency map of the RR signal.

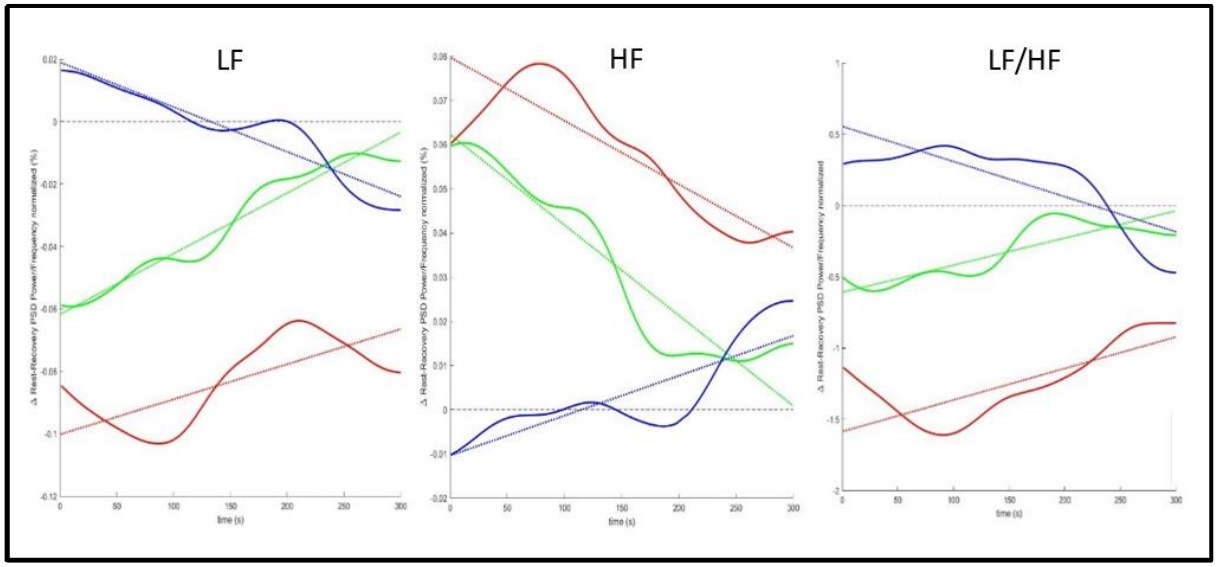

Fig.2 Kinetics of the delta rest-recovery in percentage of each groups on normalized Low-Frequency (LF), normalized High Frequency (HF) and LF/HF ratio. (Red, CAN+ ; Blue, CAN- ; Green, NDO ; solid line, kinetic over time ; dotted line, linear regression).

ASSOCIATION OF CARDIAC AUTONOMIC DYSFUNCTION WITH PLASMA BIOMARKERS OF LIPID METABOLISM IN RECENT-ONSET TYPE 2 DIABETES

Gidon J Bönhof[1,2,3], Alexander Strom[1,3], Klaus Straßburger[4,3], Birgit Knebel[5,3], Jörg Kotzka[5,3], Julia Szendroedi[1,3,2], Michael Roden[1,2,3], Dan Ziegler[1,2,3]

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Objectives: Emerging evidence suggests that obesity and insulin resistance play a role in the development of diabetic cardiac autonomic neuropathy (CAN) characterized by reduced heart rate variability (HRV).

Methods: We assessed the relationship of 127 biomarkers of lipid metabolism (11 acylcarnitines, 39 free fatty acids, 12 sphingomyelins, 56 phosphatidylcholines, and 9 lysophosphatidylcholines) in plasma using mass spectrometry with HRV indices in individuals with recent-onset type 1 (T1D) or type 2 diabetes (T2D) from the baseline cohort (known diabetes duration (DD) ≤1 year) of the German Diabetes Study (T1D/T2D [mean±SD]: n=126/243; age: 34.5±12.9/53.4±11.0 years; BMI: 24.7±4.3/31.7±6.0 kg/m²; DD: 211±93/198±90 days; HbA1c: 6.8±1.4/6.5±0.9 %). Time domain and frequency domain HRV indices were derived from NN intervals recorded during a 3 h hyperinsulinemic-euglycemic clamp.

Results: After adjustment for age, sex, and BMI as well as Bonferroni correction including seven HRV parameters and the number of metabolites of the corresponding lipid class, higher levels of three free fatty acids (myristic acid: β=-0.14, p=0.049; palmitic acid: β=-0.19, p=0.007; palmitoleic acid: β=-0.15, p=0.048), eight phosphatidylcholines (e.g. phosphatidylcholine diacyl (PC aa) C32:0: β=-0.28, p<0.001; phosphatidylcholine acyl-alkyl C34:3: β=-0.20, p<0.004), and two sphingomyelins (sphingomyelin C16:0: β=-0.15, p=0.028; sphingomyelin C16:1: β=-0.18, p=0.020) were inversely associated with the standard deviation of NN intervals (SDNN) in recent-onset T2D but not T1D. PC aa C32:0 was inversely associated with both low (LF) and high frequency (HF) power spectrum in T2D (LF: β=-0.23, p=0.001; HF: β=-0.23, p=0.001).

Conclusions: The link between higher plasma levels of specific lipid metabolites and early cardiac autonomic dysfunction in recent-onset type 2 diabetes suggests that plasma lipid panels could be useful to improve the prediction of the development or progression of CAN.

STRUCTURAL GREY MATTER ALTERATIONS AND COGNITIVE FUNCTION IN DIABETES: A UK BIOBANK STUDY

Jamie Burgess[1], Ioannis, N Petropoulos[2], Jonathan Z Lim[3], Bernhard Frank[4], Marta-Garcia Finana[5], Daniel J Cuthbertson[6], Simon Keller[7,8], Dinesh Selvarajah[9], Solomon Tesfaye[10], Uazman Alam[1, 11]

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Background: Structural alterations of the central nervous system are associated with cognitive decline and have been demonstrated in people with diabetes.

Methods: We aimed to identify cognitive function at baseline and at follow-up and characterise areas of global and anatomical grey matter volumes using T1-weighted magnetic resonance (MR) brain imaging (3-T MR imaging machine) at follow-up using participants from the UK Biobank dataset. Participants with diabetes (DM) (n=569) and non-diabetic participants (CON) (n=20,801) were analysed.

Results: The mean age of DM diagnosis was 49.5±15 years. Baseline demographic and anthropometric data are as follows: DM group included more men (DM: 65% vs CON: 47%) but were of a similar age (DM: 57.6±7.1 vs CON: 55±7.5 years). BMI (DM: 29.6±5.2 vs CON: 26.5±4.2 kgm^2; p<0.0001) and systolic blood pressure (DM: 141±17 vs CON: 137±19mmHg; p<0.0001) were higher in DM compared to CON with no difference in diastolic blood pressure (DM: 82±10 vs CON: 81±10mmHg; p=NS). The majority of participants in both groups were right-handed (DM: 88.9%, CON: 89.1%) with a minority reporting ambidexterity (DM: 2.1%, CON: 1.5%).

When comparing grey matter volume of DM vs CON: peripheral cortical grey matter (corrected for head size) (599002±41503mm^3 vs 621942±40421mm^3; p<0.0001), superior frontal gyrus (left: 10715±1695mm^3 vs 11056±1766mm^3; p=0.001; right: 9279±1513mm^3 vs 9608±1612mm^3; p<0.0001), left middle frontal gyrus (9894±1721mm^3 vs 10082±1786mm^3; p=0.035), right anterior division of the supramarginal gyrus (3061±598mm^3 vs 3143±614mm^3; p=0.001), right posterior supramarginal gyrus (5337±1052mm^3 vs 5476±1035mm^3; p=0.002), paracingulate gyrus (left: 5558±866mm^3 vs 5749±856mm^3; p=0.0006; right: 5456±845mm^3 vs 5700±852mm^3; p<0.0001), precentral gyrus (left: 13712±1717mm^3 vs 14065±1748mm^3; p=0.04; right: 13294±1652 vs 13711±1731 p<0.0001) and left postcentral gyrus (10905±1481mm^3 vs 11313±1492mm^3; p=0.0008) were all lower in DM compared to CON.

There were no differences in cognitive performance when comparing the number of incorrect matches recorded in cognitive function tests in DM vs CON at baseline (Pair Matching) (0.35±0.862 vs 0.375±0.903; p=NS). The number of incorrect matches increased in DM at follow-up (DM: 7.5±1.1 years vs CON: 7.66 ±-1.1 years) indicating greater cognitive decline in DM (DM: 0.45±0.953 vs CON: 0.33±0.830; p=0.003). Similarly, numeric memory (digit recall) was not different at baseline (DM: 7.28±1.17 vs CON: 6.93±1.38; p=NS) but was lower in DM at follow up (DM: 6.40±1.82 vs CON: 6.72±1.47; p = 0.05).

Conclusion: People with diabetes have a significant reduction in global grey matter volume and in distinct brain regions with greater cognitive decline at follow up.

CORNEAL CONFOCAL MICROSCOPY DETECTS SMALL FIBER NEUROPATHY IN PATIENTS WITH SEVERE HYPERTRIGLYCERIDAEMIA AND TYPE 1 DIABETES

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Objects: The aim of this study was to establish whether patients with severe hypertriglyceridaemia show evidence of small nerve fibre damage evaluated by corneal confocal microscopy (CCM), compared to patients with type 1 diabetes (T1D) and healthy subjects.

Methods: 24 patients with severe hypertriglyceridaemia (43.9±12.6 years), 21 patients with T1D (44.4±13.5 years) and 19 age-matched healthy controls (50.1±13.8 years) underwent CCM to quantify corneal nerve fiber density (CNFD) (no./mm^2), corneal nerve branch density (CNBD) (no./mm^2), corneal nerve fiber length (CNFL) (mm/mm^2) and inferior whorl length (IWL) (mm/mm^2).

Results: Age and body mass index (BMI) did not differ significantly but total cholesterol and triglycerides were significantly increased and HDL was lower in patients with hypertriglyceridaemia and controls (Table 1).

Patients with severe hypertriglyceridemia had a significantly lower CNFD ($p<0.001$), CNBD ($p<0.001$), CNFL ($p<0.001$) and IWL ($p<0.001$) compared to controls and significantly lower CNFD ($p<0.05$) and CNFL ($p<0.001$) compared to T1D. Patients with T1D showed significantly lower CNFD ($p<0.05$), CNBD ($p<0.05$) and IWL ($p<0.001$) compared to control subjects (Table 2). In patients with severe hypertriglyceridemia there was a significant negative correlation between serum triglycerides and CNFD (rho= -0.234, $p<0.01$), CNBD (rho= -0.644, $p=0.043$), CNFL (rho= -0.164, $p=0.006$) and IWL (rho= -0.359, $p=0.034$) after adjustment for age.

Conclusions: Hyperglycaemia was confirmed as a major risk factor for small-fibre neuropathy, in patients with T1D, however, this study shows that hypertriglyceridaemia *per se* is associated with small fibre damage observed using CCM.

Table 1. characteristics of patients enrolled	Controls (n=19)	T1D (n=21)	Severe Hypertrigliceridemia (n=24)	p	Post hoc analysis - P		
					hypertrig. Vs controls	hypertrig. Vs T1D	T1D Vs controls
Age (years)	50.1±13.8	44.4±13.5	43.9±12.6	n.s.			
BMI (kg/m2)	26.7±5.7	27.5±6.1	27.6±3.9	n.s.			
Total cholesterol (mg/dL)	204 (185-223)	158 (139-178)	232 (185-278)	**<0.001**	**<0.05**	**<0.001**	**<0.001**
HDL (mg/dL)	58.0±15.4	61.8±19.3	30.9±7.7	**<0.001**	**<0.001**	**<0.001**	n.s.
Triglycerides (mg/dL)	150 (115-177)	88 (62-115)	770 (380-1159)	**<0.001**	**<0.001**	**<0.001**	**<0.05**
LDL (mg/dL)	116±27	81±19		**<0.001**			
HbA1c (%)	5.5 (5.2-5.8)	7.4 (6.5-8.3)	5.4 (5.2-5.5)	**<0.001**	n.s.	**<0.001**	**<0.001**

Table 2. CCM parameters	Controls (n=19)	T1D (n=21)	Severe Hypertrigliceridemia (n=24)	p	Post hoc analysis - P		
					hypertrig. Vs controls	hypertrig. Vs T1D	T1D Vs controls
CNFD (n/mm^2)	35.94 (31.25-40.62)	31.25 (24.93-37.56)	27.08 (24.61-29.56)	**<0.001**	**<0.001**	**<0.05**	**<0.05**
CNBD (n/mm^2)	91.56±30.77	66.65±28.31	55.38±22.26	**<0.001**	**<0.001**	n.s.	**<0.05**
CNFL (mm/mm^2)	25.59 (22.35-28.83)	25.55 (22.56-28.54)	19.73 (16.78-22.68)	**<0.001**	**<0.001**	**<0.001**	0.058
IWL (mm/mm^2)	36.64±9.98	23±11	24.33±6.93	**<0.001**	**<0.001**	n.s.	**<0.001**

ALTERED MICROVASCULAR PERFUSION OF THE PAIN PROCESSING AREAS OF THE BRAIN DURING THE EXPERIENCE SPONTANEOUS NEUROPATHIC PAIN

Marni Greig[1], Gordon Sloan[1], Sharon Caunt[1], Pallai Shillo[2], Dinesh Selvarajah[3], Iain D. Wilkinson[4], Solomon Tesfaye[1]

[1]Diabetes Research Unit, Royal Hallamshire Hospital, Sheffield Teaching Hospitals NHS Foundation Trust, Glossop Road, Sheffield S10 2JF, UK, [2]Department of Diabetes, Chesterfield Royal Hospital, Chesterfield UK, [3]Department of Oncology and Human Metabolism, University of Sheffield, Sheffield UK, [4]Academic Unit of Radiology, University of Sheffield, Sheffield, UK

Objective We have previously reported increased thalamic vascularity in painful diabetic peripheral neuropathy (PDPN) but the microvascular perfusion characteristics of the other pain processing areas of the brain (pain matrix) with or without pain at the time of scanning have not been assessed. The aim of this study was to measure cerebral perfusion of pain matrix areas using MR-Dynamic Susceptibility Contrast (MR-DSC).

Methods: 55 T1DM subjects (20 PDPN, 23 painless-DPN, 13 no-DPN) and 19 healthy volunteers (HV) underwent detailed clinical and neurophysiological assessments. MR-DSC images assessed the passage of intravenous-gadolinium-chelate through cerebral vascular bed (3-Tesla, Philips, Netherlands) at rest. The PDPN group was further divided into those that had neuropathic pain during the scan P+ and no pain P- and the intensity of pain at the time of scanning was recorded. The Mean Transit Time (MTT) and the time-to-peak (TTP) concentrations of gadolinium in pain matrix areas (Thalamus, insular cortex - IC, anterior cingulate cortex – ACC), were measured.

Results: Subjects experiencing spontaneous neuropathic pain (P+, n=10, VAS score $\geq$ 4) during scanning had significantly shorter mean TTP at the Right-Thalamus: P+ vs DPN p=0.017, P+ vs HV p=0.033, Right-IC: P+ vs DPN p=0.048, and POWM: P+ vs P- p=.009, P+ vs DPN p=.034, P+ vs HV p=0.011. MTT at the Right-Thalamus: P+ vs HV was significant p=0.043, and at the Left-IC HV vs No-DPN was also significant p=0.036.

Conclusion This is the first study to show there is altered cerebral perfusion in the pain processing areas of the brain, with shorter TTP during spontaneous pain at the time of scanning. This seems to be related to a bolus dispersal factor as the MTT, and CBF do not match the TTP and the control area is also affected. However, whether this altered perfusion is primary or secondary to the experience of pain is yet to be determined. This novel finding may serve as an objective marker of spontaneous neuropathic pain, and a target for the development of novel treatments.

RELATIONSHIP BETWEEN HYPOGLYCAEMIA UNAWARENESS AND CARDIOVASCULAR AUTONONIC NEUROPATHY IN DISABLED PATIENTS WITH T1DM

Olga Svetlova[1], Irina Gurieva[1]
[1]*Federal Bureau of Medical and Social Expertise, Moscow, Russia*

Objectives: Hypoglycemia unawareness (HU) affects patients with T1DM and associated with severe hypoglycaemia. Cardiovascular autonomic neuropathy (CAN) is one of important factors associate with HU, although its role is not fully understood. Restriction of various types of life activity in T1DM is a relevant problem.
Methods: The 80 patients of T1DM (age 35,7±1,3 y.o., HbA1c 9,2±1,4%) of 13,9±1,0 years duration were examined.
Those patients have been submitted to continuous glucose monitoring (CGM, Medtronic MiniMed) within 72-hours. Hypoglycaemia was defined as lower 3,9 mmol/l and measured as ≥ 3 consecutive readings of CGM. HU was defined using special questionnaires and was scored as points (1-3 or more points). HU was evaluated as an absence of neuroglycopenic symptoms. CAN was diagnosed using 5 cardiovascular reflex tests (by Ewing) and scored (maximum 10) as being normal, parasympathetic (CANp), sympathetic (CANs) and combined lesions (CANps). Diabetic patients were designated CAN+ when two or more tests were abnormal or CAN-score≥4. Patients have been examined with special medical-social expert committee to determine abilities to work, mobility and selfcare.
Results: Patients were divided into 3 groups: 1st - with symptomatic hypoglycaemia (42,5%), 2nd - with 1-2 episodes of HU (35%), 3rd – with 3 and more episodes of HU (22,5%).
The 91,25% of patients had abnormal autonomic tests.
CAN differed statistically between 1 and 2(3) groups ($p<0,01$) for sympathetic, parasympathetic and combined scores. The 3rd group was characterized by prevalence parasympathetic (6,3±0,5) and the combined lesion (7,2±0,3) over sympathetic (5,3±0,9) ($p<0,01$).
CAN score ≥7 predicted HU with 84,0% of sensitivity and 96,3% of specificity.
The relation between CAN and HU ($r=0,76$; $p<0,001$), HbA1c and HU ($r=-0,44$; $p<0,01$) were found.
Disability was detected in 17 (21,25%) patients. In the 1st group disabled patients were not identified. Among the patients of the 2nd group 6 (21,4%) disabled patients were identified, while in the 3rd group 11 (61,1%) were disabled due to different compications of diabetes.
Those considerable limitations of the ability to work, self-care, mobility and learning in the 3rd group differed compared to the 2nd group ($p<0,05$).
Conclusions: The patients with hypoglycemia unawareness episodes were characterized by pronounced autonomic failures. The most severe group of patients with 3 or more episodes of HU was identified, which were characterized by the longest duration of T1DM, significant autonomic disorders, disability due to diabetic complications.

CARDIOVASCULAR AUTONOMIC NEUROPATHY IN TYPE 1 DIABETES IS ASSOCIATED WITH SEVERAL METABOLIC PATHWAYS – NEW RISK MARKERS ON THE HORIZON?

Christian S. Hansen[1], Tommi Suvitaival[1], Simone Theilade[1], Ismo Mattila[1], Maria Lajer[1], Kajetan Trošt[1], Linda Ahonen[1], Tine W Hansen [1], Cristina Legido-Quigley[1], Peter Rossing[1,2], Tarunveer S Ahluwalia[1]

[1]Steno Diabetes Center Copenhagen, Gentofte, Denmark, [2]Department of Clinical Medicine, University of Copenhagen, Copenhagen, Denmark

Objective: People with diabetes have increased risk of cardiovascular autonomic neuropathy (CAN), which leads to increased mortality and morbidity. CAN is difficult to prevent and yet not treatable. Thus, investigating new risk markers for CAN is a prerequisite for improved prevention. We investigated the association between circulating metabolites and presence of CAN in persons with type 1 diabetes (T1D).

Methods: CAN was assessed by cardiovascular reflex tests (CARTs) in 302 persons with T1D as heart rate response to: deep breathing; lying-to-standing test; and the Valsalva manoeuvre. Minimum of 2 pathological CARTs defined the CAN diagnosis. Moreover, 2 minutes resting heart rate (rHR) was assessed as an index of CAN.

Serum metabolomics and lipidomics profiles were analysed with two complementary non-targeted mass-spectrometry methods. Cross-sectional associations between single metabolites and CAN were assessed by linear regression and visualized as a chord diagram in R, where lines indicate significant associations. Models were fitted with and without adjustments (age, BMI, systolic blood pressure, cholesterol, HbA1c, smoking, statin use and total triglycerides) and $P_{corrected} < 0.05$ (Benjamini-Hochberg corrected) were reported.

Results: Participants were mean (SD) aged 59.7 (9.4) years, 50% males, with diabetes duration 39.9 (9.1) years, HbA1c 63.0 (11.1) mmol/mol, estimated glomerular filtration rate (eGFR) 78.7 (27.4) ml/min/1.73m^2, and 34% had the CAN diagnosis.

A total of 75 metabolites and 106 lipids were identified. In crude models, CAN diagnosis was associated with higher levels of hydroxy fatty acids (2,4- and 3,4-dihydroxybutanoic acids, 4−deoxytetronic acid), creatinine, sugar derivates (ribitol, ribonic acid, myo-inositol), citric acid, glycerol, phenols, phosphatidylcholines and lower levels of free fatty acids and amino acid methionine (see Figure). Further 23 associations were observed with the specific CAN measures (Figure). Upon adjustment, positive associations with CAN were retained with hydroxy fatty acids, tricarboxylic acid (TCA) cycle based sugar derivates, and citric acid, creatinine and phenols.

Conclusions: Multiple metabolic pathways, including the TCA cycle, hydroxy fatty acids, phosphatidylcholines and sugar derivatives, were associated with CAN in persons with T1D. This indicates that the novel metabolic pathways leading to CAN pathogeneses could prove to be future modifiable risk factors.

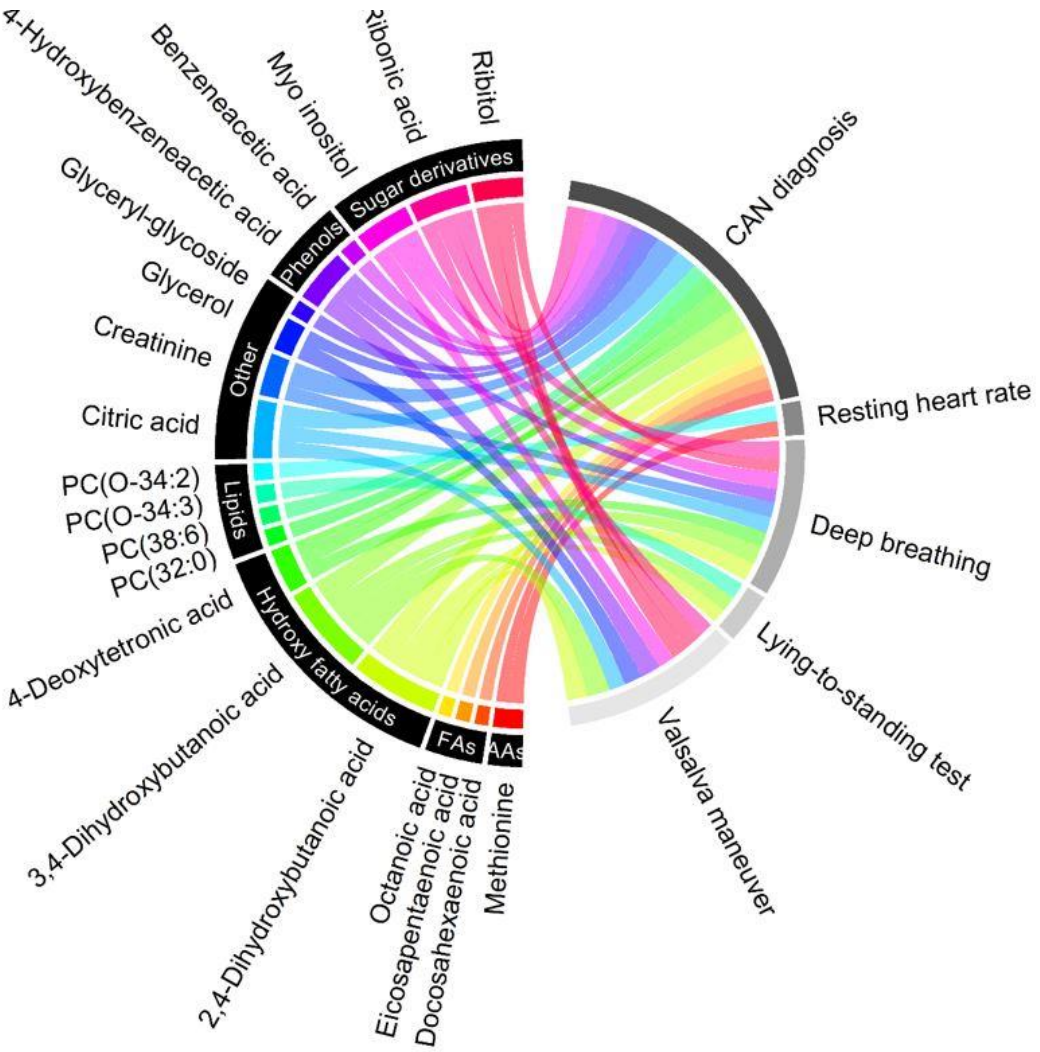

Figure: Chord diagram of the detected associations between metabolites (left) and CAN measures (right) from the crude model. Metabolites are categorized into pathways (left) and shown with unique colors. Width of a line indicates the strength of the respective association.

ARE THERE ECG PARAMETERS REPRESENTING CARDIAC REPOLARIZATION INFLUENCED BY THE PRESENCE CARDIOVASCULAR AUTONOMIC NEUROPATHY IN TYPE 1 DIABETES DURING EXERCISE?

Viktor Horváth[1], Gergely Szabó[1], Emese Szelke[1], Péter Szelke[1], Anna Erzsébet Körei[1], Magdolna Békeffy[1], Ádám Tabák[1], Péter Kempler[1]
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Introduction: Alterations of repolarisation markers in resting ECG (QT, QTc, Tpeak-to-Tend; TpTe) correlate significantly with ventricular arrhythmias. Among diabetic patients autonomic neuropathy is also a risk factor of malignant arrhythmias. In this case report we compared chanages of ECG repolarisation markers during ergometry among a healthy and an otherwise healthy type 1 diabetic (DM1) patient, as well as a type 1 diabetic patient with autonomic neuropathy (AN).
Methods: Age of the participants were similar (33-43 years) and so the diabetes duration among diabetic induviduals (18 and 20 years). Diabetics underwent standard neuropathy tests not earlier than six month prior to ergometry. The indication of the ergometry was undefined chest pain, the study was completed by using MDE Heidelberg ergometry system with modified Bruce protocoll. During the test we measured changes in heart rate (HR) QRS, QT, QTc and TpTe time.
Results: Compared to the controll and otherwise healty type 1 diabetic individual, patient with autonomic neuropathy produced a moderate increase in heart rate (ΔHR: controll=54/min; DM1=71/min, AN=36/min). Also, QT and TpTe times shortened moderately (ΔQT: controll=-63 msec; DM1=-99 msec; AN=-9 msec; ΔTpTe: controll=-44 msec, DM1=-42 msec, AN=-7 msec), but QTc time lenghtened (ΔQTc: kontroll=-39 msec; DM1=-56 msec; AN=45 msec). QRS duration did not change during any phase of the ergometry.
Conclusion: Our ergometry system may be helpful for evaluating cardiac complications related to autonomic neuropathy. Further involvment of patients is necessary to investigate whether the severity of autonomic neuropathy could correlate with the ECG markers of repolarisation.

TREATMENT OF PAINFUL DIABETIC NEUROPATHY USING FREQUENCY RHYTHMIC ELECTRO MAGNETIC NEURAL STIMULATION (FREMS); EFFECTIVENESS IN DAILY PRACTICE

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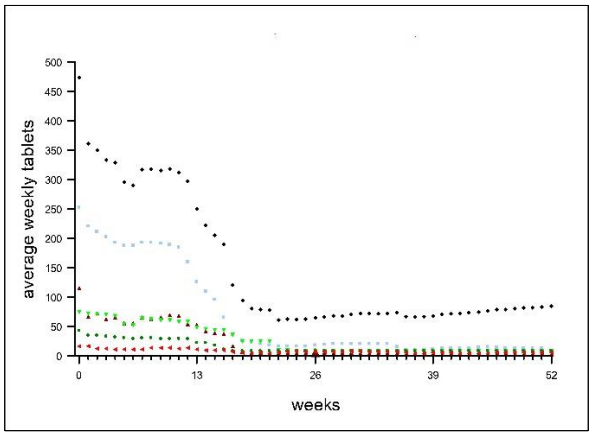
Background and aims: Painful Diabetic Peripheral Neuropathy (PDPN) is a common and difficult to treat condition with limited treatment options. In this study we assessed the efficacy of Frequency Electro Magnetic neural Stimulation (FREMS) in patients with PDPN.
Materials and methods: An uncontrolled prospective study of patients with PDPN and persistent pain despite at least two lines of pharmacotherapy (including pregabalin or duloxetine or similar). The primary outcome was 50% reduction in pain scores at 1 and 3 months post FREMS. FREMS was applied as per the manufacturer protocol to both legs below the knees using 4 sets of electrodes per leg; the treatment consisted of 10 sessions of 35 min applications given over 14 days. FREMS was repeated every 4 months and patients were followed up for 12 months. Pain was assessed using the Neuropathic Pain Symptom Inventory (NPSI). Quality of life (QOL) was assessed using the EQ-5D. Results:
Results: Out of 336 subjects 248 patients met the inclusion criteria (56% men, average age and diabetes duration were 65 and 12.6 years respectively. FREMS was associated with a median decrease NPSI of 31% at M1 (range -100;+93%), and a median decrease of -37.5% at M3 (range -100;+250%). The needed 50% reduction in pain severity was reached in 80/248 (32.3%) and 87/248 (35.1%) after M1 and M3 respectively. The change in NPSI was accompanied by an decrease in self reported use of opiates of over 50 % (see Figure)



Explenation: Effect of FREMS on self-reported used medication for Neuropathy during the 52 week period of follow-up. The diamonds represent all medications (solid black), the use of pregabalin (bleu squares), the use of amitriptyline (light-green downward arrows), the use of gabapentin (black upward arrow), morphine (green dots) and duloxetine (red arrow).
Conclusion: In this study, FREMS treatment was associated with significant reduction in pain severity over three months period in patients who did not have adequate response to pharmacotherapy. RCTs examining the role of FREMS as a treatment for PDPN in non-responders to pharmacotherapy are needed.

EFFICACY OF AN ORAL DISPERSIBLE TABLET CONTAINING VIT. B12 AFTER 12 MONTHS OF ADMINISTRATION IN PATIENTS WITH DIABETIC NEUROPATHY

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Aim: To investigate the efficacy and safety of the administration for 12 months of an oral dispersible tablet containing Vit. B12 (1000 μg/24h) in patients with Diabetic Neuropathy (DN).
Patients – methods: In current prospective, double-blind, placebo controlled, age matched study, 90 patients participated with Diabetes Mellitus Type 2 (DMT2), who received metformin for at least four years previously, mean age 63±11 years and they randomized in two groups: group A: n=44 received the tablet and group B: n=46 placebo. All patients had been diagnosed with neuropathy peripheral and autonomic and they were Vit. B12 deficient (normal values >450 pmol/L). The following methods used for detecting Diabetic Peripheral and Autonomic Neuropathy (DPN, DAN): Michigan Neuropathy Screening Instrument Questionnaire and Examination (MNSIQ and MNSIE), measurement of vibration perception threshold with biothesiometer (BIO) and Cardiovascular Autonomic Reflex Tests (CARTS: MCR, Vals, 30:15 ratio and Orthostatic Hypotension). Sural nerve functions were measured using DPN Check [sural nerve conduction velocity (SNCV) and amplitude (SNAP)]. Moreover, sudomotor function was assessed with measurement of hand and foot Electrochemical Skin Conductance (H and FESC) using the Sudoscan device. We used a pain (PAIN) and a quality of life (QL) questionnaire, also.
Results: All values of laboratory tests and indices of measurements between the two groups did not differ at baseline A vs B including HbA1c (6.79±0.69% vs 6.81±0.72% p=0.874, Vit.B12 235±73 vs 231±86 pmol/L p=0.817). The following indices improved significantly in group A (baseline vs final): BIO 32±13 vs 25±14 volts (p<0.001), MNSIQ 5.8±2.2 vs 5.4±2.1 (p=0.002), QL 39.9±10.3 vs 38.1±9.5 (p<0.0001), PAIN 18.4±9.7 vs 17.1±9.0 (p<0.0001), SNCV 28.1±22.7 vs 30.3±23.2 m/s (p<0.0001), SNAP 5.4±4.3 vs 7.3±4.7 uV (p<0.0001) and FESC 72.8±10.1 vs 74.5±10.1 μS (p=0.014). Indices of CARTS and MNSIE did not differ significantly in group A (baseline vs final). Vit. B12 increased in group A 235±73 vs 776.7±242.2 pmol/L (p<0.0001) and was unchanged in group B. We observed a significant deterioration in the following indices in group B: MCR (p=0.025), MNSIQ (p=0.017), SNCV (p=0.045), SNAP (p<0.0001) and PAIN (p<0.0001).
Conclusions: In current study after 12 months from the administration of the tablet in patients with DMT2, we observed a beneficial effect on all indices of peripheral neuropathy including neurophysiological parameters, sudomotor function, Pain and Quality of Life except CARTS and MNSIE. Levels of Vit. B12 normalized in group A with the tablet.

DIFFUSION TENSOR IMAGING OF THE SCIATIC NERVE DETECTS A LOSS OF SENSORIMOTOR FUNCTION IN PATIENTS WITH TYPE 2 DIABETES

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Objectives: Diabetic polyneuropathy (DPN) is one of the most poorly understood complications of diabetes mellitus. Recent studies showed that peripheral nerve lesions due to diabetic neuropathy are detectable with magnetic resonance diffusion tensor imaging (DTI). We investigated a functional relevance of DTI in proximal sciatic nerve in patients with type 2 diabetes.

Methods: Twenty-seven healthy controls and 64 patients with type 2 diabetes (32 with, 32 without DPN) underwent detailed clinical and electrophysiological assessments, and complete quantitative sensory testing (QST) as well as diffusion-weighted magnetic resonance neurography (MRN) of the sciatic nerve with subsequent automated calculation of the nerve's fractional anisotropy (FA).

Results: The mean FA value was significantly lower in sciatic nerves in patients with type 2 diabetes compared to healthy controls (p<0.001). Nerve integrity correlated with neuropathy disability score (NDS) (r=-0.49; p<0.001), but not with neuropathic symptoms or pain. Sciatic nerve FA values correlated with electrophysiological parameters such as tibial and peroneal nerve conduction velocity (NCV) (r=0.56; p<0.001 and r=0.54; p<0.001) as well as nerve amplitudes (r=0.51, p<0.001 and r=0.63; p<0.001) and sural NCV (r=0,28; p=0.04). There were significant differences in thermal and mechanical detection as well as mechanical pain clusters between the groups (p<0.01), but no correlation between FA and thermal nociception could be detected. Patients with a lower FA values in a sciatic nerve showed a loss of function regarding thermal and mechanical detection (r=0.35; p<0.01 and r=0.44; p<0.001) as well as mechanical nociception (r=0.38; p<0.01). In a linear regression only NDS was independently associated with a reduced nerve integrity in patients with type 2 diabetes.

Conclusion: This is the first study showing that the sciatic nerve's FA codifies a loss of function of different nerve fibers leading to neuropathic disabilities in patients with type 2 diabetes. Furthermore, our findings suggest that proximal nerve damage in diabetes parallels distal nerve function even before clinical symptoms occur.

FALLS IN INDIVIDUALS WITH TYPE 2 DIABETES; A CROSS-SECTIONAL STUDY ON THE IMPACT OF MOTOR DYSFUNCTION, POSTURAL INSTABILITY AND DIABETIC POLYNEUROPATHY

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Objectives: To estimate the incidence of falls in individuals with type 2 diabetes (T2DM) compared to healthy controls and to describe the characteristics of fallers with T2DM in relation to motor dysfunction, postural instability and diabetic polyneuropathy (DPN).
Methods: This is a cross-sectional study of individuals with T2DM with DPN (n=54), without DPN (n=38), and healthy controls (n=39). Falls were recorded within the preceding year. DPN was defined by clinical scores and nerve conduction studies. Motor function was assessed by a six-minute walk test (6MWT), a five-time sit-to-stand test (FTSST) and isokinetic dynamometry at the non-dominant ankle and knee. An instability index (ST) was measured using static posturography. Univariate and bivariate descriptive statistics were used for group comparisons.
Results: Compared with healthy controls, individuals with diabetes had a higher incidence of falls 36%, (n= 33) vs. 15%, (n=6), p=0.02. There were no differences in falls when comparing individuals with and without DPN. Fallers had an impaired 6MWT vs. non-fallers (450±153m vs. 523 ±97m, respectively), a slower FTSST (11.9± 4.2 sec. vs. 10.3±2.9 sec. respectively) and a higher ST (53±29 vs 41±17 respectively), $p<0.02$ for all.
Conclusion: Individuals with T2DM reported a higher number of falls within the preceding year compared to healthy controls, irrespective of the presence of DPN. The main risk factors associated with falls were increased postural instability, lower walking capacity and slower sit to stand movements.

IS THERE ANY INDICATION FOR PLASMAPHERESIS AND OPIOID THERAPY IN THE TREATMENT OF DIABETIC NEUROPATHY? – A CASE REPORT

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Our 72-year-old patient had type 2 diabetes (T2DM), hypertension, lower limb deep vein thrombosis, chronic granulomatous colitis and depression in his past medical history. He has had T2DM for 27 years and he has received insulin therapy for many years.
He was diagnosed with diabetic neuropathy 30 years ago. In 2016, he got metatarsal bone resection due to osteomyelitis of the right IV toe. To resolve obliterating artery disease, percutaneous transluminal angioplasty (PTA) and stent implantation were performed on the left anterior tibial and peroneal artery (2016, 2018 and 2019). Coronarography revealed significant stenoses of LAD, CX and RCA behind recurrent episodes of angina in 2017 and 2019 (DES implantations). Concerning antecedent frequent hypoglycaemias and the high cardiovascular risk of the patient, his multiple daily injection insulin treatment was switched to basal insulin analogue+GLP-1 receptor agonist therapy in 2018.
This time, our patient was admitted to hospital because of poor glycaemic control (HbA1c: 11%) and falls. To achieve better metabolic control in the obese patient (BMI: 39.2 kg/m2), we titrated doses of SGLT2-inhibitor and GLP-1 receptor agonist therapy. The patient has already been on combination therapy for severe painful diabetic neuropathy including both pathogenetically oriented (benfotiamine and alpha-lipoic acid) and symptomatic (duloxetine and pregabalin) treatment options. Despite, he still suffered from typical neuropathic pain. On neuropathy examination, severe sensory impairment was confirmed on all extremities by diminished current perception thresholds (CPT) measured by Neurometer (Neurotron Inc.) (CPT: 9,99 mA for all sensory nerve fibre types), by the Vibratip, Tiptherm, the monofilament (0/5 on all limbs), the tuning fork (0/8 on the lower limbs and 4/8 on the upper limbs) and thermal perception thresholds detected by Q-Sense (Medoc Ltd.). Moderate cardiovascular autonomic neuropathy was also proven. Based on the neuropathy studies, the frequent falls complained by our patient might have resulted from his severe distal sensorimotor neuropathy and orthostatic hypotension (32 mmHg). Interestingly, extremely severe sensory deficit and severe neuropathic pain were present at the same time in this patient. As the so far administered fourfold combination therapy did not provide sufficient pain relief, the patient underwent plasmapheresis and opioid therapy was initiated with approving result.
Conclusions: Diabetic neuropathy may be characterized by extremely severe hypaesthesia and neuropathic pain simultaneously. Good glycaemic control is a cornerstone in the treatment of diabetic neuropathy. When treating painful diabetic neuropathy, both pathogenetically oriented and symptomatic therapy should be implemented. Besides, plasmapheresis and opioid supplementation should be considered for some patients. The elimination of “metabolic endotoxaemia” and proinflammatory mediators may underlie the therapeutic effect of plasmapheresis in diabetic neuropathy.
Keywords: diabetic neuropathy, plasmapheresis

CARDIOVASCULAR AUTONOMIC DYSFUNCTION IS ASSOCIATED WITH DECLINE IN KIDNEY FUNCTION IN TYPE 2 DIABETES AND HEALTHY CONTROLS

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Background and aims: Cardiovascular autonomic dysfunction is a prevalent and severe complication in type 2 diabetes and has been associated with a decline in renal function in various populations. We assessed the impact of cardiac autonomic dysfunction on change in kidney function and albuminuria in a cohort of persons with type 2 diabetes and in healthy controls.
Materials and methods: In 2013 we recruited 60 persons with type 2 diabetes and 30 controls. At baseline, estimated glomerular filtration rate (eGFR) and urinary albumin excretion rate (UAER) were measured. All participants underwent cardiovascular reflex testing (response in heart rate variability from lying to standing (30:15), during expiration vs. inspiration (E/I) and during Valsalva's manoeuvre (Valsalva)) and had continuous parameters of cardiovascular autonomic function assessed from heart rate variability in a 5-minute resting ECG, including the standard deviation of the normal to normal interval (SDNN), root mean square of the successive differences (RMSSD), the low- (aLF) high frequency power (aHF), total power (aTotal) and the LF/HF interval (LF/HF). At follow up, kidney function parameters were measured again (albuminuria was evaluated as urinary albumin creatinine ratio).
Results: For the follow up, 32 persons with type 2 diabetes and 21 controls were willing to participate and included in the analyses. Median [interquartile range] follow-up time was 6.2 [6.0 to 6.3] years. At baseline, mean ± SD age was 60 ± 10 years, median known diabetes duration was 12 [5 to 21] years and mean Hba1c in the type 2 diabetes group was 54 ± 11 mmol/mol. At baseline, mean eGFR was similar between groups (type 2 diabetes: 79 ± 21 ml/min/1.73m^2 and controls: 86 ± 12 ml/min/1.73m^2; p=0.183) and median UAER was higher (p<0.001) in the type 2 diabetes group (33.5 [6.5 to 107.5] mg/24-h) than controls (5.5 [5.0 to 6.5] mg/24-h).
During follow up, eGFR decreased in both groups (type 2 diabetes: -1.0 (95%CI: -1.4 to -0.5) ml/min/1.73m^2/year p<0.001 and controls: -0.7 (95%CI: -1.1 to -0.3) ml/min/1.73m^2/year p=0.001) and the change was similar between groups (p=0.179). Albuminuria did not change significantly in any of the groups during follow up.
In univariate analyses, a lower response in heart rate variability during Valsalva (p=0.018), and a higher SDNN (p=0.027), aHF (p=0.037) and aTotal (p=0.043) was correlated with a steeper yearly decline in eGFR. After adjustment for age, sex, smoking, Hba1c, body mass index, heart rate, 24-hour systolic blood pressure, plasma cholesterol, baseline UAER and baseline eGFR, only a lower SDNN remained significantly (p=0.029) associated to a steeper yearly decline in eGFR. Measures of cardiovascular autonomic function were not associated with change in albuminuria.
Conclusion: Cardiovascular autonomic dysfunction assessed by heart rate variability was associated with steeper decline in kidney function during 6 years of follow up. Cardiovascular autonomic dysfunction may be a marker of higher risk of decline in eGFR. Whether there is a causal link remains to be established.

A CLINICAL SCORING SYSTEM FOR THE RISK OF CARDIOVASCULAR AUTONOMIC NEUROPATHY IN TYPE 1 DIABETES

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Objectives. A reasonable approach to the under diagnosis of cardiovascular autonomic neuropathy (CAN) consists in identifying the best candidates for CAN screening. We developed a clinical scoring system for CAN risk in diabetes 2 with an acceptable diagnostic performance for CAN. Similarly, this study was aimed at developing a CAN risk score for type 1 diabetes, based on associations between CAN and clinical variables observed in a retrospective cross-sectional one-centre study in an unselected population with type 1 diabetes.
Methods: Eighty-nine participants with type 1 diabetes (age 43±12 years, duration 25±13 years, HbA1c 7.7±1.1%, 35 males), free from conditions affecting autonomic function and well-characterised for clinical variables, underwent standard cardiovascular reflex tests (CARTs).
Results: Confirmed CAN (based on 2 abnormal CARTs) was present in 16 participants (18%). In multivariate logistic regression analyses adjusted for sex, age, BMI and diabetes duration, confirmed CAN was associated with retinopathy (P=0.0175), cardiovascular disease (P=0.0155), low HDL (<40 mg/dl in males and <50 mg/dl in females) (P=0.0152), resting heart rate (HR) ≥80 bpm (measured as the average HR obtained from two 10 second resting ECG recordings in lying position) (P=0.0055), and casual systolic blood pressure (SBP) >140 mmHg (P=0.0221). Using the same model, early CAN (based on 1 abnormal CART and present in 18% of participants) was associated also with microalbuminuria (P=0.0045) and smoking (P=0.0170). Thus, a risk score was built, according to the strength of associations in multivariate analyses, by giving a score of 3 to HR ≥80 bpm, a score of 1 or 2 to SBP >130 or >140 mmHg, a score of 2 to the presence of cardiovascular disease, and a score of 1 to each of the following: low HDL, smoking, and the presence of retinopathy and/or microalbuminuria (range: 0-10). This CAN risk score was associated with confirmed CAN (P<0.0001), was related to CARTs (deep breathing: rho=-0.499, P<0.0001; lying to standing: rho=-0.453, P<0.0001; overall CARTs score: rho=0.57, P<0.0001), and showed good diagnostic accuracy for both confirmed CAN and CAN (early and confirmed). The table shows the area under the ROC curve (AUC), sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) of CAN risk score at the cut-off of 3.
Conclusions: This newly developed CAN risk score identifies the subjects with confirmed CAN with a high sensitivity and NPV. It is based on easily detectable parameters and hence accessible in clinical practice. If confirmed in a validation study in a larger population with a shorter diabetes duration, it might identify individuals with type 1 diabetes at greater risk of CAN to be referred to CARTs performance and limit the burden of a universal screening.

Table. Diagnostic characteristics of the CAN risk score (cut-off 3) for CAN and confirmed CAN

	AUC	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)
Confirmed CAN	0.86±0.039 (CI 0.78-0.94	100 (CI 100-100)	60.3 (CI 49.0-71.5)	35.6 (CI 21.6-49.5)	100 (CI 100-100)
CAN (early and confirmed)	0.75±0.053 (CI 0.65-0.86)	78.1 (CI 63.8-92.4)	64.9 (CI 52.5-77.3)	55.6 (CI 41.0-70.1)	84.1 (CI 73.3-94.9)

AUTONOMIC NEUROPATHY AND THE FREQUENCY OF HYPOGLYCAEMIA IN PATENTS WITH TYPE 1 AND INSULIN-TREATED TYPE 2 DIABETES. IS THERE A RELATIONSHIP?

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Background and aims: Autonomic neuropathy (AN) may play an important role in the pathogenesis of hypoglycemia, but the relationship between autonomic dysfunction and low glucose levels in the clinical practice is poorly documented. The aim of our study was to evaluate the incidence and severity of AN and to assess the risk and awareness of hypoglycemia in our patients with long-standing type 1 and insulin-treated type 2 diabetes (DM) with unstable glucose metabolism.

Materials and methods: 52 diabetic patients (40 type 1 and 12 type 2 insulin-treated DM patients, age: 46.4 ± 2.3 years, disease duration: 18.5 ± 1.5 years; HbA1c: 8.3 ± 0.2%; mean ± SE). 10 healthy subjects were included as controls. The five standard cardiovascular reflex tests were performed to determine AN. Tissue glucose values were monitored by subcutaneous continuous glucose monitoring (CGM) for 6 days.

Results: Significant AN was demonstrated in the patient group (AN score: 2.5±0.2 vs 09±0.2 $p<0.05$, heart rate change during deep breathing: 18.2±1.3 vs 32.6±3,8 beats/min, $p<0.01$; DM vs control). The mean frequency of hypoglycemic episodes measured with CGM over a 6-day period was 4.5±0.5, while 2±0.3 events were reported by the patients only. There was no correlation between AN and frequency of hypoglycemia awareness. The incidence of hypoglycaemia was not correlated with DM duration, but DM duration was associated with more severe AN (DM duration-AN: $r=0.29$, $p<0.05$). Higher HbA1c was found in patients with less hypoglycemia ($r=-0.30$, $p<0.05$) and with more severe AN ($r=0.51$, $p<0.01$).

Conclusion: Hypoglycaemic episodes are common in our long-standing type 1 diabetic and insulin-treated type 2 diabetic patients, but more than half of the episodes are silent. In this patient group, hypoglycaemia was less frequent in the presence of higher HbA1c. As a key finding, autonomic neuropathy associated with longer disease duration and higher HbA1c did not affect the frequency of hypoglycaemia awareness in this study.

AUTONOMIC NEUROPATHY AND GLUCOSE VARIABILITY IN PATIENTS WITH TYPE 1 DIABETES. A POTENTIAL ROLE OF IMPAIRED GASTRIC EMPTYING?

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Autonomic neuropathy (AN) and the associated impaired gastric emptying may play an important role in the pathogenesis of permanently unstable glucose metabolism.
The aim of this study was to measure cardiovascular autonomic neuropathy (AN) and gastric emptying in type 1 diabetic patients with extreme fluctuations of blood glucose levels.
Patients, methods: 11 type 1 diabetic patients were included (age: 54,7±5 years, disease duration: 28,3±4,5 years; HbA1c: 9,1±0,2%; mean±SE), who had alternating hyper- and hypoglycemic episodes of unknown reasons despite treatment reconsiderations in the past 6 months. We performed cardiovascular reflex tests (CRT) to identify AN. Glucose metabolism was detected by continuous glucose monitory system (CGMS) for 6 days. Each patient had a gastric emptying scintigraphy**.**
Results: High glucose variability was found (Continuous overlapping net glycemic action [CONGA]: 9,2±1,5, Standard deviation [SD]: 3,9±0,2, Mean amplitude of glycemic excursions: [MAGE]: 7,5±0,6, Mean absolute glucose [MAG]: 2,1±0,1). The patients documented 4,5±1,8 hypoglycemic episodes during 6 days of monitoring. The half time of gastric emptying was longer than normal (96,6±19 minutes). We found positive correlation between MAG and AN ($r=0,63$, $p<0,05$), and also positive correlation was confirmed between HbA1c and the half time of gastric emptying ($r=0,80$, $p<0,001$). No correlation was found among AN, gastric emptying and further parameters of glucose metabolism.
Conclusion: The frequency of hypoglycemia is high in patients with 3 decades of type 1 diabetes and increased glucose variability. Higher glucose variability was associated with more severe autonomic neuropathy in these patients. The strong correlation between higher HbA1c and slower gastric emptying proves an important role of gastric motility in the development of unstable glucose metabolism.

RELATION BETWEEN HAPTICS AND STANDARD NEUROLOGICAL ASSESSMENT FOR THE EVALUATION OF TACTILE SENSITIVITY IN TYPE 1 DIABETES MELLITUS

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Objectives: The sense of touch is mechanical and it depends on different types of skin deformations. Tactile dysfunctions are frequent in diabetic patients with peripheral neuropathy. Haptics is a novel discipline that studies touch by means of mechatronic devices artificially recreating tactile stimuli. Here, we developed a novel test based on haptics for the evaluation of tactile sensitivity (TS) and we tested the relationship between TS as measured with haptic test, biothesiometry and standard sensory motor nerve conduction studies (NCS), in type 1 diabetic patients (DM1).
Methods: 20 DM1 patients (HbA1c < 9.5%) and 13 healthy control subjects (C). Patients underwent a neurological assessment with monofilament and vibratory perception (VP) using biothesiometry and bilateral NCS to upper and lower limbs. Patients were divided in two groups based on VP alterations (VP- and VP+). TS has been evaluated using a haptic mechatronic device that produced highly precise motions. The protocol was replicated with and without masking vibrations (MV). By means of Generalized Linear Mixed Models (GLMM), we tested the ability of the participants to discriminate motion speed in the two conditions.
Results: None of the DM1 patients tested positive in the monofilament test. Mean HbA1c was equal to 7.8% +/- 0.86 (mean +/- SD). DM1 group was divided in 12 VP+ and 8 VP- patients. TS in the upper limbswas significantly lower in VP+ as compared to the C with and without MV (GLMM difference in the slope was -0.27 +/- 0.11, p = 0.01; GLMM difference in slope = -0.11 +/- 0.03, p<0.001, respectively). Considering the three groups, we observed the following trend: TS in VP+ < TS in VP- < TS in C. The effect of MV significantly impaired TS in the three groups (p < 0.0001). A positive significant linear relationship between TS with and without MV and conduction velocity (estimate = 0.009 , p = 0.017; (estimate = 0.012, p = 0.01, respectively) and amplitude (estimate = 0.006, p = 0.03; estimate = 0.0087, p = 0.011) of sural and radial nerve were observed in DM1 patients.
Conclusions: TS in fingertips was significantly lower in patients with reduced vibration sensitivity in lower limbs with respect to controls. A significant relationship between sensory nerve conduction in the upper and lower limbs and TS was also observed. In the future, it will be possible to extend our test for lower limbs and introduce haptics for the evaluation of peripheral diabetic neuropathy.

EFFECTS OF INTENSIVE RISK FACTOR MANAGEMENT ON CARDIOVASCULAR AUTONOMIC NEUROPATHY IN TYPE 2 DIABETES: FINDINGS FROM THE ACCORD CLINICAL TRIAL

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Background and aims: Cardiovascular autonomic neuropathy (CAN) is a common complication that independently predicts cardiovascular (CV) morbidity and mortality in persons with type 2 diabetes (T2D). The effects of preventive interventions on CAN remain unclear. We examined the effect of intensively targeting traditional risk factors for CAN, including hyperglycemia, hypertension, and dyslipidemia, in persons with T2D and high CV risk participating in the Action to Control Cardiovascular Risk in Diabetes (ACCORD) trial.

Materials and methods: CAN was defined as heart rate variability indices below the 5th percentile of the normal distribution (standard deviation of all normal-to-normal R-R intervals [SDNN] <8.2 ms and root mean square of successive differences between normal-to-normal R-R intervals [rMSSD] <8.0 ms). Of the 10,250 ACCORD participants, 71% (n=7,275) had valid CAN evaluations at study entry and at least once after randomization. The effects of intensive interventions on CAN were tested among these subjects by means of generalized linear mixed models.

Results: As compared to standard treatment, the intensive glycemia intervention significantly reduced CAN risk during the entire duration of the study (OR=0.84, 95% CI 0.75 – 0.94, p=0.003). This effect was present among individuals with no cardiovascular disease (CVD) history (OR= 0.73, 95%CI 0.63 – 0.85, p<0.0001) but not among those with a positive CVD history (OR=1.10, 95% CI 0.91 - 1.34, p=0.34) (p for interaction=0.001). Intensive BP therapy also decreased the odds of CAN (OR=0.75, 95% CI 0.63 – 0.89, p=0.001), with no evidence of heterogeneity based on CVD history or other clinical characteristics. Fenofibrate did not have a significant impact on CAN outcome (OR=0.91, 95%CI 0.78 – 1.07, p=0.26). No significant interactions were observed between treatment strategies

Conclusions: Our data confirm the beneficial effect of intensive glycemic therapy and demonstrate, for the first time, a similar benefit of intensive BP control on CAN in T2D. They also suggest that a negative CVD history could be used as a criterion to select those T2D patients who would most benefit from intensive glycemic control for CAN prevention, whereas BP control is effective regardless of CVD history.

POOR ORAL HEALTH PREDICTS PROGRESSION OF DIABETIC PERIPHERAL NEUROPATHY

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Background and aims: Poor oral health (OH) manifested mainly as gingivitis/periodontitis is emerging as a serious diabetes complication. Recent reports suggest that poor OH may share pathogenic mechanisms with diabetic neuropathy (DN). We previously reported a high prevalence of poor OH in a large Romanian cohort of >1300 participants with diabetes phenotyped for OH and DN in 2016, particularly among participants with DN. This follow-up study aimed to further evaluate associations between DN and OH in this cohort over time.
Materials and methods: 104 participants were selected for this follow-up study, after signing the inform consent and obtaining the approval of the Local Ethics Committee in order to complete a second evaluation in 2018/2019. The characteristics of the study population were as follows: median age (25^{th}-75^{th} percentile) 63 (59-70) years, 53% male, median diabetes duration 13 (8-17) years, mean A1c 7.8±1.5%. DN was assessed with the Michigan Neuropathy Scoring Instrument (MNSI), questionnaire (MNSIq) and clinical examination (MNSIe). Clinical DN was defined as MNSIe score of >2; symptomatic DN as MNSIq score of ≥4. OH was assessed using a validated questionnaire that includes questions about: 1.-gingival pain, 2.-gingival bleeding and 3.-existing complete dentures. OH was defined as good (no symptoms/signs), poor (symptoms/signs often/very often) or very poor (edentulous patients wearing complete dentures).
Results: Preliminary data is presented for 104 participants who completed a second evaluation in 2018/2019. Among them 62 % presented with MNSIe>2 and 44 % with MNSIq>4. Poor and very poor OH at baseline (2016) were significantly correlated with MNSIe at follow-up (2018) ($r = 0.20$, $p = 0.04$). After adjusting for age and duration, there was a significant positive correlation between worsening in OH and DN ($r = 0.26$, $p = 0.037$) at follow-up. In multivariate analysis, after controlling for age and diabetes duration, there was a significantly higher change in the overall MNSI scores during follow-up in those with poor and very poor OH (0.97 +/- 1.9 vs. 0.16 +/- 1.8 $p = 0.036$).
Conclusion: These data show that in this longitudinal cohort with diabetes DN worsened over time particularly in those with poor OH, suggesting that OH may directly affect risk of DN and other complications.

DAPAGLIFLOZIN AND MEASURES OF CRADIOVASCUALR AUTONOMIC FUNCTION IN PATIENTS WITH TYPE 2 DIABETES

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Objectives: Beneficial effects of sodium-glucose cotransporter-2 inhibitors on cardiovascular outcomes in patients with type 2 diabetes (T2D) have been reported. We hypothesized that these benefits may be due to modulatory effects on the sympathetic/parasympathetic imbalance through blunting of the expected compensatory increase in heart rate associated with lowering blood pressure. We aimed to evaluate the effect of dapagliflozin (DAPA) on measures of cardiovascular autonomic neuropathy (CAN) and cardiac function as assessed by the B type natriuretic peptide (BNP) in patients with T2D.

Methods: We performed a pilot, randomized, 2-period crossover clinical trial comparing 12 weeks of glucose lowering intervention with DAPA versus glimepiride on measures of CAN [standardized cardiovascular autonomic reflex tests (CARTs) and heart rate variability (HRV)] assessed at baseline and at the end of each drug period. Signed rank tests and mixed models were used to evaluate the differences in CARTs and HRV indices from baseline to 12 weeks between each drug period. Serum BNP was collected as a biomarker of left ventricular function during each study drug period.

Results: Preliminary data are presented for 41 participants with T2D on metformin monotherapy (mean age 57 ± 8 years, mean diabetes duration 7 ± 6 years, mean HbA1c 7.8 ± 1.3%) at baseline. Although there were no significant differences in indices of CAN between the 2 study drug periods, there was a trend for higher expiration and inspiration (E/I) ratio during DAPA treatment compared with glimepiride (mean change 0.02 ± 0.10; p=0.07). Using mixed effects models, we found significant or near significant interactions between sex and treatment for the root mean square of the differences of successive RR intervals (rmsSD) (p=0.021) and Valsalva ratio (p=0.06) in women on DAPA versus glimepiride compared with men. In women, the mean 12-week change for both measures on DAPA was larger than the mean change on glimepiride, whereas in men, the mean 12-week change was larger on glimepiride than DAPA. The changes in the BNP levels from baseline were similar in the 2 study drug periods (mean change 3.99 ± 16.62 pg/ml, p=0.23, with DAPA vs. glimepiride).

Conclusion: These pilot data suggest that DAPA may have beneficial effects on measures of CAN particularly in women with T2D, in spite of short treatment duration. These findings need to be confirmed in larger prospective studies with longer follow-up.

nella presentazione risultati differenti, le piccole differenze mediate da peso e variabilità glicemica?

ROLE OF MECHANOINSENSITIVE NOCICEPTORS IN PAINFUL DIABETIC PERIPHERAL NEUROPATHY

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The mechanisms or the processes underlying painful diabetic peripheral neuropathy (PDPN) are far from clear, especially, cutaneous mechanisms that trigger spontaneous neuropathic pain. It represents a critical gap in the treatment PDPN and the development of novel analgesics. In fact, the only measurement that has been correlated to ongoing pain in PDPN patients is the number of spontaneously active cutaneous nociceptors. Two types of nerve fibers are found within the epidermal and dermal skin layers. Small-diameter lightly myelinated Aδ and unmyelinated C cutaneous nociceptors transmit pain from periphery to central nerve system. Aδ and C fibers are divided by sensitivity: mechanical and heat sensitive (AMH and CMH) are mainly located at epidermis and C mechano-insensitive (CMi) fibers mainly in the dermis. In animals and humans, dying back intraepidermal AMH and CMH fibers lead to reduced pain sensitivity, rather than pain, which suggests fiber loss alone is not sufficient to account for the development of neuropathic pain. However, in these patients CMi fibers are abnormally spontaneously active. The differences in these two fiber types may allow to differentiate patients with painful and painless neuropathy. Therefore, a tool that can measure, track, and predict the development of abnormal function of CMH and CMi fibers is a critical unmet medical need.

In certain types of painful neuropathy, such as PDPN, metabolic syndrome and chemotherapy-induced peripheral neuropathy (CIPN), there is a dramatic dying back or degradation of epidermal fibers. Despite symptoms of pain, these patients have significantly increased pain thresholds when tested with currently available methods, which primarily activate epidermal fibers, such as the CO_2 laser, radiant heat or contact thermode. These tests are not fiber-type selective. Only microneurographic recording is able to separate fiber type and to access single fibers. Due to its complexity, microneurography is not practical in the clinical settings. In contrast, the newly developed diode laser fiber selective stimulation (DLss) technique by Lasmed, allows to safely and selectively stimulate Aδ and C fibers in superficial and deep skin layers. The DLss is a fiber specific, noninvasive and portable technology that selectively activates small nerve fibers at a depth that is not possible with other techniques. DLss data demonstrate that patients with painful DPN, who have decreased epidermal Aδ and C-fiber densities, have increased Aδ pain thresholds, while C-fiber thresholds are intact. The Aδ:C pain threshold ratio is consistently higher in PDPN than healthy volunteers. It is also possible to determine the involvement of CMi fibers by measuring the area of DLss induced neurogenic reflex flare. The size of the flare mediated by CMi fibers are much larger than the size of the receptive field of CMH fibers. Furthermore, we propose that spontaneously active CMi fibers could be accessed by using nanoparticle cream formulations such as Resinizin™ (a RTX cream formulation) that allows deeper penetration to induce pain relief in PDPN and DLss provides treatment efficacy feedback. This study is supported by a grant from NIH/NIDDK-DK117674) to LSP and NIH/NCI-CA206796 to MIN.

SPECTRAL ANALYSIS OF THE VENOARTERIOLAR REFLEX IN TYPE 2 DIABETIC WITH AND WITHOUT PERIPHERAL NEUROPATHY

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Objectives: Veno-arteriolar reflex (VAR) causes skin arteriolar vasoconstriction secondary to venous congestion. VAR response occurs through previously reported local (neurogenic, myogenic and/or endothelial) and/or systemic (baroreflex) mechanisms. The postural VAR is impaired in patients with type 2 diabetes (DT2) with a greater extent in DT2 with peripheral neuropathy (NP). However, factors involved in this altered response remain unknown. The aim of this study was to compare the underlying physiological mechanisms in response to VAR using spectral analysis of cutaneous blood flow (CBF) in DT2 with and without NP.
Methods: Thirty-seven DT2 patients: 16 without NP (DT) and 21 with NP (NP), and 28 nondiabetic subjects: 9 normal-weight (CT) and 19 obese (NDO) were included. CBF was recorded using laser Doppler flowmeter while participants were submitted to a leg-lowering maneuver to evoke VAR during 6 minutes after 10 minutes at rest. Spectral analysis was performed with Morlet wavelet transform and was split into 5 frequency components related to endothelial, neurogenic, myogenic activities, and respiratory and cardiac rhythms. VAR indices were analyzed: the lowest CBF observed reach during the 6 minutes, the percent change of CBF, and the area under the curve (AUC) during VAR. Flowmotion data were expressed as total power (TP) and relative power of each frequency band expressed as the ratio of TP.
Results: Basal CBF was not different between groups. During VAR, the lowest CBF and the percent change were not different between groups (-33.2±16.9; -37.3±19.5; -40.8±18.9 and -30.3±20.7% in CT, NDO, DT2 and NP, respectively). However, AUC was higher in CT than DT and NP (respectively 76.5±63.4; 41.5±18.7 and 39.5±14.3, $p<0.05$) (Fig1). According to flowmotion, resting TP was not different between groups. Relative contribution of endothelial band increased during VAR without difference between groups whereas myogenic band did not change. Contribution of neurogenic band during VAR tended to increase in CT and NDO, decrease in DT and not change in NP ($p=0.1$) (Fig2).
Conclusion: Spectral analysis of CBF provide further information on impaired underlying mechanisms of VAR response with neurogenic dysfunction in DT2 with and without NP.

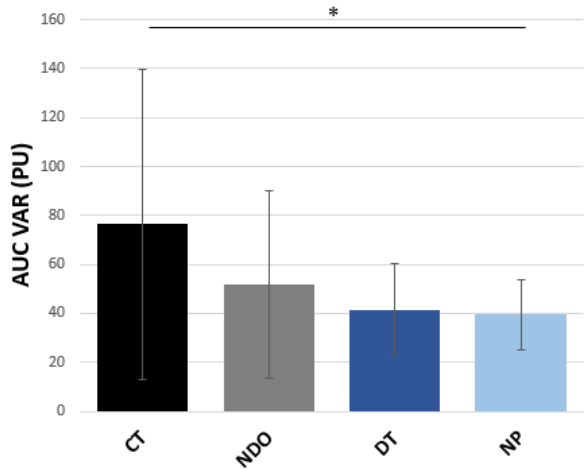

Figure 1 : Area under curve during VAR in each group.

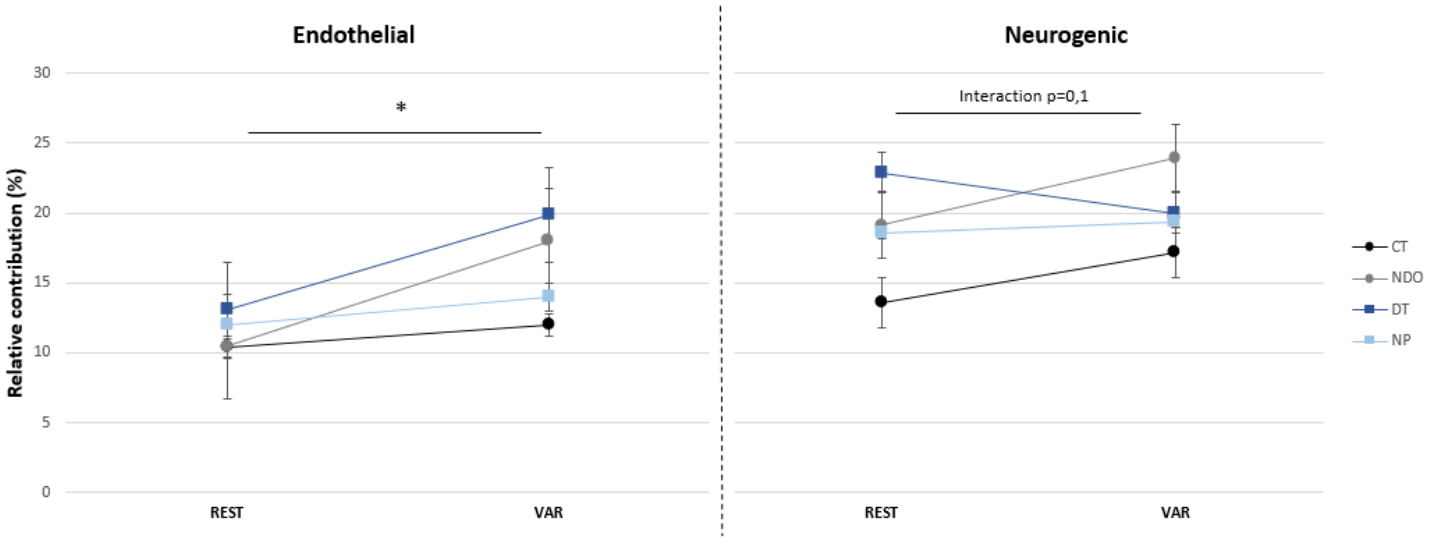

Figure 2 : Relative contribution of endothelial and neurogenic band at rest and during VAR.

INCIDENCE AND RISK FACTORS FOR DIABETIC POLYNEUROPATHY AFTER BARIATRIC SURGERY

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Objectives: Bariatric surgery (BS) improves glycemic control in patients with type 2 Diabetes Mellitus (T2DM). The effect of BS on diabetic polyneuropathy (DPN) is not well known. Our purpose was to evaluate incidence and progression of DPN in T2DM patients after BS as well as to identify risk factors for DPN.
Methods: Follow up of DPN in a prospective cohort of 52 severely obese patients with T2DM who underwent Roux-en-Y gastric bypass (59.6%) and sleeve gastrectomy (40.4%). DPN was assessed before and after 6 months of BS using the Michigan Neuropathy Screening Instrument (MNSI) with a cut-off value ≥ 2.5. In order to evaluate incidence and progression of DPN, patients were divided according to presence (+) or absence (-) of DPN. Patients with other known causes of polyneuropathy were excluded. Body weight, stature, BMI, % total weight loss, waist circumference, blood pressure, fasting glucose, glycated hemoglobin and serum lipids were evaluated before and 6 months after BS.
Results: Before BS, we found a prevalence of DPN of 34.6% (n=18) associated with higher fasting glucose (124.0 mg/dl versus 129.0 mg/dl, p = 0.038). After 6 months follow-up, 61.5% of the cohort experienced diabetes remission, 25.0% showed a partial remission, while 13.5% had non-remission (p < 0.001). In DPN (-) patients, the incidence of post-BS DPN was 5.9% (n=2) and was associated with higher fasting glucose (83.0 mg/dl versus 127.5 mg/dl, p = 0.021) but not with HBA1C (p = 0.060). In DPN (+) patients, the persistence of DPN after BS decreased to 27.8% (n = 5) and was associated with aging (48 years old versus 55 years old, p = 0.035) and higher serum triglyceride levels (74 mg/dl versus 112 mg/dl, p = 0.009). In multivariate analysis, DPN persistence was independently associated with aging and serum triglyceride levels. The risk ratio of DPN persistence increased 9.5% (95% CI: 3.9%–15.3%, p = 0.001) for each year of age increase over 55 years and 3.5% (95% CI: 0.9%–6.2%, p = 0.009) for each mg/dl increase in the serum triglyceride level over 112.0 mg/dl.
Conclusions: Since incidence of DPN after BS was associated with higher fasting blood glucose but not with HbA1c and DPN persistence decreased after BS and was independently associated with aging and higher serum triglyceride levels, we concluded that incidence and persistence of DPN after BS could be not related to glycemic control.

PERIPHERAL POLYNEUROPATHY AFTER BARIATRIC SURGERY IN SEVERELY OBESE PATIENTS WITH PREDIABETES AND WITHOUT DIABETES: A COHORT STUDY

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Objectives: Our aim was to evaluate after bariatric surgery (BS), incidence and progression of polyneuropathy (PPN) in patients with Pre-Diabetes (PreDM) and without Diabetes (NoDM) and to identify risk factors for it.
Methods: We performed a prospective cohort study in 150 PreDM and 215 NoDM patients who underwent BS, Roux-en-Y gastric bypass (42.0% and 39.5%, respectively) and sleeve gastrectomy (58.0% and 60.5%, respectively). PPN was assessed before and after 6 months of BS using the Michigan Neuropathy Screening Instrument (MNSI) with a cut-off value ≥ 2.5. Patients were divided according to the presence (+) or absence (-) of PPN before BS. Other known causes of PPN were excluded.
Results: Before BS, in PreDM we found a 26.0% PPN prevalence and in NoDM a 18.1% PPN prevalence ($p = 0.094$). Firstly, we looked to the PreDM group. After 6 months of follow-up, glucose levels normalized in 90.1%. PPN prevalence was associated with postmenopausal status ($p = 0.017$) and aging ($p = 0.037$). In multivariate analysis, PPN prevalence was independently associated with aging and stature. The odds ratio of PPN increased 3.8% (95% CI: 1.0%–6.6%) for each year of age increase over 41.0 years ($p = 0.007$) and 3.1% (95% CI: 0.3%–6.0%) for each cm of stature increase over 165.0 cm ($p = 0.031$). The incidence of post-BS PPN (6.3%) was associated with higher stature ($p = 0.028$) and lower serum HDL-C ($p = 0.035$). In multivariate analysis, PPN incidence was independently associated with lower serum HDL-C. The risk ratio of PPN decreased 4.6% (95% CI: 0.5%–8.6%) for each increase in mg/dL in serum HDL-C over 37.7 mg/dL ($p = 0.029$). PPN persistence decreased to 15.4% without association with the evaluated parameters. In NoDM, PPN prevalence was associated with postmenopausal status ($p = 0.050$) and PPN incidence (4.0%) was associated with lower %TWL ($p = 0.010$) and higher serum triglyceride ($p = 0.019$). In multivariate analysis, lower %TWL was independently associated with PPN incidence. The risk ratio of PPN decreased 17.9% (95% CI: 5.6%–28.6%) for each percent increase in %TWL over 22.9% ($p = 0.006$). PPN persistence was 17.9% without association with evaluated parameters.
Conclusions: Six months after BS, PPN incidence was 4.0 and 6.0% in NoDM and PreDM, respectively. In PreDM, PPN was independently associated with lower serum HDL-C and, in NoDM, with lower %TWL.

FOLLOW-UP OF PERIPHERAL POLYNEUROPATHY IN SEVERELY OBESE PATIENTS WITH METABOLIC SYNDROME (WITHOUT DIABETES) SUBMITTED TO BARIATRIC SURGERY

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Objectives: Previous studies demonstrate that the Metabolic Syndrome (MetS) components can be associated with peripheral polyneuropathy (PPN) independent of glycemic status. Association between obesity, MetS, and PPN after bariatric surgery is less evident. Our objective was to describe the incidence and progression of PPN in severely obese patients with MetS but without diabetes submitted to BS and to identify risk factors.
Methods: A prospective cohort study was performed in 239 severely obese patients with MetS but without diabetes who underwent Roux-en-Y gastric bypass (45.6%) and sleeve gastrectomy (54.4%). The Michigan Neuropathy Screening Instrument (MNSI) with a cut-off value ≥ 2.5 was used for defining PPN before and 6 months after BS. In order to evaluate the incidence and progression of PPN, the patients were divided according to the presence (+) or absence (-) of PPN before BS. Other known causes of PPN were excluded. MetS was defined using the International Diabetes Federation criteria.
Results: The prevalence of PPN was 21.3% (n=51) and it was associated with postmenopausal status (p = 0.019) and higher HbA1c level (p = 0.024). In multivariate analysis, PPN was independently associated with post-menopause. The odds ratio of PPN increased 2.8 times in post-menopause (p = 0.007). After 6 months of follow-up, MetS improved in 73.9% of patients. In PPN(-) patients, the incidence of post-BS PPN was 3.2% (n=6) and was associated with higher stature (p = 0.024). However, in multivariate analysis, PPN incidence was independently associated with male gender and serum triglycerides. The risk ratio of PPN was 88.8% lower in females and increased 1.2% (95%IC: 0.1%–2.4%, p = 0.009) for each mg/dl increase in serum triglyceride levels over 127.0 mg/dl. In PPN(+) patients, PPN persistence after BS decreased to 9.8% (n=5) and was associated with higher prevalence of MetS (p = 0.047). Nevertheless, in multivariate analysis, only body weight was independently associated with PPN persistence. The risk ratio of PPN persistence increased 2.2% (95%IC: 0.3%–4.0%, p = 0.022) for each kg of body weight increase over 111.2 kg.
Conclusions: The prevalence of PPN was high in severely obese patients with MetS without diabetes and decreased after BS. News cases of PPN showed independently association with male gender and serum triglycerides.

CLASSIFYING PAINFUL DIABETIC NEUROPATHY INTO CLINICAL SENSORY PHENOTYPES: A NOVEL, MULTIMODAL MAGNETIC RESONANCE IMAGING AND A MACHINE LEARNING APPROACH

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Pharmacotherapy is the mainstay of treatment for painful distal symmetrical diabetic polyneuropathy (DSP) but the best we can hope for is 50% pain relief in only a third of patients. There is an emerging theory, which postulates that this wide variability in treatment response may in part be due to an underlying heterogeneity in clinical pain phenotypes. We examined brain anatomical and resting-state functional connectivity in painful diabetic polyneuropathy (DSP) patients with the irritable (IR) and non-irritable (NIR) nociceptor phenotype.
Methods: 43 painful DSP patients (10 IR and 33 NIR) underwent neurophysiological and magnetic resonance (MR) neuroimaging. The German research network of neuropathic pain (DFNS) protocol was used to subdivide patients into **IR nociceptor phenotype** (defined as the presence of either dynamic mechanical allodynia, reduced mechanical or pressure threshold, increased mechanical pain sensitivity, or lower cold or heat pain threshold or any combination of these signs of hyperexcitability) or **NIR nociceptor phenotype** (patients not classified as IR nociceptor phenotype i.e. sensory loss with no signs of hyperexcitability).
Results: Somatosensory cortex surface area (p=0.04) and right thalamic volume (p=0.01) was significantly reduced in NIR patients. IR patients had significantly greater thalamic-insula (p-FDR=0.03) and reduced thalamic-somatosensory (p-FDR=0.03) functional connectivity. There was positive correlation between thalamic-insula functional connectivity with the NTSS-6 pain scores (r=0.41; p=0.01) and negative correlation between thalamic-somatosensory functional connectivity and Toronto Clinical Neuropathy Score (r=-0.35; p=0.03).
Conclusions: MRI measures of cortical structure and functional connectivity relates to both the somatic and non-somatic assessments of painful DSP. This could serve as a painful DSP biomarker which not only relates to underlying pain mechanisms but is sensitive to the different sensory phenotypes.

LONG-TERM TREATMENT AND PREDICTORS OF OUTCOME IN PAINFUL DIABETIC POLYNEUROPATHY: AN OBSERVATIONAL STUDY

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Objectives: Information on long-term outcomes of treatment of painful diabetic polyneuropathy (PDPN) is very limited. The response to treatment and its duration in the individual patient are difficult to predict. This is a long-term retrospective observational monocentric study aimed at evaluating the effectiveness and the duration of treatment of PDPN, and at identifying the factors related to the response.

Methods: Sixty-seven patients with a diagnosis of PDPN, at least one follow-up visit, and absence of non-diabetic neuropathies, chronic pain of other causes, and severe comorbidities, were selected (age 62±11 years, duration 17±11 years, 39 with obesity, 9 with type 1 diabetes, 27 male). Neuropathic symptoms and signs, vibratory and thermal perception thresholds, and neuropathic pain [using the questionnaires DN4, BPI and PGIC, and numerical rating scale (NRS)] were evaluated. Analgesic agents, response to treatment and adverse events were recorded. Patients who were Responder 30% and 50% (decrease of pain intensity on NRS by 30% and 50%, respectively), and those with remission (pain free without treatment) at follow-up were identified.

Results: Median duration of the follow-up was 12 months (interquartile range 8-28 months), with values ≥12 months in 38 participants. At the end of the follow-up, 26 participants (38.8%) were at least Responder 30%, among which 19 were Responder 50% and 5 pain free without treatment. Fifty % of responders reached this state within 10 months, 19.2% within 20 months, and 30.8% by more than 20 months. Treatment remained necessary until the end of the follow-up even beyond 4 years, except for those with remission. Twelve participants were responders during the follow-up and became non-responders at the end of the follow-up. The state of responder at the follow-up was associated with a baseline lower BMI (P=0.0023), with the absence of obesity (P=0.0002) and hypertension (P=0.0252), and with lower scores of symptoms (P=0.0402), signs (P=0.0127), DN4 (P=0.0047), and BPI Pain Interference Index (P=0.0106). In a multiple logistic regression analysis, obesity and BPI Pain Interference Index were independently associated with lower odds of being responder (Table). Percentage reduction of pain intensity from baseline to the end of the follow-up was inversely related to baseline BMI (rho=-0.308, P=0.0129).

Conclusions: Less than 40% of the patients reached a meaningful pain relief at the end of the follow-up and almost all responders required prolonged treatment to keep pain relief. Obesity and a greater impact of pain on quality of life independently predicted the treatment failure. Uncertain and poor outcome and long treatment duration call for appropriateness and continuity of care, increase in treatment options, and multidisciplinary approach including psychosocial assessment.

Table. Multivariate logistic regression analysis: odds ratio for the state of responder (r^2=0.34, P=0.045).

Variables	Odds Ratio	95% CI	P
Age (years)	1.01	0.95-1.07	0.824
Sex (male)	0.45	0.11-1.95	0.288
Obesity (present)	0.12	0.03-0.47	**0.003**
Hypertension (present)	0.16	0.17-1.43	0.100
Michigan Neuropathy Screening Instrument Questionnaire	0.95	0.63-1.44	0.821
Michigan Diabetes Neuropathy Score	0.96	0.81-1.15	0.689
Douleur Neuropathique in 4 Questions	0.79	0.47-1.33	0.371
Brief Pain Inventory Pain Interference Index	0.71	0.53-0.94	**0.019**

THE IPSWICH NEURODIAB STUDY: A 5-YEAR LONGITUDINAL STUDY EXAMINING THE PATHOPHYSIOLOGY AND NATURAL HISTORY OF DIABETES POLYNEUROPATHY (DPN)

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Aims: Few data are available on the natural history and rate of progression of DPN. Various cross-sectional studies have demonstrated that small fibre neuropathy (SFN) precedes large fibre neuropathy (LFN) in diabetes but this is yet to be demonstrated longitudinally. In a linear mixed-effects model, this longitudinal, case-control study compares the progression of both SFN and LFN in Type-1 (T1DM) and Type-2 diabetes (T2DM) and examines the key determinants affecting their pattern.
Methods: 50 subjects of each T1DM & T2DM along with 50 healthy controls (HC) were evaluated at the Ipswich diabetes trials unit between 2014 and 2019. All subjects had annual anthropometry, blood pressure (BP), relevant biochemistry and neuroexamination using Neurology Disability score (NDS). DPN was present (DPN+) if NDS of ≥3. SFN was assessed using the Laser Doppler imaging (LDI_{FLARE}) and Corneal confocal microscopy for corneal nerve fibre density (CCM_{CNFD}). LFN was assessed using vibration perception threshold (VPT) and sural nerve conduction velocity (SNCV) and amplitude (SNAP)
Results: The mean (±SD) age and sex distribution at baseline for T1DM was (41.4±15.0; 27 males), T2DM (54.38±9.1; 25 males) and HC (40.7±15.1yrs; 24 males). When comparing between DPN+ vs DPN- groups, in T1DM, linear rate of decline of LDI_{FLARE} at 0.15cm^2/yr; n=21 was significantly more when compared to T1DM/DPN- (0.08 cm^2/yr; n=29); p=0.001. Similarly, significant decline of CCM_{CNFD} was seen in DPN+ (0.16 fibres/mm^2/yr vs 0.10 fibres/mm^2/yr; p=.005).
In T2DM, between DPN+ and DPN- groups, there was no significant difference in the rate of decline of both LDI_{FLARE} (0.22cm^2/yr vs 0.15cm^2/yr; p=0.09) and CCM_{CNFD} (0.23 fibres/mm^2/yr vs 0.16 fibres/mm^2/yr; p=.0.06). In HC, Rate of decline of LDI_{FLARE} was 0.07cm2/yr and CCM_{CNFD} 0.05 fibres/mm2 /yr.
In T1DM, the decline of LDI_{FLARE} significantly correlated with only HbA1c change (p=0.006) but in T2DM there was significant correlation with HbA1c, triglycerides (TG) and BP changes (p=<0.05). There was no significant change of LFN indices (VPT, SNCV and SNAP; p=>0.05) over the 5-year period and no correlation with any of the above determinants.
Conclusions: In this first longitudinal study studying small and large fibre nerves simultaneously in bothT1DM and T2DM groups, some important conclusions can be made: Firstly, changes in SFN occur earlier than LFN and furthermore only the former is affected by HbA1c, BP and TG changes. Secondly, the progression of DPN in T1DM and its determinants is different to T2DM. Methods for assessing SFN may have superior value in the study of DPN and its prevention.

CEREBRAL MORPHOMETRIC ABNORMALITIES IN PAINLESS AND PAINFUL DIABETIC PERIPHERAL NEUROPATHY

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Objectives: Magnetic resonance imaging (MRI) studies have found structural alterations in brain regions involved with the somatosensory and motor system in diabetic peripheral neuropathy (DPN) and painful-DPN (pDPN). However, most of these studies have involved small cohorts of subjects, without consideration of different pDPN phenotypes. Here we present the largest DPN neuroimaging study to date, which aims to examine morphological differences in brain structure in DPN and different phenotypes of painful-DPN.

Methods: A total of 229 participants were enrolled, 177 with diabetes (46 no-DPN, 56 painless-DPN and 75 pDPN; 24 irritable [IR] and 50 non-irritable [NIR] phenotype), and 52 healthy volunteers underwent detailed clinical and neurophysiological assessments. All subjects underwent 3-dimensional T1-weighted brain MRI (3.0T, Phillips). Brain volume analysis was performed using Freesurfer (http://surfer.nmr.mgh.harvard.edu/). We used the German Research Network on Neuropathic Pain (DFNS) quantitative sensory testing (QST) profile to phenotype patients with pDPN.

Results: There was a significant group effect in the cortical thickness at the pre-central gyrus (ANOVA P=0.001), anterior cingulate cortex (ACC, p=0.036), insula cortex (p=0.021) and post-central gyrus (p=0.015), where there was also a group effect in grey matter volume (p=0.037). At the post-central gyrus, in comparison with HV (1.92mm±0.11) and NoDPN (1.90mm±0.14), there was a significantly reduced cortical thickness in DPN (1.85mm±0.14), in pDPN (1.87mm±0.12) cortical thickness was reduced compared with HV. At the precentral gyrus, both DPN (2.29mm±0.16) and pDPN (2.28mm±0.16) had significantly reduced cortical thickness compared with HV (2.37mm±0.14) and NoDPN (2.36mm±0.13). At the insula, compared with HV (2.93mm±0.15) the cortical thickness was reduced in DPN (2.85mm±0.18) and pDPN (2.84mm±0.17). The cortical thickness at the pre and postcentral gyrus, and insula correlated with measures of nerve conduction. At the ACC mean cortical thickness was reduced in the pDPN group (2.55mm±0.23) compared to DPN (2.62mm±0.25). Moreover, at the ACC the mean cortical thickness was significantly reduced in the IR- (2.40mm±0.23) compared to NIR-pDPN (2.58mm±0.20; p=0.003).

Conclusions: This is the largest study to investigate regional brain morphometric alterations in patients with DPN and pDPN. We confirm that key somatomotor brain regions have a reduced cortical thickness in patients with DPN and pDPN, which correlate with neurophysiological measures suggestive of an ascending axonopathy. Moreover, we found that the cortical thickness at the ACC differentiated patients with the IR and NIR, suggesting neuroplasticity in this region may play a role determining clinical phenotypes in pDPN.

CARDIAC AUTONOMIC FUNCTION IN DIABETIC GASTROPARESIS

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Objectives: Gastroparesis is a diabetes (DM) complication leading to nausea, bloating, pain, vomiting and challenging glucose control. Although widely indicated in the literature, the association between diabetic gastroparesis and cardiovascular autonomic neuropathy (CAN) remains poorly investigated.
Methods: 72 DM patients (59 type 1, 49 female, average DM duration 27 yrs) with symptoms suggestive of gastroparesis were investigated by ventricular scintigraphy and hence divided into two groups based on the presence or absence of delayed gastric emptying. CAN status was tested in terms of resting heart rate variability, baroreceptor sensitivity, heart rate changes in response to standing up (Heart Rhythm Scanner PE).
Results: Patients with gastroparesis had reduced heart rate variability in several time- and frequency domain measures, correlating with gastric emptying rate (Table 1). Similar impairments were found in the other autonomic function tests (Table 2). Symptoms of nausea/vomiting, excessive fullness – but not bloating, dyspepsia or abdominal pain – correlated with several CAN tests (Table 3).
Conclusions: We found statistically and clinically meaningful differences in the cardiac autonomic function tests between diabetes patients with vs. without gastroparesis, and a correlation between CAN tests and gastric emptying rate & symptoms. The study thus strengthens the evidence base for the involvement of the autonomic nervous system in diabetic gastroparesis.

Table 1 | Heart rate variability

	Between groups comparison			Correlation	
Variable (reference value), unit	No gastroparesis	Gastroparesis	*P*-value	r_s	*P*-value
Time-domain measures					
Mean HRT	71.3 (17.5)	79.3 (20.3)	.06	.32	.01
SDNN	29.3 (18.4)	17.6 (11.4)	.02	-.40	.002
RMSSD	18.7 (17.8)	10.3 (7.3)	.009	-.38	.003
Frequency-domain measures					
Total power	108.2 (290.2)	52.2 (151.0)	.59	-.17	.20
VLF	62.5 (134.8)	27.1 (135.9)	.34	-.30	.04
LF	28.8 (84.5)	14.3 (44.3)	.50	-.22	.09
HF	17.5 (67.3)	8.1 (20.0)	.20	-.27	.04
LF/HF	1.2 (2.7)	2.0 (2.6)	.43	.03	.87
Parasympathetic activity level	8.6 (7.1)	4.8 (4.7)	.02	-.38	.009
Sympathetic activity level	7.4 (6.1)	4.8 (5.6)	.12	-.32	.03

Data are given as median and interquartile range. Abbreviations: HRT: Heart Rate, SDNN: standard deviation of normalized RR-intervals, RMSSD: root mean square of the standard deviation, VLF: Very Low Frequency bands, LF: Low Frequency bands, HF: High Frequency bands

Table 2 | Cardiac autonomic function tests

Variable (reference value), unit	Between groups comparison			Correlation	
	No gastroparesis	Gastroparesis	*P*-value	r_s	*P*-value
Baroreflex sensitivity					
SD of HR	3.7 (2.2)	2.6 (2.5)	.13	-.28	.06
Max variance	11.7 (10.7)	6.3 (6.6)	.03	-.40	.002
Mean variance	8.1 (7.5)	4.0 (5.8)	.03	-.41	.001
E-I ratio	1.110 (0.120)	1.052 (0.070)	.04	-.38	.003
Heart rate upon standing up					
30:15 ratio	1.078 (0.200)	1.040 (0.080)	.06	-.30	.03

Data are given as median and interquartile range. Abbreviations: SD of HR: Standard Deviation of Heart Rate, E-I: Expiration-Inspiration

Table 3 | Correlations between symptoms and cardiac autonomic function tests

Autonomic function parameter	Nausea/retching/ vomiting	Fullness after meal/ inability to finish meal	GCSI score	PAGI-SYM total score
Time-domain measures				
Mean HRT	r_s = 0.29, P = 0.038	r_s = 0.24, P = 0.100	r_s = 0.26, P = 0.071	r_s = 0.22, P = 0.123
SDNN	r_s = -0.47, P = 0.001	r_s = -0.36, P = 0.010	r_s = -0.31, P = 0.030	r_s = -0.19, P = 0.193
RMSSD	r_s = -0.36, P = 0.011	r_s = -0.28, P = 0.051	r_s = -0.28, P = 0.052	r_s = -0.25, P = 0.081
Frequency-domain measures				
Total power	r_s = -0.26, P = 0.068	r_s = -0.31, P = 0.027	r_s = -0.23, P = 0.112	r_s = -0.18, P = 0.221
VLF	r_s = -0.45, P = 0.003	r_s = -0.37, P = 0.018	r_s = -0.28, P = 0.077	r_s = -0.05, P = 0.750
LF	r_s = -0.31, P = 0.028	r_s = -0.32, P = 0.026	r_s = -0.24, P = 0.091	r_s = -0.18, P = 0.206
HF	r_s = -0.25, P = 0.082	r_s = -0.27, P = 0.057	r_s = -0.28, P = 0.049	r_s = -0.28, P = 0.055
LF/HF	r_s = -0.09, P = 0.570	r_s = 0.03, P = 0.872	r_s = 0.13, P = 0.443	r_s = 0.21, P = 0.189
Parasympathetic activity level	r_s = -0.47, P = 0.002	r_s = -0.43, P = 0.005	r_s = -0.46, P = 0.003	r_s = -0.28, P = 0.075
Sympathetic activity level	r_s = -0.54, P < 0.001	r_s = -0.38, P = 0.014	r_s = -0.33, P = 0.036	r_s = -0.10, P = 0.540
Baroreflex sensitivity				
E-I ratio	r_s = -0.28, P = 0.048	r_s = -0.36, P = 0.009	r_s = -0.27, P = 0.054	r_s = -0.21, P = 0.149
Heart rate upon standing up				
30:15 ratio	r_s = -0.13, P = 0.390	r_s = -0.17, P = 0.287	r_s = -0.13, P = 0.397	r_s = -0.21, P = 0.183

Data are given as Spearman's rank correlation coefficients and two-sided P-values. Abbreviations: GCSI: Gastroparesis Cardinal Symptom Index, PAGI-SYM: Patient Assessment of Gastrointestinal Disorders Symptom Severity Index

PROGRESSION OF THE CARDIAC AND THE MICROVASCULAR COMPLICATIONS IN YOUNG TYPE 1 DIABETIC PATIENTS DURING 10 YEARS

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Introduction: The parallel observation of the progression in the cardiac and microvascular conditions in type-1 diabetic patients would supply important facts about the nature of the complications. Objectives: The aim of our study was to characterize and follow-up the neuronal, renal, ophthalmic and cardiac complications.
Materials and methods: 21 young type 1 diabetic patients with long-term disesae (age: 28.9±1.5 years, duration of DM: 13.5±1.7 years, HbA1c: 8.2±0.4%; BMI: 23.3±0.7; mean±SE) were involved in the study. Autonomic neuropathy (AN) was assessed by cardiovascular reflex tests (CRT-s). The peripheral sensory function was detected with Neurometer. Cardiac morphology and function were measured with conventional and Doppler echocardiography. The urinary protein content, the kidney function and the state of the retina were also determined. The tests were started in 2008 and repeated 10 years later.
Results: Left ventricular (LV) muscle mass changed the most prominently during 10 years (141±10 vs 172±11 g $p<0.05$, baseline vs follow-up, increased in 19 from 21 patients). From the CRT-s the heart rate response to breathing worsened frequently (25.5±2.4 vs 18.5±1.6 beats/min. $p<0.01$, decreased in 17 from 21 patients). The current perception threshold (CPT) of the large myelinated fibres at the peroneal nerve became higher in 14 from 21 patients (CPT: 3,18±0,4 vs 4,35±0,4 mA, $p<0,05$). All of the 17 patients with worsened heart rate response to breathing had an increase in the LV mucle mass as well. The urinary protein excretion and severity of retinopathy progressed less frequently (increase in protein excretion: in 11 from 21 patients, worsening retinopathy in 4 from 21 patients). There was no correlation between the progression of AN and sensory function as well as the nephro-or retinopathy.
Conclusions: Worsening of parasympathetic dysfunction and the increase in the left ventricular muscle mass were frequently found and these complications had a parallel progression in young type 1 diabetic patients. The progressive impairment of the large myelinated fibre function at the lower extremity was also a characteristic finding, while the more severe alteration of the kidney and retina was a less frequent phenomenon. Our data draw the attention of the common progression of the parasympathetic and cardiac dysfunctions as well as the independent appearance of the microvascular complications in type 1 diabetic patients.

MAXIMAL DEGREE OF SENSORY HYPAESTHESIA AND ASYMPTOMATIC SEVERE OBLITERATIVE ARTERIAL DISEASE IN THE BACKGROUND OF A PAINLESS TOE GANGRENE

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The 85-year old woman was diagnosed with hypertension in 1985 and with diabetes in 1995. Her renal insufficiency and diabetic neuropathy are known since 2013. Insulin therapy was also started in 2013. She is now a non-smoker, but has smoked in the past for 20 years.
She was admitted to our Department with suspected osteomyelitis because of a fetid, moist, superficial erosion on the second toe of her right leg. Some weeks before she kicked a chair without any pain.
X-rays showed no signs of osteomyelitis. Doppler pressure measurement revealed excessively high ankle-branch indices, arteries were not compressible. The surgical consultation suggested angiography and amputation. The angiography of the lower extremities showed a 80-90 % stenosis of the proximal tibial and proximal superficial femoral arteries. The stenosis were solved by percutaneous transluminal angioplasty.
Sensory nerve function was assessed by Neurometer. Higher CPT values reflecting hypoaesthesia of small myelinated and unmyelinated, as well as of large myelinated fibres on both lower extremities. Examination by Q-sense showed pathological cold and heat threshold values. Tuning fork tests showed the absence of sense of vibration of both feet. There were no sense of vibration on the right foot and on the left sole tested by VibraTip. The result of the Tip-Therm test was also abnormal. Assessing the Ipswich Touch Test, a loss in sensation was detected on the left foot. In summary, in the background of the painless injury of the second toe of the right leg severe sensory neuropathy was established. Alpha-lipoic acid infusion treatment was administered.
Our case demonstrates how important is to consider both neuropathy and ischaemia behind signs of the diabetic foot syndrome. The painless foot injury, the extremely severe hypaesthesia and the extremely high ankle-branch indices - referring to Mönckeberg-sclerosis – were the results of neuropathy. On the other hand, the 80-90 % stenosis of the arteries were the consequence of obliterative arterial disease. Based on the diagnostic procedures, treatment of both complications could be administered.

CARDIOVASCULAR AUTONOMIC AND PERIPHERAL SENSORY FUNCTION IN TOP ATHLETES AT CONDITIONED AND DECONDITIONED STATES

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Objectives: Adaptation of the nervous systems to contact sports is not well understood. The aim of our work was to identify the cardiovascular autonomic and peripheral sensory nervous system adaptation in top athletes in a conditioned and a deconditioned state.
Methods: Autonomic function was characterized by the five standard cardiovascular reflex tests while peripheral sensory system was studied by Neurometer assessing the threshold of the current sensations at the median and peroneal nerves. 22 male soccer players, 8 male basketball players, 12 female handball players, 13 female water polo players as active athletes were included. 21 healthy women and 20 men were involved as controls.
Results: The Valsalva ratio in conditioned soccer players (mean ± SD, athletes vs. controls: 1.71 ± 0.32 vs.2.15 ± 0.48; p =0.0018) and in conditioned handball players (1.63 ± 0.26 vs. 1, 87 ± 0.51; p = 0.0019) was lower than in controls. During the deconditioning period, the Valsalva ratio for soccer (1.7±0.34 vs. 1.94±0.43; p=0.025) and water polo players (1.71±0.54 vs. 2.66±0.27; p=0.007) was significantly higher than their conditioned values. In the conditioned state, Neurometer showed a higher sensory threshold at the index finger at 2000 Hz (234.8 ± 36.07 vs. 144.9 ± 50.47 mA; p<0.001) and at 5 Hz (68.15±33.06 vs 42.3±32.27 mA; p<0.001) in water polo players and in football players at 250 Hz (104.6±40.47 vs. 72.2±23.36 mA; p=0.002) compared to controls. At the hallux at 2000 Hz (399.5±111.2 vs. 323.2±94.14 mA; p=0.02) and at 5 Hz (108.1±56.55 vs. 81.55±38.38 mA; p=0.02) football players had significantly higher sensory thresholds compared to controls. During the deconditioning period, a significant decrease in the sensory threshold on the index was found in football players at 5 Hz (73.2±20.25 vs. 57.1±29.06 mA; p=0.023), and in water polo players at 2000 Hz (229.6±44.43 vs. 169.38±70.33 mA; p=0.033) compared to their conditioned state.
Conclusions: The conditioned seasonal reduction in Valsalva ratio for handball and football players indicates sympathetic predominance over controls. For football and water polo players, the higher Valsalva ratio during the deconditioning period indicates a decreased sympathetic tone. The decreased sensory threshold during the deconditioning period in football and water polo players may reflect an increased peripheral sensitivity. Our results might contribute to the better understanding of autonomic regulation during intensive sport and might serve as a starting point in assessing autonomic changes in diabetic patients during sport activities.
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SEVERE ORTHOSTATIC HYPOTENSION WITH HYPORENINISM AND HYPOALDOSTERONISM IN A YOUNG DIABETIC PATIENT

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Objectives: To present a case of severe diabetic autonomic neuropathy (DAN) with orthostatic hypotension (OH) associated with hyporeninism-hypoaldosteronism.
Methods and Results: A 32-year-old woman, known with diabetes since 2006, presented with a severe OH compromising daily life. There was no evidence of type 1 diabetes: anti-GAD and anti-A2 antibodies were negative, anamnesis revealed a strong family history of early-onset diabetes in the maternal branch with no familial or personal history of autoimmunity, the patient displayed overweight; however basal c-peptide was slightly reduced and diagnosis with diabetes was made at 18 years with a cardinal syndrome. She started metformin treatment and unfortunately interrupted the follow-up. She presented in August 2018 with a weight loss of 25 kg, HbA1c 16.4%, severe OH and gastroparesis with reduced food intake. She started a treatment with midodrine 22.5 mg/d without benefit and a basal-bolus insulin regimen. The glycemic status rapidly improved, but she needed a prescription of fludrocortisone 100 mg/d. To further evaluate the neurological diabetes complications and to ensure cardiovascular rehabilitation she was hospitalized in December 2018. Plasma renin and aldosterone were low and not stimulated by standing, while the cortisol and aldosterone response to Synacthen was normal. The disease complications evaluation found moderated diabetic retinopathy, severe cardiac autonomic neuropathy, hypoglycemia unawareness, inappropriate level of erythropoietin in presence of anemia and peripheral neuropathy without vitamins deficit: abnormal NSS 4/4, abnormal DN4 4/10, impaired small fibers (cold and pain) at nerve Check Master examination. After improvement of glycemic control, gastroparetic symptoms resolved, erythropoietin rose and levels of renin and aldosterone normalized with a clinical benefit on OH.
Conclusions: The features including hyporeninism-hypoaldosteronism and low erythropoietin have been reported in some patients with severe DAN. Many mechanisms have been described to explain hyporeninism in diabetic patients: i) diabetic nephropathy with the fibrosis of juxtaglomerular cells; ii) blood volume expansion in response to hyperglycemic hyperosmolarity; iii) sympathetic failure and catecholamines depletion; iv) metabolic defect in renin synthesis. Our case report shows that glucotoxicity damage to the autonomic nervous system including gastroparesis, OH and hyporeninism may be reversible with sustained glycemic control.

RELATIONSHIP BETWEEN CARDIAC AUTONOMIC NEUROPATHY AND STRUCTURAL AND FUNCTIONAL ALTERATIONS OF THE LEFT VENTRICLE IN ASYMPTOMATIC PATIENTS WITH TYPE 2 DIABETES

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Introduction: In patients with type 2 diabetes (T2D) we previously showed that left ventricle hypertrophy (LVH) is common and can develop even in the absence of hypertension and coronary artery disease. The relationship between cardiac autonomic neuropathy (CAN) and structural and functional alterations of the left ventricle (LV) is poorly known. The aim of this study was to examine this relationship in a population of T2D patients without cardio-vascular disease.
Patients and Methods: We included 250 T2Ds, aged 56.6±10.0 years. CAN was diagnosed when at least one out of three standard tests (deep-breathing, lying-to-breathing, Valsalva) was abnormal (according to age reference). We performed an echocardiography and calculated the LV mass indexed on body surface area (LVMi) and measured e/a ratio using transmitral doppler, and a stress myocardial scintigraphy to assess for silent myocardial ischemia (SMI).
Results: CAN was present in 173 patients, LVH (as defined by LVMi ≥110 g/m^2 and ≥106 g/m^2 for men and women, respectively) in 71 patients and SMI in 79 patients. There was no association between CAN and LVH. Then we stratified the population in 4 groups according to the presence or absence of CAN and LVH. LV ejection fraction and e/a were different in the 4 groups ($p=0.03$ and <0.0001). As compared to the group CAN-/LVH-, LV ejection fraction was lower in the group CAN+/LVH+ ($p=0.03$) and e/a lower in the groups CAN+/LVH+ ($p<0.0001$) and CAN+/LVH- ($p=0.008$). Among the patients without LVH, BMI ($p<0.0001$) and the proportion of male ($p=0.07$) were higher in CAN+ than in CAN-; multivariate analysis confirmed the association between CAN and LV ejection fraction ($p<0.05$), independently of sex, age, BMI, systolic blood pressure, creatinine clearance and SMI.
Conclusion: Our data suggest that in T2D, CAN plays a role in the development of LV systolic dysfunction but not in diastolic impairment nor LVH.

IN OBESE PATIENTS AT HIGH RISK OF DIABETES CARDIAC AUTONOMIC DYSFUNCTION IS ASSOCIATED WITH HIGHER BLOOD GLUCOSE LEVELS AND EARLY INSULIN RESISTANCE MARKERS

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Background and aims: Some new metabolic indexes combining anthropometric (waist circumference, BMI) and lipid (triglycerides, HDL-cholesterol) parameters have been shown to be early markers of insulin resistance and predictors of incident type 2 diabetes. The aim of this study was to examine, in obese patients at risk of diabetes, the relationship of cardiac autonomic dysfunction (CAD) and metabolic disorders and these new indexes.

Materials and methods: We included 462 patients without known diabetes, age 37.8±14.5 years, BMI 37.2±7.1 kg/m^2. CAD was defined by having one or more abnormal tests among three tests of heart rate variability depending mostly on vagal control (Valsalva, deep-breathing, lying-to-standing). The 10-years risk of diabetes was considered elevated if Findrisk score was ≥12. Total cholesterol, triglycerides and HDL-cholesterol were measured, and LDL-cholesterol was calculated (Friedewald formula). Plasma glucose (G0 and G120) and insulin were measured at fasting and 2 hours after an oral glucose challenge. The new combined metabolic indexes: visceral adiposity index (VAI), lipid accumulation product (LAP) and TyG index [log (triglycerides x fasting glucose)], several insulin resistance indexes: HOMA-IR, Matsuda, QUICKI, FIRI, Gutt, ISIT0 and ISIT120, and HOMA-insulin secretion index were calculated.

Results: CAD was present in 198 patients. Findrisk was ≥ 12 in 227 patients. Among the patients with Findrisk ≥ 12, 48.5% were CAD+. The patients were separated in 4 groups: CAD- with Findrisk < 12 (G1), CAD- with Findrisk ≥ 12 (G2), CAD+ with Findrisk < 12 (G3) and CAD+ with Findrisk ≥ 12 (G4). G0 (p=0.002), G120 (p=0.03), logHOMA-IR (p=0.01), TyG (p=0.04) and LAP (p=0.007) differed between the four groups and were significantly higher in G4 than in G1. Lipid parameters, VAI, the other insulin resistance indexes and HOMA-insulin secretion index did not differ significantly between the four groups.

Conclusions: These data indicate that in obese patients at high risk of diabetes, CAD is associated with higher glycemic levels and with early markers of insulin resistance and suggest the role of vagal defects and sympathetic predominance in these disorders.

EFFECT OF EARLY INTERVENTION WITH A LONG LASTING INSULIN ANALOGUE ON PERIPHERAL NEUROPATHY IN TYPE 2 DIABETIC SPRAGUE-DAWLEY RATS

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Objective: Current treatment for type 2 diabetes fails to prevent the development of peripheral neuropathy. In this study we examined whether treatment with insulin 700, a long lasting insulin analogue very similar in structure to insulin degludec (Tresiba®) could provide a favorable outcome in preventing the onset of diabetic neuropathy related pathologies.
Methods: Rats were fed a high fat diet (45% kcal primarily lard) for 8 weeks and then treated with a low dose of streptozotocin in order to induce hyperglycemia. These rats model late stage type 2 diabetes. After 2 weeks, diabetic rats were treated with a sub-optimal or optimal dose of insulin 700 twice daily. The treatment period was 18 weeks. The endpoints evaluated included vascular reactivity of epineurial arterioles and motor and sensory nerve conduction velocity, thermal and corneal sensitivity and innervation of sensory nerves in the cornea and skin (as shown below).
Results: Prior to treatment vascular relaxation by epineurial arterioles to acetylcholine and nerve related outcome measures were impaired. The higher dose of the insulin analogue was effective in correcting hyperglycemia as determined by examining blood glucose profile and HbA_1C levels. Treatment also improved the lipid serum profile and serum thio barbituric acid levels, a marker for oxidative stress. Treatment of diabetic rats with the insulin analogue improved vascular relaxation to acetylcholine and calcitonin gene-related peptide and, as shown below, neural outcome measures were also improved with the higher dose of the insulin analogue being statistically more effective.
Conclusion: These studies demonstrate that treating rats, modeling type 2 diabetes, with insulin 700 is an effective treatment for diabetic vascular and peripheral nerve complications. Should the treatment strategy for type 2 diabetes be reconsidered?

Determination	Control (10)	Diabetic (16)	Diabetic + Low Dose Ins700 (20)	Diabetic + High Dose Ins700 (19)
HbA_1C	3.61 ± 0.03	7.61 ± 0.19 **a**	5.39 ± 0.33 **a,b**	4.05 ± 0.07 **b,c**
MNCV (m/sec)	56. ± 2.7	40.1 ± 1.1 **a**	48.0 ± 1.9 **a,b**	56.7 ± 1.5 **b,c**
SNCV (m/sec)	36.9 ± 0.4	29.3 ± 0.4 **a**	31.9 ± 0.7 **a**	36.9 ± 0.7 **b,c**
IENF (profiles/mm)	24.6 ± 0.4	12.7 ± 0.2 **a**	19.2 ± 0.3 **a,b**	21.2 ± 0.3 **a,b,c**
Corneal nerve fiber length (mm/mm^2)	8.3 ± 0.3	3.7 ± 0.3 **a**	5.7 ± 0.3 **a,b**	8.5 ± 0.3 **b,c**
Cornea sensitivity (AUC)	28.7 ± 5.4	109.6 ± 3.1 **a**	62.8 ± 6.7 **a,b**	40.1 ± 4. **b,c**
Thermal nociception (sec)	13.8 ± 0.4	19.7 ± 0.8 **a**	16.4 ± 0.5 **b**	12.9 ± 0.3 **b,c**

Data presented as mean ± SEM. **a** $P < 0.05$ compared to Control; **b** $P < 0.05$ compared to Diabetic; **c** $P < 0.05$ compared to Diabetic + Low Dose Ins700.

TRANSGENIC MICE UBIQUITOUSLY OVEREXPRESSING HUMAN 15-LIPOXYGENASE-1: CHARACTERIZATION OF DIABETIC PERIPHERAL NEUROPATHY AND EFFECT OF ENRICHING THE DIET WITH MENHADEON OIL

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Objective: To rigorously explore the role of omega-6 and omega-3 polyunsaturated fatty acids (PUFA) and their metabolism as it relates to diabetic peripheral neuropathy (DPN) we have created a transgenic mouse utilizing a Cre-lox promotor to control overexpression of human 15-lipoxygenase-1 (15-LOX-1) (Tg(CAG-eGFP,Alox15,tdTomato)#Iowa). In this study we sought to determine the effect of feeding type 2 diabetic wild type mice and transgenic mice ubiquitously overexpressing 15-LOX-1 a normal chow diet vs. a diet enriched in menhaden (fish) oil on endpoints related to DPN.
Methods: Wild type and Tg(CAG-eGFP,Alox15,tdTomato)#Iowa mice on a C57Bl/6J background were divided into three groups. Two of each of these groups was fed a 60% kcal high fat diet prior to treatment with streptozotocin to induce type 2 diabetes. The remaining mice were fed a standardized diet and were deemed to be control mice. Four weeks after the induction of hyperglycemia one set of diabetic mice in each group were fed a high fat diet with 50% of the kcal derived from lard replaced with menhaden oil. Twelve weeks later the endpoints evaluated included motor and sensory nerve conduction velocity, thermal and mechanical sensitivity and innervation of sensory nerves in the cornea and skin.
Results: Wild type (-/-) and transgenic (+/-) diabetic mice developed peripheral neuropathy as determined by slowing of nerve conduction velocity, decrease in sensory nerve fibers in the skin and cornea and impairment of thermal and mechanical sensitivity of the hindpaw compared to their respective control mice (see table below). Although not significant there was a trend for the severity of these DPN related deficits to be less in the diabetic transgenic mice compared to the diabetic wild type mice. Treating diabetic wild type and transgenic mice with menhaden oil improved the DPN related endpoints with a trend of greater improvement or protection by menhaden oil observed in the diabetic transgenic mice treated with menhaden oil.
Conclusions: Targeting pathways that will increase production of the anti-inflammatory metabolites of omega-3 PUFA may be another approach to developing an effective treatment for DPN.

Determination	Control -/- (14)	Control +/- (11)	Diabetic -/- (12)	Diabetic +/- (14)	Diabetic+ MO -/- (14)	Diabetic+ MO +/- (14)
Final Weight (g)	27.8 ± 1.1	27.5 ± 1.0	34.1 ± 2.4	31.8 ± 1.3	39.6 ± 3.3[a]	33.7 ± 2.8
Fasting blood glucose (mg/dl)	195 ± 8	200 ± 10	449 ± 28[a]	463 ± 32[a]	352 ± 25[a]	401 ± 24[a]
MNCV (m/sec)	41.2 ± 1.9	42.9 ± 2.1	28.5 ± 1.4[a]	34.0 ± 1.9[a]	38.3 ± 1.3[b]	42.7 ± 2.3[b]
SNCV (m/sec)	27.3 ± 0.9	27.5 ± 0.7	22.0 ± 0.5[a]	22.8 ± 0.6[a]	26.5 ± 0.7[b]	26.9 ± 0.4[b]
IENF (profiles/mm)	23.8 ± 0.5	24.8 ± 0.4	14.8 ± 0.7[a]	15.5 ± 0.6[a]	18.4 ± 0.4[a,b]	18.9 ± 0.8[a,b]
Corneal nerve fiber length (mm/mm^2)	1.42 ± 0.11	1.65 ± 0.16	0.72 ± 0.06[a]	1.14 ± 0.09	1.96 ± 0.18[a,b]	2.31 ± 0.11[a,b]
Thermal nociception (sec)	5.1 ± 0.2	4.9 ± 0.2	6.5 ± 0.2[a]	6.7 ± 0.3[a]	5.8 ± 0.13	5.4 ± 0.13[b]
Mechanical allodynia (g)	2.77 ± 0.09	2.87 ± 0.10	1.27 ± 0.07[a]	1.23 ± 0.06[a]	1.79 ± 0.12[a,b]	1.87 ± 0.14[a,b]

Data are presented as the mean ± S.E.M. a $P < 0.05$ compared to respective control; b $P < 0.05$ compared to respective diabetic. Number of experimental animals in ().