13 - 16 September 2019

NEURODIAB

Group of European Association of
Study of Diabetes EASD

Meliá Sitges Hotel
Sitges - Barcelona

29TH ANNUAL MEETING

OF THE DIABETIC NEUROPATHY STUDY
GROUP OF THE EUROPEAN ASSOCIATION
FOR THE STUDY OF DIABETES

ABSTRACT BOOK   FINAL PROGRAM

INDEX

NEURO**DIAB**

Meliá Sitges Hotel
Sitges - Barcelona

NEURODIAB**2019** COMMITTEE

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SECRETARY

Dr. Dinesh Selvarajah

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Prof. Gerry Rayman

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Dr. Tamas Varkonyi

29TH ANNUAL MEETING

Of the Diabetic Neuropathy Study Group of the European Association for the Study of the Diabetes

Dear colleagues, it is a pleasure to invite you to participate in **NEURODIAB 2019**, the 29th Annual Meeting of the Diabetic Neuropathy Study Group of the EASD, which will be held on 13-16 September 2019 in Sitges-Barcelona, Spain.

The 2019 meeting will be, as usual, a formidable occasion to share ideas and scientific findings on diabetic neuropathy. The focus will be on original research work, including both oral and poster sessions, keynote lectures and symposia. As in the past editions, young investigators will be encouraged to participate, warranting them a redused registration fee and providing specific awards for their category.

The meeting **NEURODIAB 2019** is considered the most important international annual event in the field of diabetic neuropathy.

The venue of the meeting is **Melià Sitges Hotel**, which is located approximately 27 kilometers from the Josep Tarradellas Barcelona El Prat airport. We hope you will join us in Sitges.

Kind regards

On behalf of the Organizing Committee
Local Chairman Dr. Ariel Odriozola
Barcelona, Spain

PROGRAM
OVERVIEW

NEURODIAB

Meliá Sitges Hotel
Sitges - Barcelona

DAY 1
Friday 13/9/19

10.00 . 18.00	Registration
14.00 · 14.30	Welcome ***Profs. Peter Kempler, Hungary*** and ***Ariel Odriozola, Spain***
14.30 · 15.00	Gøran Sundkvist Clinical Award I
	Chair : *Prof. Rayaz Malik, United Kingdom/Qatar*
	Presenter : *Dr. Uazman Alam, United Kingdom*
	Title : **Diabetic Neuropathy: A Journey From Animals to the Eyes and Beyond**
15.00 · 15.30	*Coffee Break*
15.30 · 17.30	**Oral Session :** Young Investigators Oral Presentations
	Chairs : *Drs. Dinesh Selvarajah, United Kingdom* and *Fabiana Picconi, Italy*

DAY 2
Saturday 14/9/19

08.30 · 9.00 Gøran Sundkvist Clinical Award II
Chair : *Prof. Dan Ziegler, Germany*
Presenter : *Dr. Gidon Bönhof, Germany*
Title : Emerging biomarkers and tools for diabetic neuropathy

09.00 · 10.00 **Invited Lecture :** 10-Year Anniversary of Toronto Consensus Statement: Somatic Neuropathy.
Chair : *Prof. Solomon Tesfaye, United Kingdom*
Speaker : *Prof. Robert Singleton, United States of America*

10.00 · 10.15 *Coffee Break and Exhibition*

10.15 · 10.45 **Invited Lecture :** Future Therapies and Diabetic Neuropathy : Hypes, hopes and facts
Chairs : *Profs. Ariel Odriozola, Spain*, *Hermelinda Pedrosa*, President of Diabetes *Brazilian* Society, *Jaime Davidson*, former President of Worldwide diabetes University of Texas, Southwestern Medical Center Dallas, *United States of America* and *Shaukat Sadikot*, Former IDF President and India Diabetes Association President, *India*
Speaker : *Prof. Bernat Soria*, former Health Minester of Health, Director del Departamento de Células Troncales de CABIMER, *Spain*

10.45 · 12.15 **Oral Session :** Pathogenesis
Chairs : *Profs. Rayaz Malik, United Kingdom/Qatar* and *Dan Ziegler, Germany*

12.15 · 13.15 **Wörwag Pharma Symposium :**
Diabetic Neuropathy – the still forgotten complication
Chairman : *Prof. Peter Kempler, Hungary*
Speaker 1 : *Prof. Dan Ziegler, Germany*
German Diabetes Center, Düsseldorf, Germany
Early detection of diabetic neuropathy in patients with prediabetes and diabetes.
Speaker 2 : *Prof. Tamás Várkonyi, Hungary*
University of Szeged, Hungary
Neuropathy Center Network in Hungary – increasing awareness and diagnosis rate of diabetic neuropathy.

NEURODIAB

Meliá Sitges Hotel
Sitges - Barcelona

DAY 2
Saturday 14/9/19

13.15 · 14.15	*Lunch*
14.15 · 15.45	**Poster Session :** Young Investigators
	Poster Presentations - Platform Session
	Chairs : *Profs. Gerry Rayman, United Kingdom* and
	Ariel Odriozola, Spain
15.45 · 16.00	*Coffee Break and Exhibition*
16.00 · 18.00	**Poster Session :** Small Fibres
	Chair : *Dr. Abd Tahrani, United Kingdom*
16.00 · 18.00	**Poster Session :** Autonomic Neuropathy
	Chair : *Dr. Anna Korei, Hungary*
18.00 · 18.15	Remembrance Memorial
	Profs. Mezinger, Jon Ward and ***Peter Watkins***
	Speakers : *Profs. Vincenza Spallone, Solomon Tesfaye*
	and ***Dr. Prashant Vas***
18.15 · 18.30	Lifetime achievement award ceremony
	Prof. Luciano Bernardi, Italy
	Speaker : *Prof. Simona Frontoni, Italy*
18.30 · 19.30	**General Assembly**

DAY 3
Sunday 15/9/19

08.00 · 08.30	**Invited Lecture :** High resolution nerve ultrasound:
	a complementary method in the diagnosis of neuropathies.
	Chair : *Prof. Peter Kempler, Hungary*
	Speaker : *Prof. Zsuzsanna Arányi, Hungary*
08.30 · 10.00	**Oral Session :** Autonomic Neuropathy
	Chairs : *Prof. Rodica Pop-Busui, United States of America*
	and ***Dr. Uazman Alam, United Kingdom***
10.00 · 10.30	*Coffee Break and Exhibition*

DAY 3
Sunday 15/9/19

10.30 · 11.15   **Invited Lecture :** 10-Year Anniversary of Toronto
Consensus Statement: Autonomic Neuropathy.
Chair : *Prof. Peter Kempler, Hungary*
Speaker : *Prof. Vincenza Spallone, Italy*

11.15 · 12.45   **Oral Session :** Treatment.
Chairs : *Prof. Mark Yorek, United States of America* and
Dr. Gidon Bönhof, Germany

12.45 · 13.45   *Lunch*

13.45 · 15.45   **Poster Session :** Diagnosis and Epidemiology
Chair : *Dr. Prashanth Vas, United Kingdom*

13.45 · 15.45   **Poster Session :** Pathogenesis and treatment
Chair : *Dr. Tamas Varkonyi, Hungary*

16.15 · 20.00   **Social Program in Barcelona**

20.30 · 22.30   **Gala Dinner**

DAY 4
Monday 16/9/19

08.30 · 10.00   **Oral Session :** Diagnosis and Epidemiology
Chairs : *Profs. Vincenza Spallone, Italy* and
Simona Frontoni, Italy

10.00 · 10.15   *Coffee Break and Exhibition*

10.15 · 11.45   **Oral Session :** Small Fibres
Chairs : *Dr. Dinesh Selvarajah, United Kingdom* and
Prof. Solomon Tesfaye, United Kingdom

11.45   **Closing Remarks :**
Profs. Peter Kempler, Hungary and
Ariel Odriozola, Spain

DAILY
PROGRAM

NEURODIAB

Meliá Sitges Hotel
Sitges - Barcelona

DAY 1
Friday 13/9/19

10.00 · 18.00 Registration

14.00 · 14.30 Welcome
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Chair : *Prof. Rayaz Malik, United Kingdom/Qatar*
Presenter : *Dr. Uazman Alam, United Kingdom*
Title : Diabetic Neuropathy: A Journey From Animals to the Eyes and Beyond.

15.00 · 15.30 *Coffee Break*

15.30 · 17.30 **Oral Session :** Young Investigators Oral Presentations
Chairs : *Drs. Dinesh Selvarajah, United Kingdom* and *Fabiana Picconi, Italy*

15.30 · 15.45 **O1**
SMALL FIBRE NEURAL ASSESSMENT IN PEOPLE WITH TYPE 2 DIABETES, WITH OR WITHOUT LIRAGLUTIDE, A GLP-1RA ANALOGUE TREATMENT
Victoria Tobin, United Kingdom

15.45 · 16.00 **O2**
ALTERED MITOCHONDRIAL FUNCTION OF THE THALAMUS IN PAINFUL DIABETIC PERIPHERAL NEUROPATHY
Gordon Sloan, United Kingdom

16.00 · 16.15 **O3**
BARIATRIC SURGERY IS ASSOCIATED WITH REDUCED RISK OF THE DEVELOPMENT AND PROGRESSION OF FOOT DISEASE IN PATIENTS WITH TYPE 2 DIABETES: A MATCHED CONTROLLED COHORT STUDY
Pushpa Singh, United Kingdom

DAY 1
Friday 13/9/19

16.15 · 16.30   **O4**
CIRCULATING MIRNAS (MIR-155, MIR-128 AND MIR-499) AS POTENTIAL BIOMARKERS OF DIABETIC NEUROPATHIES
Carla Greco, Italy

16.30 · 16.45   **O5**
THE RELATIONSHIP BETWEEN OBSTRUCTIVE SLEEP APNEA AND DIABETES-RELATED PERIPHERAL AND AUTONOMIC NEUROPATHY IN ADULTS WITH TYPE 1 DIABETES: A SYSTEMATIC REVIEW AND META-ANALYSIS LIRAGLUTIDE, A GLP-1RA ANALOGUE TREATMENT
Ziyad Alshehri, United Kingdom

16.45 · 17.00   **O6**
AUTONOMIC NEUROPATHY IN TYPE 1 DIABETES (T1D): FINDINGS FROM THE T1D EXCHANGE
Kara Mizokami-Stout, United States of America

17.00 · 17.15   **O7**
EXERCISE-INDUCED VASODILATION: USEFUL EARLY TOOL TO DETECT DIABETIC NEUROPATHY? PRELIMINARY RESULTS
Cécile Reynès, France

17.15 · 17.30   **O8**
PREDICTION OF PARASYMPATHETIC FUNCTION BASED ON CLINICAL APPLICABLE BEDSIDE METHODS FOR TESTING THE AUTONOMIC REFLEX IN TYPE 1 DIABETES
Anne-Marie Langmach Wegeberg, Denmark

NEURODIAB

Meliá Sitges Hotel
Sitges - Barcelona

DAY 2
Saturday 14/9/19

08.30 · 9.00 Gøran Sundkvist Clinical Award II
Chair : *Prof. Dan Ziegler, Germany*
Presenter : *Dr. Gidon Bönhof, Germany*
Title : **Emerging biomarkers and tools for diabetic neuropathy.**

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Speaker : *Prof. Bernat Soria,* former Health Minester of Health, Director del Departamento de Células Troncales de CABIMER, *Spain*

10.45 · 12.15 **Oral Session :** Pathogenesis
Chairs : *Profs. Rayaz Malik, United Kingdom/Qatar* and *Dan Ziegler, Germany*

10.45 · 11.00 **O9**
DIABETIC NEUROPATHY INFLUENCES THE PERIPHERAL AND CENTRAL NERVOUS INTEGRATION OF THE NOCICEPTIVE WITHDRAWAL REFLEX
Christina Brock, Denmark

DAY 2
Saturday 14/9/19

11.00 · 11.15   **O10**
RISK FACTORS FOR PERIPHERAL AND CARDIOVASCULAR
AUTONOMIC NEUROPATHY IN TYPE 1 DIABETES: 30 YEARS
OF FOLLOW-UP IN DCCT/EDIC
Rodica Pop-Busui, United States of America

11.15 · 11.30   **O11**
THALAMIC ATROPHY IS ASSOCIATED TO INTRA-THALAMIC
METABOLITES IN TYPE 1 DIABETES WITH SEVERE DISTAL
SYMMETRICAL POLYNEUROPATHY
Christina Brock, Denmark

11.30 · 11.45   **O12**
REDUCTION OF TERMINAL PARASYMPATHETIC FIBERS IN
ISLETS IS CORRELATED WITH β CELL VOLUME IN LEAN
TYPE 2 DIABETIC GOTO-KAKIZAKI RAT
Hiroki Mizukami, Japan

11.45 · 12.00   **O13**
CUTANEOUS CARBONYL STRESS MEDIATED
POST-TRANSLATIONAL PROTEIN MODIFICATIONS ARE
ASSOCIATED WITH PERIPHERAL NERVE DYSFUNCTION IN
PATIENTS WITH RECENT-ONSET TYPE 2 DIABETES
Gidon Bönhof, Germany

12.00 · 12.15   **O14**
EXENDIN-4 PROMOTES NEURITE OUTGROWTH, NEURONAL
SURVIVAL AND MYELINATION VIA ACTIVATING PI3 KINASE
SIGNALING PATHWAY IN VITRO
Kazunori Sango, Japan

NEURO**DIAB**

Meliá Sitges Hotel
Sitges - Barcelona

DAY 2
Saturday 14/9/19

12.15 · 13.15   **Wörwag Pharma Symposium :**
Diabetic Neuropathy – the still forgotten complication
Chairman : *Prof. Peter Kempler, Hungary*
Speaker 1 : *Prof. Dan Ziegler, Germany*, German Diabetes
Center, Düsseldorf, Germany
**Early detection of diabetic neuropathy in patients with
pre diabetes and diabetes.**
Speaker 2 : *Prof. Tamás Várkonyi, Hungary*, University of
Szeged, Hungary
**Neuropathy Center Network in Hungary – increasing
awareness and diagnosis rate of diabetic neuropathy.**

13.15 · 14.15   *Lunch*

14.15 · 15.45   **Poster Session :** Young Investigators Poster Presentations
Chairs : *Profs. Gerry Rayman, United Kingdom* and
Ariel Odriozola, Spain

P1
OBSTRUCTIVE SLEEP APNOEA IS ASSOCIATED WITH
INCREASED RISK OF INCIDENT PERIPHERAL NEUROPATHY
AND FOOT DISEASE IN PATIENTS WITH TYPE 2 DIABETES: A
POPULATION-BASED MATCHED CONTROLLED COHORT STUDY
Abd Tahrani, United Kingdom

P2
EFFECT OF FENOFIBRATE TREATMENT IN PATIENT WITH
DIABETIC PERIPHERAL NEUROPATHY AND HYPERTRIGLY
CERIDEMIA IN PATIENTS WITH TYPE 2 DIABETES IN GEORGIA
Tamar Maghradze, Georgia

DAY 2
Saturday 14/9/19

P3

VARIATION IN DIABETES PERIPHERAL NEUROPATHY (DPN) PREVALENCE AND LACK OF AGREEMENT BETWEEN NEUROPAD, SUDOSCAN, VIBRATION PERCEPTION THRESHOLD AND THE MICHIGAN NEUROPATHY SCREENING INSTRUMENT IN DIAGNOSING DPN IN PATIENTS WITH LONGSTANDING TYPE 1 DIABETES
Ziyad Alshehri, United Kingdom

P4

CORNEAL CONFOCAL MICROSCOPY AND NOT OCULAR COHERENCE TOMOGRAPHY DETECTS DIABETIC PERIPHERAL NEUROPATHY IN TYPE 1 DIABETES
Jonathan Lim, United Kingdom

P5

CCM DEMONSTRATES INCREASED CORNEAL LANGER HANS CELLS IN PATIENTS WITH LADA COMPARED TO TYPE 1, TYPE 2 DIABETES AND HEALTHY SUBJECTS
Luca D'Onofrio, Italy

P6

NATIONAL TRENDS IN LOWER EXTREMITY AMPUTATION IN SINGAPORE FROM 2008 TO 2017
Kavita Venkataramran, Singapore

15.45 · 16.00 *Coffee Break and Exhibition*

16.00 · 18.00 **Poster Session :** Small Fibres
Chair : *Dr. Abd Tahrani, United Kingdom*

P7

CORNEAL KERATOCYTE DENSITY IMPROVES IN ASSOCIATION WITH CORNEAL NERVE FIBRE REGENERATION IN SUBJECTS WITH MORBID OBESITY AFTER BARIATRIC SURGERY
Zohaib Iqbal, United Kingdom

DAY 2
Saturday 14/9/19

P8

OBSTRUCTIVE SLEEP APNOEA IS ASSOCIATED WITH
PAINFUL PERIPHERAL NEUROPATHY AND WORSE
QUALITY OF LIFE IN PATIENTS WITH LONGSTANDING
TYPE 1 DIABETES
Ziyad Alshehri, United Kingdom

P9

IMPAIRED CURRENT PERCEPTION, THERMAL PERCEPTION,
AND NERVE CONDUCTION VELOCITY IN GLUCOSE-
RESPONSIVE ATP-SENSITIVE POTASSIUM CHANNEL
DEFICIENT MICE
Hiromi Shimoda, Japan

P10

RELATIONSHIP BETWEEN CEREBRAL HEMODYNAMICS,
SYSTEMIC ENDOTHELIAL FUNCTION AND RETINAL
MICROVASCULAR DENSITY IN TYPE 2 DIABETES MELLITUS
Fabiana Picconi, Italy

P11

RETINAL NEURODEGENERATION IN PEDIATRIC PATIENTS
WITH TYPE 1 DIABETES MELLITUS
Fabiana Picconi, Italy

P12

EVALUATION OF THE DIAGNOSIS OF ELASTOGRAPHY ON
THE TIBIAL NERVE AND THE SUBCUTANEOUS PLANTAR
FOOT OF DIABETIC PATIENTS WITH DYSFUNCTION OF
DIFFERENT SUBTYPES OF PERIPHERAL NERVES
Artur Crespo, Spain

DAY 2
Saturday 14/9/19

P13

PREVALENCE AND CLINICAL CHARACTERISTICS OF DIABETIC PERIPHERAL NEUROPATHY IN TYPE 2 DIABETES: RESULTS FROM A NATIONAL HEALTH INSURANCE SERVICE–NATIONAL SAMPLE COHORT, 2006-2015
Chong Hwa Kim, Republic of Korea

P14

THERAPEUTICAL APPROACH IN DIABETIC NEUROPATHY – DATA FROM THE 2016 CLUJ-NAPOCA FOLLOW-UP COHORT OF THE QoL-DN ROMANIA STUDY
Daniel -Tudor Cosma, Germany

P15

CLINICAL CHARACTERISTICS OF DIABETIC PERIPHERAL NEUROPATHY IN TYPE 2 DIABETES: RESULTS FROM A NATIONAL HEALTH INSURANCE SERVICE–NATIONAL SAMPLE COHORT, 2015
Chong Hwa Kim, Republic of Korea

16.00 · 18.00   **Poster Session :** Autonomic Neuropathy
Chair : *Dr. Anna Korei, Hungary*

P16

PREVALENCE OF CARDIAC AUTONOMIC NEUROPATHY AND HYPERTRIGLYCERIDEMIA IN OBESE PATIENTS BY SUDOSCAN
Ana Kopaleishvili, Georgia

P17

INTEREST OF SLOW BREATHING TEST TO EVALUATE THERAPEUTIC EFFICACY AND ADHERENCE TO CONTINUOUS POSITIVE AIRWAY PRESSURE TREATMENT IN TYPE 2 DIABETES AND OBESE PATIENTS WITH OBSTRUCTIVE SLEEP APNOEA SYNDROME
Paul Valensi, France

DAY 2
Saturday 14/9/19

P18

RELATIONSHIP BETWEEN THE SURVEY OF THE
AUTONOMIC SYMPTOMS SCORE AND NORFOLK QOL-DN
QUESTIONNAIRE IN ROMANIAN PATIENTS WITH DIABETES
Diana Sima, Romania

P19

DIASTOLIC BLOOD PRESSURE RESPONSE TO HANDGRIP TEST
AND ECHOCARDIOGRAPHIC PARAMETERS OF LEFT
VENTRICULAR HYPERTROPHY – A RETROSPECTIVE ANALYSIS
Anna Korei, Hungary, Hungary

P20

A CLINICAL SCREENING SCORE FOR THE RISK OF
DIABETIC CARDIOVASCULAR AUTONOMIC NEUROPATHY
IN TYPE 2 DIABETES
Andrea Abbatepassero, Italy

P21

THE ASSOCIATION BETWEEN ELECTROCHEMICAL SKIN
CONDUCTION AND NORFOLK QOL-DN QUESTIONNAIRE IN
ROMANIAN PATIENTS WITH DIABETES
Bogdan Horia Apan, Romania

P22

THE ASSOCIATION BETWEEN SKIN AUTOFLUORESCENCE
AND NORFOLK QOL-DN QUESTIONNAIRE IN ROMANIAN
PATIENTS WITH DIABETES
Camelia Vonica, Romania

P23

RESISTANT TO TREAT DIABETIC FOOT IN TYPE 1 DIABETIC
PATIENT WITH RHEUMATHOID ARTHRITIS AND HALLUX
VALGUS DEFORMATION: A CASE REPORT
Jurate Peceliuniene, Lithuania

DAY 2
Saturday 14/9/19

P24
ETHNIC DIFFERENCES IN INSULIN SENSITIVITY BETWEEN
FILIPINO IMMIGRANT WOMEN AND KOREAN RESIDENTS IN
KOREA: FILIPINO WOMEN'S DIET AND HEALTH STUDY
Sung Hoon Yu, Republic of Korea

P25
TYPE 2 DIABETIC PATIENTS WITH PERIPHERAL
NEUROPATHY DISPLAY AN INCREASED RISK OF
DEVELOPING HYPERTENSION
Paul Valensi, France

18.00 · 18.15   Remembrance Memorial
Profs. Mezinger, Jon Ward and *Peter Watkins*
Speakers : *Profs. Vincenza Spallone, Solomon Tesfaye*
and *Dr. Prashant Vas*

18.15 · 18.30   Lifetime achievement award ceremony
Prof. Luciano Bernardi, Italy
Speaker : *Prof. Simona Frontoni, Italy*

18.30 · 19.30   **General Assembly**

NEURO**DIAB**

Meliá Sitges Hotel
Sitges - Barcelona

DAY 3
Sunday 15/9/19

08.00 · 08.30   **Invited Lecture :** High resolution nerve ultrasound : a complementary method in the diagnosis of neuropathies.
Chair : *Prof. Peter Kempler, Hungary*
Speaker : *Prof. Zsuzsanna Arányi, Hungary*

08.30 · 10.00   **Oral Session :** Autonomic Neuropathy
Chairs : *Prof. Rodica Pop-Busui, United States of America* and *Dr. Uazman Alam, United Kingdom*

08.30 · 08.45   **O15**
INTEREST OF NERVE CHECK MASTER FOR SCREENING AND DIAGNOSING PERIPHERAL NEUROPATHY IN PATIENTS WITH TYPE 1 DIABETES
Paul Valensi, France

08.45 · 09.00   **O16**
HEART RATE VARIABILITY IS NOT RELATED TO CARDIOVASCULAR EVENTS, IRRESPECTIVE OF DYSGLYCAEMIA. DOWNFALL OF RISK MARKERS? THE WHITEHALL II STUDY
Christian Stevens Hansen, Denmark

09.00 · 09.15   **O17**
RELATIVE HYPOXIA IN SUPINE AND STANDING POSITION IN TYPE 1 DIABETES: IMPAIRED AUTONOMIC CARDIORESPIRATORY CONTROL AROUND THE CLOCK?
Jens Christian Laursen, Finland

09.15 · 09.30   **O18**
ASSESSMENT OF THE SKIN MICROVASCULAR BLOOD FLOW IN DIABETIC PATIENTS WITH CARDIAOVASCULAR AUTONOMIC NEUROPATHY
Tatiana Zelenina, Russia

DAY 3
Sunday 15/9/19

09.30 · 09.45   **O19**
THE RELATIONSHIP BETWEEN CARDIOVASCULAR
AUTONOMIC NEUROPATHY AND CEREBRAL BLOOD FLOW
IN PATIENTS WITH TYPE 2 DIABETES MELLITUS
Boris Mankovsky, Ukraine

09.45 · 10.00   **O20**
SYSTEMATIC REVIEW AND META-ANALYSIS ON THE
PREVALENCE OF CARDIAC AUTONOMIC NEUROPATHY
IN PRE-DIABETES AND METABOLIC SYNDROME
Aikaterini Eleftheriadou, United Kingdom

10.00 · 10.30   *Coffee Break and Exhibition*

10.30 · 11.15   **Invited Lecture :** 10-Year Anniversary of Toronto
Consensus Statement: Autonomic Neuropathy.
Chair : *Prof. Peter Kempler, Hungary*
Speaker : *Prof. Vincenza Spallone, Italy*

11.15 · 12.45   **Oral Session :** Treatment
Chairs : *Prof. Mark Yorek, United States of America*
and *Dr. Gidon Bönhof, Germany*

11.15 · 11.30   **O21**
TOPICAL OXYBUTYNIN, A MUSCARINIC RECEPTOR
ANTAGONIST, IMPROVES EPIDERMAL NERVE FIBER
DENSITY AND NERVE FUNCTION IN SUBJECTS WITH
TYPE 2 DIABETES
Carolina Casellini, United States of America

11.30 · 11.45   **O22**
EFFICACY AND SAFETY OF A PILL CONTAINING SOD, ALA,
VIT. B12 AND CARNITINE AFTER 12 MONTHS OF
ADMINISTRATION IN PATIENTS WITH DIABETIC NEUROPATHY
Triantafyllos Didangelos, Greece

DAY 3
Sunday 15/9/19

11.45 · 12.00 **O23**

A CREAM FORMULATION OF TRPV1 AGONIST
RESINIFERATOXIN FOR THE TREATMENT OF PAINFUL
DIABETIC PERIPHERAL NEUROPATHY
Louis Premkumar, United States of America

12.00 · 12.15 **O24**

IMPACT OF NORMALISED HBA1C AND WEIGHT LOSS ON
NEUROPATHY AND OTHER MICROVASCULAR
COMPLICATIONS IN TYPE 2 DIABETES MELLITUS
Mitra Tavakoli, United Kingdom

12.15 · 12.30 **O25**

EFFECT OF LATE INTERVENTION WITH MENHADEN OIL ON
PERIPHERAL NEUROPATHY IN DIET-INUDCED OBESE AND
TYPE 2 DIABETIC SPRAGUE-DAWLEY RATS
Mark Yorek, United States of America

12.30 · 12.445 **O26**

PERIPHERAL POLYNEUROPATHY PREVALENCE IN GRADE
II AND III OBESE SUBJECTS WITHOUT DIABETES BEFORE
AND AFTER BARIATRIC SURGERY
Helena Schmid, Brazil

12.45 · 13.45 *Lunch*

13.45 · 15.45 **Poster Session :** Diagnosis and Epidemiology
Chair : *Dr. Prashanth Vas, United Kingdom*

P26

LESIONS OF THE SMALL FIBERS OF THE AUTONOMIC
NERVOUS SYSTEM AND GRADATION OF THE DIABETIC
FOOT RISK IN PATIENTS WITH DIABETES
Jean-Henri Calvet, France

DAY 3
Sunday 15/9/19

P27

THE MICROBIOME IN THE SKIN OF THE FOOT, DIABETIC
PERIPHERAL NEUROPATHY, PLANTAR SUBCUTANEOUS
STIFFNESS AND PEAK PRESSURE GRADIENT, RISK
FACTORS TO PROMOTE INFECTIONS AND WOUNDS:
NEW DIAGNOSTIC OBJECTIVES TO PREVENT WOUNDS
AND INFECTIONS
Ariel Andrés Odriozola Orlandi, Spain

P28

NORMAL HIGH HbA1c IS A RISK FOR ABNORMAL PAIN
THRESHOLD IN A GENERAL JAPANESE POPULATION
Hiroki Mizukami, Japan

P29

WHAT ELSE (COULD THERE BE), BEYOND A FOOT ULCER
Iris Marolt, Slovenia

P30

PREULCERATIVE LESIONS IN DIABETIC INPATIENTS IN
LATIN AMERICAN HOSPITALS
Gabriela Carro, Argentina

P31

CLASSIFYING PAIN SCORES USING MAGNETIC RESONANCE
IMAGING IN PAINFUL DIABETIC NEUROPATHY
Kevin Teh, United Kingdom

P32

VALIDATION OF THE SIMPLE DIAGNOSTIC CRITERIA OF
DIABETIC POLYNEUROPATHY IN JAPAN
Tatsuhito Himeno, Japan

NEURODIAB

Meliá Sitges Hotel
Sitges - Barcelona

DAY 3
Sunday 15/9/19

P33
THE SEVERITY OF PERIPHERAL NEUROPATHY AND INCIDENCE OF OTHER DIABETIC COMPLICATIONS IN DIABETES NEUROPATHY CENTER OF UNIVERSITY OF DEBRECEN
Ferenc Sztanek, Hungary

P34
THE PREVALENCE OF DIABETIC PERIPHERAL NEUROPATHY AMONG THE FUTSAL PLAYERS PARTICIPATING IN THE DIAEURO 2015 CHAMPIONSHIP
Daniel -Tudor Cosma, Germany

P35
CHARCOT-FOOT IN A 25 YEARS OLD PATIENT WITH TYPE 1 DIABETES – CASE REPORT
Orsolya Vági, Hungary

13.45 · 15.45   **Poster Session :** Pathogenesis and treatment
Chair : *Dr. Tamas Varkonyi, Hungary*

P36
INDEPENDENTLY ASSOCIATION OF PERIPHERAL POLYNEUROPATHY WITH SERUM HIGH-DENSITY LIPOPROTEIN (HDL) CHOLESTEROL AFTER BARIATRIC SURGERY: A COHORT STUDY
Helena Schmid, Brazil

P37
MAGNESIUM PREVENTS CARBONYL STRESS-MEDIATED NEURONAL DAMAGE VIA UPREGULATION OF INTRACELLULAR GLUCOSE METABOLISM:
A BACK-TRANSLATIONAL APPROACH
Alexander Strom, Germany

DAY 3
Sunday 15/9/19

P38

A1C VARIABILITY IS ASSOCIATED WITH DIABETIC
PERIPHERAL NEUROPATHY IN ADULTS WITH TYPE 1
DIABETES PARTICIPATING IN POZNAN PROSPECTIVE
STUDY (PoProStu)
Aleksandra Araszkiewicz, Poland

P39

IS ALPHA LIPOIC ACID HYPE OR HOPE FOR CARDIOVASCULAR
AUTONOMIC NEUROPATHY? – A CASE REPORT
Camelia Vonica, Romania

P40

PERIPHERAL NERVE PRESERVATION OF METFORMIN
COMPARE TO ALPHA LIPOIC ACID (ALA) IN STZ/HFD
INDUCED MILD DIABETIC RATS
Tae Sun Park, Korea

P41

GAMMA-LINOLENIC ACID VERSUS α-LIPOIC ACID TO
TREAT PAINFUL DIABETIC NEUROPATHY IN ADULTS:
A 12-WEEK, RANDOMIZED, NON-INFERIORITY,
DOUBLE PLACEBO TRIAL
Jong Chul Won, Korea

P42

EFFECT OF GOOD GLYCEMIC CONTROL ON THE
DEVELOPMENT OF DIABETIC PERIPHERAL NEUROPATHY
IN A RAT MODEL OF TYPE 2 DIABETES
Laura Jul Andreasen, Denmark

DAY 3
Sunday 15/9/19

P43

HYPOGLYCEMIA AND HYPERGLYCEMIA ENHANCE
OXIDATIVE STRESS THROUGH POLYOL PATHWAY
IN SCHWANN CELLS: NOVEL ANTIOXIDATIVE MECHANISMS
OF ALDOSE REDUCTASE INHIBITORS
Koichi Kato, Japan

P44

EFFECT OF MITOQUINONE (MITO-Q) ON NEUROPATHIC
ENDPOINTS IN AN OBESE AND TYPE 2 DIABETIC RAT MODEL
Mark Yorek, United States of America

16.15 · 20.00   **Social Program in Barcelona**

20.30 · 22.30   **Gala Dinner**

DAY 4
Monday 16/9/19

08.30 · 10.00 **Oral Session :** Diagnosis and Epidemiology
Chairs : *Profs. Vincenza Spallone, Italy* and
Simona Frontoni, Italy

08.30 · 08.45 **O27**
CENTRAL BRAIN MECHANISMS THAT PREDICT TREATMENT
RESPONSE IN PAINFUL DIABETIC NEUROPATHY
Dinesh Selvarajah, United Kingdom

08.45 · 09.00 **O28**
PANCREATIC EXOCRINE INSUFFICIENCY AND AUTONOMIC
NEURONAL DYSFUNCTION IN DIABETES – A PILOT STUDY
Eirik Søfteland, Norway

09.00 · 09.15 **O29**
HAPTICS FOR EVALUATION OF TOUCH DYSFUNCTION IN
TYPE 1 DIABETES MELLITUS
Fabiana Picconi, Italy

09.15 · 09.30 **O30**
DYSFUNCTION IN THE SUBTYPES OF PERIPHERAL NERVE
FIBRES AND THEIR RELATION TO THE FOOT PLANTAR
PEAK PRESSURE REGISTERED BY WALKING SENSORS IN
DIABETIC PATIENTS
Carles Verges, Spain

09.30 · 09.45 **O31**
PERIPHERAL DIABETIC NEUROPATHY EARLY DIAGNOSIS –
SOMETHING OLD THAT SHOULD ALWAYS BE
CONSIDERED SOMETHING NEW
Teodor Salmen, Romania

NEURODIAB

Meliá Sitges Hotel
Sitges - Barcelona

DAY 4
Monday 16/9/19

09.45 · 10.00   **O32**
KEY TO THE SENSORY PARADOX OF PAINFUL DIABETIC
NEUROPATHY
Mikhail Nemenov, United States of America

10.00 · 10.15   *Coffee Break and Exhibition*

10.15 · 11.45   **Oral Session :** Small Fibres
Chairs : *Dr. Dinesh Selvarajah, United Kingdom* and
Prof. Solomon Tesfaye, United Kingdom

10.15 · 10.30   **O33**
PREDICTION OF FUTURE NEUROPATHY ONSET USING
CORNEAL CONFOCAL MICROSCOPY: A LONGITUDINAL
MULTINATIONAL CONSORTIUM STUDY
Vera Bril, Canada

10.30 · 10.45   **O34**
CORNEAL CONFOCAL MICROSCOPY IDENTIFIES EARLY
AND DEFINITE CARDIAC AUTONOMIC NEUROPATHY
Shazli Azmi, United Kingdom

10.45 · 11.00   **O35**
CORNEAL NERVE AND KERATOCYTE DENSITY ARE
REDUCED IN SUBJECTS WITH IMPAIRED GLUCOSE
TOLERANCE WHO DEVELOP TYPE 2 DIABETES
Thahiba Chowdhury, United Kingdom

11.00 · 11.15   **O36**
10-YEAR FOLLOW-UP OF CARDIAC, AUTONOMIC AND
SENSORY FUNCTIONS IN YOUNG TYPE 1 DIABETIC
PATIENTS
Tamás Várkonyi, Hungary

DAY 4
Monday 16/9/19

11.15 · 11.30   **O37**
OBSTRUCTIVE SLEEP APNOEA AND CARDIAC AUTONOMIC
NEUROPATHY IN PATIENTS WITH TYPE 1 DIABETES:
A CROSS-SECTIONAL STUDY
Ziyad Alshehri, United Kingdom

11.30 · 11.45   **O38**
CORNEAL NERVE FIBRE LOSS IS RELATED TO THE
SEVERITY OF PAIN AND QUALITY OF LIFE IN PATIENTS
WITH PAINFUL DIABETIC NEUROPATHY
Alise Kalteniece, United Kingdom

11.45   **Closing Remarks :**
Profs. Peter Kempler, Hungary and
Ariel Odriozola, Spain

ORAL
ABSTRACT

O1. SMALL FIBRE NEURAL ASSESSMENT IN PEOPLE WITH TYPE 2 DIABETES, WITH OR WITHOUT LIRAGLUTIDE, A GLP-1RA ANALOGUE TREATMENT

Victoria Tobin[1], Gerry Rayman[1], Jenna Cross[1], Sanjeev Sharma[1].

[1] *Diabetes and Endocrinology, East Suffolk and North Essex NHS Foundation Trust.*

Objectives : There is a lack of effective therapies for diabetic neuropathy, with glucose control remaining the only therapeutic tool with consistent evidence. Glucagon-like peptide-1 receptor agonist (GLP1-ra) have revolutionised glucose management, and emerging data shows that GLP-1ra may have a supportive role in neural regulation, both by hyperglycaemic correction and direct neurotrophic support. The aim of this pilot study is to determine whether Liraglutide, a GLP1-ra, has neurotropic effects on type-2 diabetes mellitus patients (T2DM) by comparing participants' small nerve fibre (SNF) structure and function over a six-month period. The novelty of this research is that such assessments might further elucidate the individual effects of diabetes therapies on neural function.

Methods : 52 participants were studied: 16 T2DM commencing liraglutide therapy as part of routine treatment, 17 T2DM without liraglutide therapy, and 19 healthy volunteers (HV). The age, sex, Hba1c, and BMI of all groups were matched to reduce bias due to demographic variation. Participants underwent clinical evaluation and fasting biochemical testing. Corneal Confocal Microscopy (CCM) was performed to assess SNF structure, and corneal nerve fibre density (CNFD) was derived using ACCMetrics® software. SNF function was assessed using the modified laser Doppler imager (LDI_{FLARE}), which measures the size of the axon mediated neurovascular response to foot-skin heating.

Results : Within each group, both LDI_{FLARE} and CCM (CNFD) showed no significant difference in neuropathy outcomes between baseline and six months (p=0.08–0.84 and p=0.21–0.75, respectively). A difference in SNF structure and function was observed between groups (p<0.0001) at baseline and six months, with the HV cohort demonstrating a larger LDI_{FLARE} area and greater CNFD (6.0 ± 3.0 cm^2 and 56.1 ± 3.7 no/mm^3, respectively) than the T2DM (3.7 ± 2.2 cm^2 and 37.5 ± 2.6 no/mm^3), and the GLP-1 treatment group (3.2 ± 2.3 cm^2 and 43.6 ± 5.5 no/mm^3). However, between groups, no significant difference was found in the change in LDI_{FLARE} and CNFD over the six months (p=0.82 and p=0.91, respectively).

Conclusions : HV had significantly greater SNF structure and function compared to both T2DM groups. However, no change in SNF structure and function was observed within or between each group after six months, so liraglutide therapy did not support neural regulation in this study. Therefore, understanding the aetiopathogenesis is key as other complex mechanisms may be involved. Further research should consider a combined therapy to halt the progression of diabetic neuropathy by helping SNF regeneration.

O2. ALTERED MITOCHONDRIAL FUNCTION OF THE THALAMUS IN PAINFUL DIABETIC PERIPHERAL NEUROPATHY

Sloan G[1], Anton A[2], Selvarajah D[3], Wilkinson ID[2], Tesfaye S[1].

[1] Academic Department of Diabetes and Endocrinology, Sheffield Teaching Hospitals NHS Foundation Trust, Sheffield, UK, [2] Academic Unit of Radiology, University of Sheffield, Sheffield, UK, [3] Department of Human Metabolism and Oncology, University of Sheffield, Sheffield, UK.

Objectives : Painful diabetic peripheral neuropathy (painful-DPN) is characterised by unremitting pain and hyperperfusion of the thalamus. In this study, we have performed Phosphorus Magnetic Resonance Spectroscopy (31P-MRS) to examine thalamic bioenergetics and mitochondrial function. We hypothesised that thalamic high energy phosphate metabolite levels may be altered in painful-DPN as a result of persistent nociceptive inputs.

Methods : A total of 41 subjects [33 with type 2 diabetes (T2DM): age: 62.3 ± 7; 11 painful-DPN, 10 painless-DPN and 11 No-DPN) and 8 healthy volunteers (HV, age 60.8 ± 14) underwent detailed clinical and neurophysiological assessments. All participants were right handed and were grouped according to their Neuropathy Impairment Score of the Lower Limb plus 7 test (NIS(LL)+7) and Douleur Neuropathique 4 (DN4) scores, and underwent 31P-Chemical Shift Imaging (CSI) of the brain at 3 Tesla (Ingenia, Philips Healthcare) to assess cerebral phosphorus metabolites (TR 4s TE 0.26ms). The current analysis examined the voxel within the right thalamus. The analysis has been performed with AMARES (Java Magnetic Resonance User Interface; jMRUI software). We calculated the ratios of adenosine tri-phospahte (ATP; α-ATP plus γ-ATP) to Phosphocreatine PCr (ATP:PCr).

Results : There was a significant group effect in ATP:PCr ratios (ANOVA $p=0.014$). In post-hoc analysis the ATP:PCr ratio was significantly higher in painful-DPN (0.53 [± 0.057]) compared to HV (0.44 [± 0.048], $p=0.002$) and T2DM without-DPN (0.44 [± 0.90], $p=0.008$), but not painless-DPN (0.49 [± 0.8], $p=0.158$). This ratio correlated to numeric pain score ratings during the scan ($r=0.404$, $p=0.010$), DN4 ($r=0.384$, $p=0.014$), Neuropathic Pain Symptom Inventory score ($r=450$, $p=0.004$) and HbA1c ($r=0.394$, $p=0.014$).

Conclusions : This is the first study to explore cerebral bioenergetics using 31P-MRS in human DPN. We have demonstrated significantly elevated thalamic ATP:PCr ratio in patients with painful-DPN, suggestive of altered cerebral bioenergetics. Thalamic mitochondrial dysfunction caused by unremitting nociceptive inputs may serve as a biomarker of neuropathic pain in diabetes. This study adds further evidence for the importance of the thalamus as a potential target for therapeutic intervention in painful-DPN.

O3. BARIATRIC SURGERY IS ASSOCIATED WITH REDUCED RISK OF THE DEVELOPMENT AND PROGRESSION OF FOOT DISEASE IN PATIENTS WITH TYPE 2 DIABETES: A MATCHED CONTROLLED COHORT STUDY

Pushpa Singh[1], Anuradhaa Subramanian[2], Nicola Adderley[2], Krishna Gokhale[2], Rishi Singhal[3], Srikanth Bellary[4,5], Krishnarajah Nirantharakumar[2], Abd A Tahrani[1,5].

[1] Institute of Metabolism and Systems Research, University of Birmingham, Birmingham, UK,
[2] Institute of Applied Health Research, University of Birmingham, Birmingham, UK,
[3] Department of Bariatric Surgery, University hospital Birmingham NHS trust, Birmingham, UK
[4] Life and Health Science, Aston University, Birmingham, UK, [5] University Hospitals Birmingham NHS Foundation Trust.

Objectives : Obesity is an established risk factor for diabetes peripheral neuropathy (DPN), peripheral vascular disease (PVD) and diabetes foot disease (DFD). Bariatric surgery (BS) is the most successful obesity treatment that results in sustained weight loss. However, the impact of BS in patients with Type 2 DM (T2D) on DPN and DFD is unknown. Hence, we conducted a population-based study examining the impact of BS on development and progression of DFD.

Methods : An age, sex, body mass index (BMI)- matched retrospective cohort study was performed using data from The Health Improvement Network (THIN), a UK database of routinely collected primary care patient records. Study period was 1st January 1990 to 31st January 2018. Adult patients with T2D and BMI ≥ 30 Kg/m² were included in the study. The exposed group were patients who had BS after their T2D diagnosis; the unexposed group were patients without BS. The primary outcome was DFD (a composite of DPN, foot ulcer, Charcot's neuro-arthropathy, PVD, amputation or foot coded as moderate or high risk). Secondary outcomes included analysis of the individual components of the composite outcome and examining the progression of foot from low to medium and high risk (based on primary care coding). All variables were identified using Read codes. Cox regression was used to calculate hazard ratios using Stata version15.

Results : 1126 exposed and 2219 unexposed patients were included. Mean (SD) age was 50 (9.3) years, 2261 (67.69%) were women, median follow-up was 3.6 years (IQR 1.7-5.9), median T2D duration for exposed vs unexposed was 4.7 (2.2- 8.9) vs 4.6 (1.9- 8.1) years. The mean (SD) preoperative HbA1c was 7.78 (1.82) % vs 7.82 (1.69) % in exposed and unexposed patients respectively. After adjusting for age, sex, smoking, alcohol, BMI, ethnicity, Townsend quintile (social deprivation), diabetes duration, baseline hypertension and HbA1c, BS was associated with reduced risk of developing DFD (adj HR 0.63, 95%CI 0.52- 0.76, p<0.001). BS was also associated with reduced risk of progression from low to moderate/high risk foot (0.87, 0.77- 0.997, p=0.046) and from moderate to high risk foot (adj HR 0.54, 0.33- 0.90, p=0.018).

Conclusions : In patients with T2D, bariatric surgery was associated with significant reduction in the risk of development or progression of foot disease.

O4. CIRCULATING miRNAs (miR-155, miR-128 and miR-499) AS POTENTIAL BIOMARKERS OF DIABETIC NEUROPATHIES

Greco C, Latini A, Ciccacci C, Colantuono A, Politi C, D'Amato C, Rinaldi ME, Lauro D, Novelli G, Borgiani P, Spallone V.

Department of Systems Medicine, Endocrinology Section, Department of Biomedicine and Prevention, Genetics Section, University of Rome Tor Vergata; UniCamillus, International University of Health and Medical Sciences, Rome, Italy.

Objectives : There is emerging evidence that microRNAs (miRNAs), as genomic regulators, might play a role in diabetic complications. Moreover, polymorphisms of MIRNA genes could alter their expression and MIR146a, MIR128a, MIR27a and MIR499 have been proposed as candidate genes for diabetic polyneuropathy (DPN) and cardiovascular autonomic neuropathy (CAN) susceptibility. However, the relation between MIRNA genes polymorphism and miRNAs expression is less explored with regard to DPN and CAN. The study was aimed at evaluating the expression of candidate miRNAs for DPN and CAN in type 2 diabetes.

Methods : In 50 participants with type 2 diabetes (age 62.5±6.6 years, duration 12.6±9.2 years, BMI 31.6±6.2 Kg/m^2, 32 males), we assessed DPN by measuring neuropathic symptoms and signs (using MNSI-Q and MDNS), vibration and thermal perception thresholds, and CAN by performing four cardiovascular reflex tests. We extracted RNA from peripheral blood mononuclear cells and quantified the expression of six miRNAs (i.e. miR-21, miR-27a, miR-128a, miR-146a, miR-155, miR-499), using TaqMan assays. Moreover, we extracted DNA from the whole blood, analysed common polymorphisms of the MIRNA genes and evaluated the possible correspondence between genetic variants and levels of miRNAs.

Results : Compared to those without DPN, patients with DPN showed higher expression of miR-128 (0.96±0.82 Vs. 0.45±0.49, P=0.015), and lower expression of both miR-155 (0.87±0.50 Vs. 1.32±0.98, P=0.04) and miR-499 (0.40±0.31 Vs. 0.63±0.44, P=0.05). We also observed a lower expression of miR-155 in patients with early CAN (based on one abnormal CART) compared to those without (0.84±0.47 Vs. 01.26±0.92, P=0.05). Genotypic analysis indicated that rs767649 polymorphism variant allele in the MIR155 promoter region was associated with a higher expression of this miRNA compared to the wild-type allele (2.14±1.06 Vs. 0.98±0.67, P=0.003).

Conclusions : This study shows changes in expression of miR-128a, miR-155, and miR-499 in patients with DPN and CAN, and confirms a correspondence between MIRNA gene polymorphism and miRNA expression at least for miR-155. Thus, MIRNA gene polymorphism and miRNAs seem to be involved in the development of diabetic neuropathies. After external validation in more numerous cohorts, these data could offer insights for both new biomarkers and therapeutic targets in diabetic neuropathies.

O5. THE RELATIONSHIP BETWEEN OBSTRUCTIVE SLEEP APNOEA AND DIABETES-RELATED PERIPHERAL AND AUTONOMIC NEUROPATHY IN ADULTS WITH TYPE 1 DIABETES: A SYSTEMATIC REVIEW AND META-ANALYSIS

Ziyad Alshehri[1,5], Abdulaziz Alzahrani[1], Janine Dretzke[4], Prem Kumar[1], Clare J. Ray[1], Muhammad Ali Karamat[3], Abd A. Tahrani[2,3].

[1] Institute of Clinical Sciences, University of Birmingham, Birmingham, United Kingdom, [2] Institute of Metabolism and Systems, University of Birmingham, Birmingham, United Kingdom, [3] Department of Diabetes and Endocrinology, University Hospitals Birmingham NHS Foundation Trust, Birmingham, United Kingdom, [4] Institute of Applied Health Research, University of Birmingham, Birmingham, United Kingdom, [5] Respiratory Therapy Department, Taibah University, Medina, Saudi Arabia.

Objectives : This systematic review aimed to investigate the relationship between obstructive sleep apnoea (OSA) and diabetic complications in adults with type 1 diabetes (T1D). Here the findings related to diabetic peripheral and autonomic neuropathy (DPN and DAN respectively) are reported.

Methods : Embase, MEDLINE, CINAHL, and Cochrane CENTRAL were searched with no date or language restrictions to May 2018 using index terms and text words related to T1D and OSA. PubMed was searched for the last 6 months to capture studies not yet indexed in MEDLINE. Other sources included ongoing trials databases, reference list checking and consulting experts in the field.
The selection of the studies was performed by two independent reviewers. Studies of any design were eligible if they examined the impact of OSA on DAN and DPN in patients with T1D. Risk of bias assessment was based on appraisal tools for cross-sectional studies. Random effects meta-analysis was performed where studies reported the same outcome and were clinically similar. Reporting was in accordance with PRISMA guidelines.

Results : Ten cross-sectional studies were included. Six studies reported DAN, three reported DPN. Meta-analysis showed that OSA was associated with DAN (pooled odd ratio (OR) 4.06, 95% CI: 2.01–8.19), and DPN (pooled OR 3.30, 95% CI: 2.06–5.31) (Figures 1 and 2). OSA was also associated with hypertension and nephropathy. The baseline characteristics showed that patients with T1D and OSA were older, had higher BMI and longer diabetes duration and similar HbA1c compared to patients with T1D only.

Conclusions : It is suggestive but based on unadjusted data that OSA is associated with DPN and DAN in patients with T1D. Due to the cross-sectional nature of the studies, no causal inferences can be drawn and longitudinal studies with long-term follow up are needed with appropriate adjustment for important potential confounders. The relationship between OSA and DPN and DAN could potentially be bi-directional.

O5. THE RELATIONSHIP BETWEEN OBSTRUCTIVE SLEEP APNOEA AND DIABETES-RELATED PERIPHERAL AND AUTONOMIC NEUROPATHY IN ADULTS WITH TYPE 1 DIABETES: A SYSTEMATIC REVIEW AND META-ANALYSIS
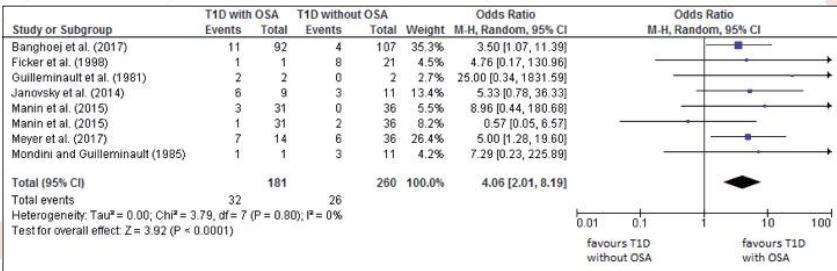

Figure 1.
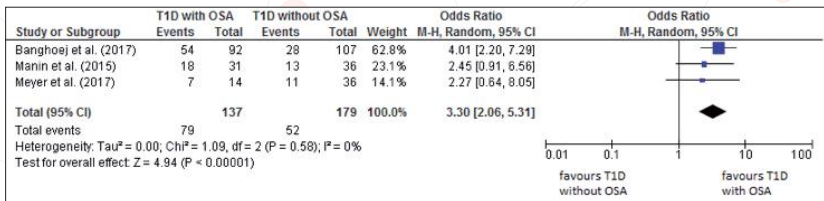Comparison of autonomic neuropathy between T1D patients with and without OSA

Figure 2.
Comparison of peripheral neuropathy outcome between T1D patients with and without OSA

O6. AUTONOMIC NEUROPATHY IN TYPE 1 DIABETES (T1D): FINDINGS FROM THE T1D EXCHANGE

Kara Mizokami-Stout, MD[1], Ryan Bailey, BS[2], Nicole Foster, MS[2], Lynn Ang, MD[1], Grazia Aleppo, MD[3], Carol J. Levy, MD[4], Michael R. Rickels, MD, MS[5], Viral Shah, MD[6], Sarit Polsky, MD, MPH[6], Michelle Katz, MD[7], Bryce Nelson, MD, PhD[8], Anders Carlson, MD[9], Francesco Vendrame, MD[10], Rodica Pop-Busui, MD, PhD[1].

[1] University of Michigan, Ann Arbor, MI, [2] Jaeb Center for Health Research, Tampa, FL, [3] Northwestern University, Chicago, IL, [4] Icahn School of Medicine at Mount Sinai, New York, NY, [5] Rodebaugh Diabetes Center, University of Pennsylvania Perelman School of Medicine, Philadelphia, PA, [6] Barbara Davis Center for Diabetes, Aurora, CO, [7] Joslin Diabetes Center, Boston, MA, [8] University of South Carolina School of Medicine – Greenville, Greenville, SC, [9] Park Nicollet International Diabetes Center, Minneapolis, MN, [10] University of Miami, Miami, FL.

Objectives : Diabetic autonomic neuropathy (DAN) may contribute to significant morbidity, including orthostatic hypotension, arrhythmia, hypoglycemia unawareness, gastroparesis, enteropathy, urinary incontinence and sexual dysfunction in T1D. Contemporary data on DAN impact are scarce. We sought to evaluate the prevalence of DAN symptoms in a large cohort of T1D participants in the United States.

Methods : We evaluated the prevalence of DAN in adult T1D patients enrolled in the T1D Exchange Clinic Network using the validated Survey of Autonomic Symptoms (SAS). Surveys were emailed to registry participants who consented to be emailed about future studies. DAN was defined as a score >3 on the Symptom Score (SS). Severity of symptoms was graded with the Total Impact Score (TIS) defined as none ((≤5th percentile), mild (≤50th percentile), moderate (≤95th percentile) and severe (>95th percentile). Multivariable linear regression and stepwise logistic regression were used to analyze SAS-defined DAN and the correlations between DAN and glycemic control, medical comorbidities and socioeconomic factors.

Results : Among 965 T1D participants, DAN prevalence was 17%, of which 76% presented with moderate and 24% with severe symptoms. Participants with DAN were older (44±16 vs 39±17 years), were more often female (73% vs 62%), had longer T1D duration (28±14 years vs 23±14 years), and had higher hemoglobin A1c (8.1±1.7% vs 7.7±1.5%) than those without DAN (all p-values <0.05). Compared with those without DAN, those with DAN were more likely to have peripheral neuropathy (OR 8.16, 95% CI 4.63-14.38), gastroparesis (OR 4.95, 95% CI 2.33-10.50), cardiovascular disease (OR 2.70, 95% CI 1.42-5.16), depression (OR 2.21, 95% CI 1.46-3.33) and use opioids (OR 4.37, 95% CI 1.82-10.47), both p-values <0.01.

Conclusions : As ascertained by the short SAS questionnaire, we found that DAN symptoms were common and should be screened for regularly. Traditional glycemic risk factors and the presence of peripheral neuropathy and CVD were associated with DAN. Opioid use also was greater in those with DAN, which might serve as a marker of more painful peripheral neuropathy.

O7. EXERCISE-INDUCED VASODILATION: USEFUL EARLY TOOL TO DETECT DIABETIC NEUROPATHY? PRELIMINARY RESULTS

C. Reynès[1], Y. Knapp[1], F. Latil-Plat[2], H. Ennaifer[2], L. Rocher[2], J.B. Beaume[1], L. Chatel[1], E. Benamo[1,2], A. Vinet[1].

[1] Avignon Université, LAPEC EA4278, F-84000, Avignon, France, [2] Service Endocrinologie-Maladies Métaboliques, Centre hospitalier Henri Duffaut, Avignon, France.

Objectives : Diabetic peripheral neuropathy (DPN) is a common chronic complication of type 2 diabetes (DT2) leading high-risk to more severe affections as foot ulcers and amputations. Its early detection is therefore of primary importance. Microvascular dysfunction plays a crucial role in development of DPN. Skin microcirculation has been proposed as a model of generalized microvascular function. Flowmotion is the periodic oscillations of microvascular blood perfusion which can be detected using laser Doppler flowmetry (LDF). Basal skin blood flow (SBF) was reported either similar or decreased in DPN. Changes in flowmotion could precede global DPN symptoms. Accordingly, exercise-induced vasodilation could worsen the microvascular alterations in DPN and may be an effective tool to sharpen diagnostic.

The aim of this study was to compare flowmotion at baseline and after a six-minutes walking test (6MWT) in 3 groups: control (CT), DT2 with and without DPN (DT2 and DPN, respectively).

Methods : Twenty-eight subjects were included (8 CT, 11 DT2 and 9 DPN). DPN diagnostic was based on sural nerve conduction measured by DPN Check and on thermal testing for the detection of small fiber neuropathy measured by NerveCheck. SBF was measured at dorsal part of foot with LDF probe during 10 minutes at rest and after 6MWT. Flowmotion was studied with Morlet wavelet analysis and was split into five frequency components: 0.0095–0.02Hz, 0.02–0.06Hz, 0.06–0.15Hz, 0.15–0.4Hz, and 0.4–1.6Hz related to endothelial, neurogenic, myogenic activities, and respiratory and cardiac rhythms, respectively. Results were expressed as total power (TP) and relative power in each frequency band expressed as the ratio of average power in a frequency band to the TP.

Results : Demographic, clinical and performance data in the 3 groups are reported in Table 1. Basal SBF time averaged absolute perfusion was not significantly different between groups. As expected, SBF increased at 10 minutes post-exercise in each group with no difference between groups. According to flowmotion, resting TP was only higher in DT2 compared to CT. Exercise induced increment in TP with higher values in DT2 and DPN compared to CT (Figure 1). Regarding low-frequency components, no difference before and after 6MWT was demonstrated for the myogenic components in all groups. Neurogenic band post-exercise and endothelial band at rest and post-exercise tended to be lower in DPN than in CT and DT2 (p=0.09).

Conclusions : In response to exercise stimulation, the spectral properties varied significantly, and the vasomotion contributed by endothelial and neurogenic control seemed to be decreased in DPN. However, more subjects are needed to confirm the clinical pertinence of this exercise-induced vasomotion changes.

07. EXERCISE-INDUCED VASODILATION: USEFUL EARLY TOOL TO DETECT DIABETIC NEUROPATHY? PRELIMINARY RESULTS

Variables	CT (3F, 5M)	DT2 (3F, 8M)	DPN (3F, 6M)
Age (years)	54.5 ± 5.8	58.8 ± 10.9	61.5 ± 7.8
BMI (kg/m^2)	31.3 ± 2.9	30.3 ± 4.7	36.1 ± 6.2†
HbA1c (%)	5.1 ± 0.5	9.0 ± 1.4*	8.7 ± 0.7*
Diabetes duration (years)	/	13,7 ± 6,8	20,3 ± 13,1
MAP (mmHg)	99.2 ± 12.1	92.1 ± 8.1	101.8 ± 9.9†
6MWT distance (m)	494.2 ± 63.3	417.0 ± 66.9*	405.2 ± 91.9*
HR_rest (bpm)	58.7 ± 6.2	66.9 ± 10.6	82.7 ± 10.6*†
HR_peak (bpm)	101.5 ± 28.6	114.7 ± 32.7	123.9 ± 14.4*
HR_10min post-ex (bpm)	58.8 ± 6.8	68.6 ± 11.1*	86.1 ± 12.2*†

BMI: body mass index; HbA1c: glycated haemoglobin; MAP: mean arterial pressure; 6MWT: 6-minutes walking test; HR: heart rate.
* significantly different from CT ($p<0.05$)
† significantly different from DT2 ($p<0.05$)

Table 1.
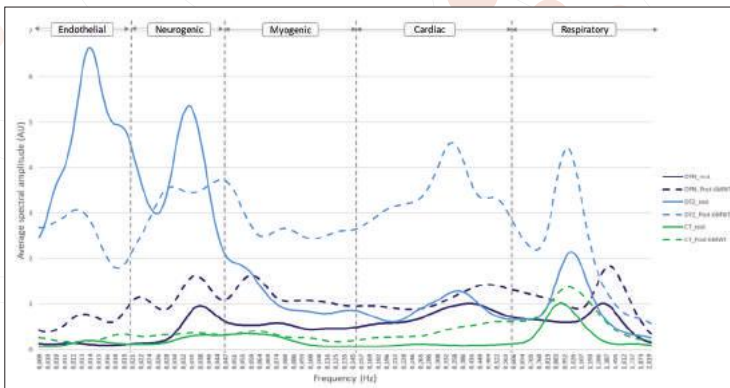Demographic, clinical and performance data in the 3 groups

Figure 1.
Time averaged power spectrum at rest (solid lines) and after (dotted lines) 6MWT of 3 groups.

O8. PREDICTION OF PARASYMPATHETIC FUNCTION BASED ON CLINICAL APPLICABLE BEDSIDE METHODS FOR TESTING THE AUTONOMIC REFLEX IN TYPE 1 DIABETES

Anne-Marie L Wegeberg[1], Elin D Lunde[2], Sam Riahi[2], Niels Ejskjaer[3], Rodica Pop-Busui[4], Asbjørn M Drewes[1,3], Birgitte Brock[5], Christina Brock[1].

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The study has been approved by the Local Ethics Committee (Diabetic Autonomic Neuropathy (DAN): BioMARKers of Cardiovascular and Autonomic Complications – N-20170045) and has been performed in accordance with the Helsinki Declaration

Objectives : Diabetic neuropathy is one of the most prevalent complications of diabetes; however, few methods for early detection exists. Cardiovascular autonomic neuropathy (CAN) can be detected in early stages by evaluating the time- and frequency domain parameters derived from heart rate variability (HRV) measures, which is the "golden standard". In recent years, there has been increased focus on parasympathetic measures of HRV (rMSSD and high-frequency power domains) as proxy for CAN. However, quick, affordable and readily available bedside screening tools are needed. Therefore, we aimed to evaluate if a combination of three short clinical tests generating a subsequent clinically applicable formula could sensitively assess parasympathetic function.

Methods : Fifty-six people with type 1 diabetes were included in the study (mean age 43 ±16 years, 46 % male, mean BMI of 25.8±3.7, mean disease duration of 23 ±14 years and mean HbA1c 63 ±15 mmol/L). All were evaluated with: 5-day continuous ECG monitoring (ePatch®), wherefrom rMSSD and high frequency power were computed (Cardioscope™), and three additional bed-side tests: 1) Cardiac vagal tone (CVT) computed from 5minute resting ECG (Faros™ – Probiometrics); 2) CAN value and scores (VAGUS™) and 3) electrochemical skin conductance (ESC) (SudoScan). Multiple logistic regressions with rMSSD or high frequency as dependent variable were performed in Stata.

Results : By combining the measures from CVT, HR response to standing (RS), CAN score and BMI, we were able to predict rMSSD with an accuracy of 85% and high frequency content with 64% ($p > 0.0001$), resulting in specific regression equations:

$\qquad$ • rMSSD = -29 +1.5CVT+27RS+0.9BMI-CAN(<1=0,1=8,>1=7)
$\qquad$ • high frequency = -1800+57CVT+905RS+35BMI-CAN(<1=0,1=222,>1=105)
ESC did not improve the model.

O8. PREDICTION OF PARASYMPATHETIC FUNCTION BASED ON CLINICAL APPLICABLE BEDSIDE METHODS FOR TESTING THE AUTONOMIC REFLEX IN TYPE 1 DIABETES

Conclusions : We showed that a combination of CVT and Vagus™ measures, which can be done in 30 minutes could assess parasympathetic function with high accuracy. Therefore these readily available tests which can be applied in outpatient settings are suitable as bedside screening tools for early detection of CAN. These may also be used in patients' risk stratification, however further validations studies are needed.

O9. DIABETIC NEUROPATHY INFLUENCES THE PERIPHERAL AND CENTRAL NERVOUS INTEGRATION OF THE NOCICEPTIVE WITHDRAWAL REFLEX

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The study has been reviewed by the Local Ethics Committee (N-20130077 and N-20090008) and performed in accordance with the Helsinki Declaration. Furthermore, the study was registered EUDRA CT (ref 2013-004375-12) and clinicaltrials.gov (ref NCT02138045).

Objectives : Diabetic neuropathy is a prevalent complications of diabetes (DM); however, differentiated comprehensive evaluation of the affected upstream sensory processing in diabetes is sparse. Hence, we investigated the spinal polysynaptic nociceptive withdrawal reflex (NWR), which integrates A-delta sensory input and is measured by electromyography (EMG) and the related A-beta elicited somatosensory evoked potentials (SEPs). We hypothesized that diabetic symmetrical polyneuropathy (DSPN) induces alterations in spinal and supra-spinal sensory-motor processing in comparison to age- and gender matched healthy; in terms of ability to elicit NWR, of the size of the NWR and the SEP measured at the vertex.

Methods : 48 patients with type 1 DM and DSPN (age 50±9, 39 men and disease duration 32±10 years) were compared to 21 healthy participants (age 51±6, 15 men) with no neurological disorders or medication that could alter neuronal function.
Perception- and reflex-threshold (RT) were determined and subjects received 6 electrical stimulations on the plantar site of the foot at RT, RT*1.3 and RT*1.6 to evoke a NWR. EMG and SEP were recorded for analysis.
A logistic regression model was used to calculate odds ratio (OR) for eliciting a NWR; a repeated measures mixed model was used to compare EMG response, and a MANOVA was used to compare amplitude and latency of the SEP peaks (P1 N1 P2) between patients and healthy.

Results : Patients with DM had significantly increased perception- ($p < 0.001$) and reflex- ($p = 0.012$) threshold. DM reduced the OR of a successful elicited reflex; (OR=0.045; $p = 0.014$). Increasing stimulation intensities increased the OR of eliciting a reflex (OR=1.073; $p = 0.009$). DM did not alter latency ($p = 0.168$) or AUC ($p = 0.081$) of the EMG response. DM changed the SEP (F=2.86 $p = 0.025$), and post hoc test revealed reduction of amplitude (-3.72mV $p < 0.021$) and prolonged latencies (15.1 ms $p < 0.013$) of the N1 peak.

O9. DIABETIC NEUROPATHY INFLUENCES THE PERIPHERAL AND CENTRAL NERVOUS INTEGRATION OF THE NOCICEPTIVE WITHDRAWAL REFLEX

Conclusions : To our knowledge this study is the first to investigate the spinal A-delta and supra-spinal A-beta responses to the NWR in diabetes and verified DSPN. The study reveals significant differences in 1) number of successfully elicited reflexes; 2) perception- and reflex-threshold 3) latency and amplitude of the N1 peak of the SEP. The findings imply that diabetes induces widespread differences in the reflex pathways and cortical signals providing differentiated A-delta and A-beta contributions which may explain the pathogenesis of DSPN.

O10. RISK FACTORS FOR PERIPHERAL AND CARDIOVASCULAR AUTONOMIC NEUROPATHY IN TYPE 1 DIABETES: 30 YEARS OF FOLLOW-UP IN DCCT/EDIC

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Objectives : The Diabetes Control and Complications Trial/Epidemiology of Diabetes Interventions and Complications (DCCT/EDIC) study reported that intensive glucose control resulting in lower hemoglobin A1c (HbA1c) reduced the risk of diabetic peripheral neuropathy (DPN) and cardiovascular autonomic neuropathy (CAN) in type 1 diabetes (T1D), with long lasting benefits. We evaluated additional clinical parameters and risk factors that are associated with DPN and CAN in this cohort, independent of HbA1c.

Methods : DPN was assessed at three different times and defined as a composite of symptoms, signs, and abnormal nerve conduction studies in ≥2 nerves; CAN was assessed seven different times and defined based on R-R variation, RR 15-20 plus Valsalva maneuver <1.5, or postural changes in blood pressure (decrease of diastolic BP>10 mmHg). We used generalized estimating equation models to evaluate the association of DPN and CAN with individual risk factors over repeated time points spanning 30 years. Covariates are listed in the order of significance as indicated by the Z-value (Tables 1&2).

Results : There were 1,386 participants with at least two DPN assessments and 1,434 participants with at least two CAN assessments during DCCT/EDIC follow-up. Among those, 32% developed DPN and 44% CAN. Higher mean HbA1c was the most significant risk factor for DPN (OR=1.56 per 1%, 95% CI 1.41,1.72). In multivariate analysis, DPN was also associated with older age (1.43 per 5 years, 95% CI 1.31,1.55), longer duration of T1D, higher albuminuria, β-blocker use, higher mean diastolic blood pressure, and higher HbA1c at DCCT eligibility. The most significant risk factor for CAN was older age (1.51 per 5 years, 95% CI 1.40,1.63). In multivariate analysis, other risk factors for CAN were longer duration of T1D (1.07 per 1 year, 95% CI 1.05,1.10), any sustained microalbuminuria (AER ≥30 mg/24 hour on two consecutive visits), higher mean HbA1c, higher mean and current pulse rate (likely as an indirect measures of CAN), higher mean systolic blood pressure, β-blocker use, any eGFR <60 mL/min/1.73 m², higher HbA1c at DCCT eligibility, and current cigarette smoking.

Conclusions : Higher mean HbA1c was the strongest correlate of DPN, but not of CAN, which was most strongly associated with age, duration of diabetes, and microalbuminuria. These findings may help identify patient phenotypes and modifiable risk factors for personalized approaches to neuropathy prevention.

O10. RISK FACTORS FOR PERIPHERAL AND CARDIOVASCULAR AUTONOMIC NEUROPATHY IN TYPE 1 DIABETES: 30 YEARS OF FOLLOW-UP IN DCCT/EDIC

Diabetic Peripheral Neuropathy	Odds Ratio (95% CI)	Z-value	p-value
Mean HbA1c (per 1%)	1.56 (1.41,1.72)	8.93	**<0.0001**
Age (per 5 years)	1.43 (1.31,1.55)	8.31	**<0.0001**
Duration of type 1 diabetes (per 1 year)	1.10 (1.08,1.13)	7.65	**<0.0001**
log AER (per 20% increase mg/24 hour)	1.33 (1.20,1.48)	5.53	**<0.0001**
β-blocker use (yes vs. no)	2.53 (1.50,4.26)	3.48	**0.0005**
Mean diastolic blood pressure (per 5 mm Hg)	1.14 (1.04,1.25)	2.85	**0.0043**

Table 1.
Final Multivariable GEE Models for DPN as a Function of Baseline and Time-dependent Covariates

Cardiovascular Autonomic Neuropathy	Odds Ratio (95% CI)	Z-value	p-value
Age (per 5 years)	1.51 (1.40,1.63)	10.59	**<0.0001**
Duration of type 1 diabetes (per 1 year)	1.07 (1.05,1.10)	5.76	**<0.0001**
Mean HbA1c (per 1%)	1.21 (1.12,1.32)	4.53	**<0.0001**
Mean pulse rate (per 1 bpm)	1.04 (1.02,1.06)	4.33	**<0.0001**
Mean systolic blood pressure (per 5 mm Hg)	1.11 (1.05,1.17)	3.73	**0.0002**
β-blocker use (yes vs. no)	2.02 (1.38,2.96)	3.61	**0.0003**
Any eGFR <60 mL/min/1.73 m^2 (yes vs. no)	2.79 (1.55,5.05)	3.40	**0.0007**

Table 2.
Final Multivariable GEE Models for CAN as a Function of Baseline and Time-dependent Covariates

O11. THALAMIC ATROPHY IS ASSOCIATED TO INTRA-THALAMIC METABOLITES IN TYPE 1 DIABETES WITH SEVERE DISTAL SYMMETRICAL POLYNEUROPATHY

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Objectives : Thalamic atrophy assessed by magnetic resonance imaging (MRI) have been shown to associate to the presence of type 1 diabetes (T1DM) (1). In addition, intra-thalamic neuronal function can be assessed by magnetic resonance spectroscopy analysis of the metabolite N-acetylaspartate/creatine (NAA/cre) (2). The aim was to explore the associations between thalamic atrophy and clinical measures such as diabetes duration, severity of peripheral neuropathy, neuropathic phenotype (painful/non-painful neuropathy) and intra-thalamic metabolites.

Methods : 48 adults with T1DM (50±9 years; diabetes duration: 32±10 years) and confirmed distal symmetric polyneuropathy (DPSN) and 28 age-matched healthy controls were MRI scanned. A composite score assessed the severity of DSPN and the questionnaire DN4 was used to determine pain (n=12)/no pain. Data were preprocessed and analyzed using Computational Anatomy Toolbox (CAT12.2, r1290) through SPM12 (Wellcome Trust Centre for Neuroimaging, London, UK). Thalamic parameters were extracted from bilateral ROIs (Marsbar toolbox, 5 mm), see Figure 1. Average values within the ROIs were used as estimates of thalamic volume. Intra-thalamic NAA/cre was assessed by spectroscopy. Group differences were calculated by an independent t-test and pearson correlation analyses were used to explore associations.

Results : 46 MRI scans were used. Regional gray matter volume group differences were identified in left thalamus/putamen/caudate and right thalamus/putamen (all p<0.001), Table 1 and Figure 1. Thalamic estimates were positively associated to intra-thalamic NAA/cre (r=0.4; p= 0.006) (Figure 1), however not to diabetes duration and severity of DSPN (p>0.4), and neuropathic phenotype did not influence the thalamic estimates (p=0.3).

Conclusions : Thalamic atrophy was associated to NAA/cre which indicates severe neuronal loss and dysfunction in this cohort with T1DM and severe DSPN. The progression of DSPN may explain the homogeneity of peripheral measures, which could hamper a potential association between thalamic atrophy and clinical measures.

O11. THALAMIC ATROPHY IS ASSOCIATED TO INTRA-THALAMIC METABOLITES IN TYPE 1 DIABETES WITH SEVERE DISTAL SYMMETRICAL POLYNEUROPATHY

References :

1. Moulton CD et al. Meta-analyses of structural regional cerebral effects in type 1 and type 2 diabetes. 2015;651–62.
2. Selvarajah D et al. Thalamic neuronal dysfunction and chronic sensorimotor distal symmetrical polyneuropathy in patients with type 1 diabetes mellitus. Diabetologia. 2008;51:2088–92.

Region name	x	y	z	Voxels	Z-score	P_{FWE}
Thalamus/putamen/caudate, L	-9	12	8	3178	5.17	**<0.001**
Thalamus/putamen, R	20	-3	8	1541	4.65	**0.001**

Table 1.
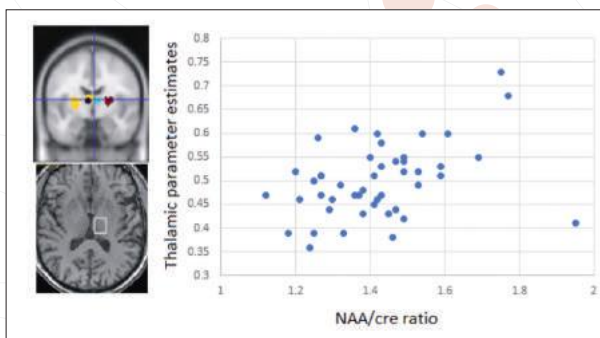Decreased thalamic volume in adults with type 1 diabetes as compared to healthy controls

Figure 1.
Top left: Decreased gray matter volume in left thalamus/putamen/caudate (yellow) and right thalamus/putamen (red) in adults with type 1 diabetes and DSPN. Thalamic volume estimates were extracted from dark and light blue ROIs. Bottom left: Brain metabolites were measured in thalamus using spectroscopy. Right: Associations between thalamic parameter estimates and NAA/cre.

O12. REDUCTION OF TERMINAL PARASYMPATHETIC FIBERS IN ISLETS IS CORRELATED WITH β CELL VOLUME IN LEAN TYPE 2 DIABETIC GOTO-KAKIZAKI RAT

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Objectives : One of pathologies in type 2 diabetes (T2D) is reduction of β cell volume($V_β$). Islets are richly innervated by both autonomic and non-autonomic nerves. In particular, the function and proliferation of β cell is properly controlled by autonomic signaling.
In T2D, small fibers in the epidermis is decreased by diabetic insult. It is not still uncovered yet, however, that the reduction of terminal parasympathetic small fibers (Psf) is associated with the alteration of $V_β$ in T2D. Herein, we explored the association between islet Psf density and $V_β$.

Methods : We recruited non-obese spontaneous T2D Goto-Kakizaki (GK) rats and control Wistar rats (W) at 5 weeks of age. GK was divided into DPP4 inhibitor (DPi)-treated group (GTe) (10mg/kg teneligliptine), SGLT2 inhibitor (SGi)-treated group (GCa) (10mg/kg canagliflozin) and both treated group (GTeCa). During experimental period, 2g/kg oral glucose tolerance test (OGTT) and glucose-stimulated insulin secretion test (GSIS) was measured. At end, pancreata were underwent for the pathological evaluation.

Results : Glucose tolerance in GK was attenuated ($p<0.01$ vs W). Although DPi and SGi in each significantly improved OGTT compared to GK, the effect was the most robust in GTeCa. Low GSIS in GK ($p<0.01$ vs W) was significantly improved in GTe and GCaTe ($p<0.05$ vs GTe, $p<0.01$ vs GCaTe), although it was comparable between GK and GCa. Pathological evaluation disclosed a significant decrease in $V_β$ in GK ($p<0.01$ vs W). $V_β$ was the most well–preserved in GCaTe ($p<0.05$ vs GTe), followed by GTe ($p<0.05$ vs GK), while it was comparable between GK and GCa. The density of Psf labeled by the antibody for vesicular acetylcholine transporter (VachT) were significantly decreased in the islet of GK ($p<0.01$ vs W). It was significantly improved in GCa, GTe and GCaTe compared to GK ($p<0.05$ vs GCa and GTe, $p<0.01$ vs GCaTe). Psf density in the islets was significantly correlated with $V_β$($r=0.53$, $p<0.01$).

Conclusions : Our results shed light on the association between Psf density in the islet and $V_β$, and the maintenance of the fibers may be beneficial for the prevention from $V_β$ loss in T2D.

O13. CUTANEOUS CARBONYL STRESS MEDIATED POSTTRANSLATIONAL PROTEIN MODIFICATIONS ARE ASSOCIATED WITH PERIPHERAL NERVE DYSFUNCTION IN PATIENTS WITH RECENT-ONSET TYPE 2 DIABETES

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Objectives : Diabetes leads to distinct carbonyl stress mediated posttranslational protein modifications (e.g. advanced glycation end-products (AGEs)), oxidative stress, and inflammation all of which are thought to contribute to the development of chronic diabetic complications. The aim of the present study was to identify and characterize novel biomarkers for carbonyl stress mediated posttranslational protein modifications, oxidative stress, immune cell population, and endothelial cell damage in skin biopsies of recently diagnosed type 2 diabetes (T2D) patients compared to glucose-tolerant individuals and to assess their associations with peripheral nerve dysfunction and diabetic sensorimotor polyneuropathy (DSPN) in a cross-sectional setting.

Methods : We assessed skin biopsies from the distal lateral calf in 160 participants with recent-onset T2D and 144 glucose-tolerant control individuals (T2D/controls: age [mean±SD]: 54.8±7.9/56.7±9.2 years; BMI: 30.8±4.4/26.9±3.7 kg/m^2; HbA1c: 6.4±1.0/5.3±0.3%; diabetes duration: -/5.8±4.1 months) from the German Diabetes Study (GDS) baseline cohort (diabetes duration ≤1 year). DSPN was diagnosed using modified Toronto Consensus (2011) criteria. Immunohistochemistry was used to assess intraepidermal nerve fibre density (IENFD), Langerhans cell density (LCD), and CD31 as a marker of endothelial cell integrity, while immunofluorescence was used to determine AGEs, argpyrimidine modifications, and poly(ADP-ribose) (PAR) as a marker of DNA damage.

Results : After adjustment for age sex, and BMI, IENFD and LCD were reduced in T2D compared to controls (IENFD: 7.45±3.34 vs 9.78±2.95 fibres/mm; LCD: 378±165 vs 479±222 cells/mm^2; both P<0.0001), whereas the dermal CD31 and epidermal PAR areas did not differ between the groups. The level of AGEs and specifically argpyrimidine modifications were higher in the diabetes group compared to controls (290±13 vs 247±12 mean intensity and 17.5±1.8 vs 11.7±1.2 mean intensity, respectively; both P<0.05). The levels of AGEs were inversely associated with peroneal motor nerve conduction velocity (NCV) (r=-0.346; P=0.0002), median motor NCV (-0.298; P=0.002), and sural sensory NCV (r=-0.311; P=0.001) in the diabetes group.

Conclusions : Patients with well-controlled recent-onset type 2 diabetes show enhanced cutaneous carbonyl stress mediated posttranslational protein modifications in association with nerve conduction slowing, but no evidence of oxidative stress and endothelial cell alterations.

O14. EXENDIN-4 PROMOTES NEURITE OUTGROWTH, NEURONAL SURVIVAL AND MYELINATION VIA ACTIVATING PI3 KINASE SIGNALING PATHWAY *IN VITRO*

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Objectives : The localization of glucagon-like peptide-1 receptor (GLP-1R) at the peripheral nervous system suggests neurotrophic and neuroprotective activities of GLP-1 following axonal injury and in diabetic and other peripheral neuropathies. In our previous studies, a GLP-1 receptor agonist exendin-4 (Ex-4) promoted neurite outgrowth and survival of adult rat dorsal root ganglion (DRG) neurons, as well as myelination process in a co-culture model of DRG neurons and immortalized adult rat Schwann cells IFRS1. However, the underlying mechanisms for these beneficial effects of Ex-4 remain unknown and therefore define the aim of this study.

Methods : 1) GLP-1R protein expression in DRG neurons from 8-week-old Wistar rats and IFRS1 cells was confirmed by using the well-characterized and validated antibody Mab7F38. 2) The effects of Ex-4 (10 nM and 100 nM) on neurite outgrowth and survival of DRG neurons, migration and proliferation of IFRS1 cells, and myelination in the DRG neuron-IFRS1 co-culture system were investigated.

Results : 1) Immunocytochemistry and Western botting with Mab7F38 revealed GLP-1R expression in both DRG neurons and IFRS1 cells. 2-1) Treatment with Ex-4 dose-dependently promoted neurite outgrowth and survival of DRG neurons, and these effects were attenuated by co-treatment with PI3 kinase (PI3K) inhibitor LY294002 (5 µM and 25 µM). 2-2) Treatment with Ex-4 tended to promote migration, but not proliferation, of IFRS1 cells. 2-3) Treatment with Ex-4 dose-dependently accelerated movement of IFRS1 cells toward the neurites growing from DRG neurons at 14 days of co-culture. Western blotting performed at 21 days of co-culture revealed that Ex-4 significantly up-regulated the expression of myelin protein zero and peripheral myelin protein 22. Moreover, Western blotting performed at 2 days of co-culture resulted in Ex-4-induced phosphorylation of a serine/threonine kinase AKT.

Conclusions : Ex-4 accelerates neurite outgrowth and myelination via activating PI3K signaling pathway. Because GLP-1R is expressed in both DRG neurons and IFRS1 cells, Ex-4 may act on both cells to promote myelination. Genetic ablation of GLP-1R in IFRS1 cells will be helpful to elucidate the precise mechanisms of Ex-4-induced myelination. The findings in this study imply the efficacy of Ex-4 in accelerating axonal regeneration and remyelination after injury, as well as preventing and ameliorating peripheral neuropathies.

O15. INTEREST OF NERVE CHECK MASTER FOR SCREENING AND DIAGNOSING PERIPHERAL NEUROPATHY IN PATIENTS WITH TYPE 1 DIABETES

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Objectives : Quantitative sensory testing (QST) is required for early detection of sensory neuropathy. Nerve Check Master (NCM) is a portable device which was designed to assess vibration (VPT), warm (WPT), cold (CPT) and heat pain (HPT) perception thresholds. Previous studies have suggested that NCM offers good diagnostic accuracy for the diagnosis of diabetic peripheral neuropathy (DPN). The aim of the present study was to test the diagnostic validity of NCM in a series of patients with type 1 diabetes.

Methods : We included 76 adults with type 1 diabetes, aged 35 (23-50) years (median, IQR), diabetes duration 13.5 (9-23.8) years, HbA1c 8.0±1.5%, who underwent QST assessment with NCM. DPN was defined according to the Michigan Neuropathy Screening Instrument (MNSI). NCM measurements were considered in favor of DPN if 2 of the 4 tests were abnormal.

Results : The prevalence of DPN was 26% and 62% according to MNSI and NCM, respectively. NCM detected DPN in 80% of the MNSI+ patients and in 55% of the MNSI- ones (p=0.05). Compared to MNSI, the NCM offered sensitivity 80%, specificity 45%, positive and negative predictive values 34% and 86%, respectively. The rates of abnormal tests were the highest for VPT and HPT (67% and 58%). VPT and WPT were more often abnormal among MNSI+ patients than among MNSI- ones (p=0.01 and 0.03, respectively) and offered sensitivity 90% and 70%, specificity 41% and 59%, positive predictive value 35% and 38%, and negative predictive value 92% and 85%.

Conclusions : These data suggest that in patients with type 1 diabetes QST with NCM may be used as a screening test to assess DPN and evaluate small and large fiber impairment. NCM shows a good sensitivity and negative predictive value compared to MNSI but may detect more patients with DPN.

O16. HEART RATE VARIABILITY IS NOT RELATED TO CARDIOVASCULAR EVENTS, IRRESPECTIVE OF DYSGLYCAEMIA. DOWNFALL OF RISK MARKERS? THE WHITEHALL II STUDY

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Objectives : Higher heart rate (HR) and lower heart rate variability (HRV) (a marker of autonomic dysfunction) have been associated with the development of cardiovascular disease (CVD) and all-cause mortality in non-diabetic and dysglycaemic individuals. Associations between temporal changes in theses indices and future CVD and death have not been assessed. We investigated associations between 5-year changes resting HR and HRV and the risk of future events in people with and without dysglycaemia.

Methods : 4,611 participants from the Whitehall II cohort study, free from CVD at baseline and with measurements of HR and/or HRV at baseline and 5 years before were included. Association between 5-year change in resting supine 2-minute HR and HRV and incidence of fatal- and non-fatal CVD, all-cause mortality and the composite of the two is assesses in a Poisson regression model with risk-time as offset. Analyses were adjusted for several confounders in steps. A modifying effect of baseline glycaemic state on the associations was tested. Glycaemic state was defined by HbA1c as normoglycaemia (< 39 mmol/mol), prediabetes (39-47 mmol/mol), diabetes (≥ 48 mmol/mol or diagnosed outside study).

Results : At baseline, mean (SD) age was 60 (5.9) years, 29% had prediabetes, 8% had diabetes, and 70% were men. During a median (IQR) follow-up time of 11.9 (11.4-12.3) years, 298 participants (6.5%) experienced a CVD event and 279 (6.1%) died from non-CVD related causes. We found no association between 5-year changes in HR and HRV and future risk of cardiovascular disease, all-cause mortality or the composite of the two (Figure 1). There was no modifying effect of glycaemic state on any of the associations. Baseline values of HR and HRV were not associated with CVD or mortality events, expect for a 10 beats per minute higher level at baseline of HR was associated with a 11.4% higher rate of all-cause mortality (95%CI: 1.0; 22.9%, P = 0.032).

Conclusions : In this large population-based cohort we found no significant associations between changes in HR and HRV and future CVD events or mortality in people with or without dysglycaemia. The same was generally true for baseline measures of HR and HRV. Our findings suggest that, presently, resting HR and HRV and changes in these measures may not constitute significant risk markers for future CVD and mortality. Autonomic challenge tests may be needed show autonomic dysfunction as a risk marker for CVD.

O16. HEART RATE VARIABILITY IS NOT RELATED TO CARDIOVASCULAR EVENTS, IRRESPECTIVE OF DYSGLYCAEMIA. DOWNFALL OF RISK MARKERS? THE WHITEHALL II STUDY
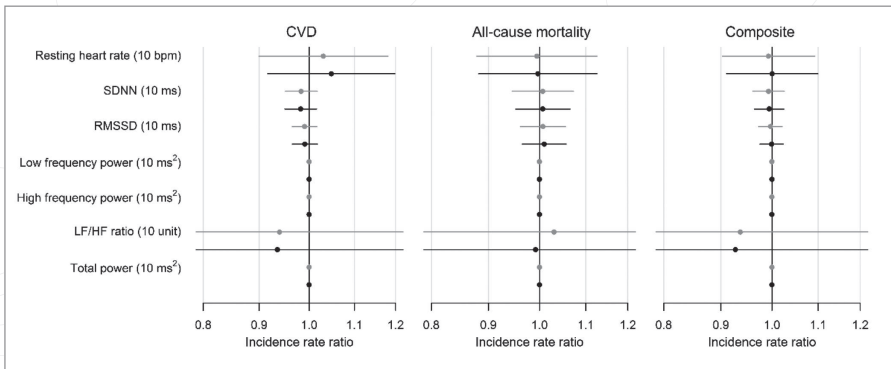

Figure 1.
Association of 5-year change in autonomic function with incidence of a fatal- or non-fatal cardiovascular disease (CVD), all-cause mortality or the composite of the two. Analyses adjusted for age, sex, ethnicity, baseline HR/HRV (model 1: grey lines). HRV indices were further adjusted for the simultaneously measured heart rate. Additional adjustments for glycaemic state, BMI, physical activity, smoking, systolic blood pressure, total cholesterol, triglycerides, tricyclic antidepressants, diuretics and β-blockers (model 2: black lines).

O17. RELATIVE HYPOXIA IN SUPINE AND STANDING POSITION IN TYPE 1 DIABETES: IMPAIRED AUTONOMIC CARDIORESPIRATORY CONTROL AROUND THE CLOCK?

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Objectives : Blood oxygen saturation levels are lower in individuals with type 1 diabetes (T1D) compared to healthy controls (CON) in supine position. Our aim was to investigate oxygen levels in peripheral blood (Sp_{O2}), forearm tissue ($Sarm_{O2}$) and the brain ($Sbrain_{O2}$) in standing position, in individuals with T1D compared to healthy controls, as this is the dominant daytime position. To explore potential pathogenic mechanisms, we investigated associations between Sp_{O2} and autonomic function.

Methods : One-hundred-and-seventeen individuals with T1D and normal albumin excretion rate (AER) were compared to 55 healthy controls. Sp_{O2} was measured with pulse oximetry and $Sarm_{O2}$ and $Sbrain_{O2}$ were measured with near-infrared spectroscopy. All subjects were fasting and abstinent from alcohol and tobacco since midnight before the examination. Measurements were obtained in supine position for one minute and subsequently in the upright position for five minutes.

Results : Mean age (SD) was: CON: 42.7 years (12.6); and T1D: 44.0 years (11.3). In T1D, mean duration of diabetes (SD) was 23.9 years (8.9). At baseline and compared to CON, T1D had lower mean log baroreflex sensitivity (SD) (CON: 2.6 (0.6) vs. T1D: 2.3 (0.8), p = 0.02 (after adjusting for age). In supine position in T1D and compared to CON, we observed a lower Sp_{O2} (SD): T1D: 97.0% (1.4) vs. CON: 97.5% (1.4), p = 0.03 after adjusting for age. $Sarm_{O2}$ and $Sbrain_{O2}$ were not significantly different after adjusting for age (p>0.05). After standing upright for five minutes, in T1D compared to CON, the difference in Sp_{O2} increased further: T1D: 97.2 (1.1) vs. CON: 98.0 (0.9) after adjusting for age (p<0.001); and $Sarm_{O2}$ was significantly lower in T1D: T1D: 64.3 (2.2) vs. CON: 64.9 (2.4) after adjusting for age (p=0.02). $Sbrain_{O2}$ was not significantly different. In all participants combined, log baroreflex sensitivity correlated positively to Sp_{O2} (β-coefficient = 12% / unit (%) Sp_{O2}, p = 0.02 after adjusting for age). In T1D alone, Sp_{O2} correlated negatively to age (p<0.001) and diabetes duration (p<0.01), but not to glycosylated hemoglobin (HbA_{1C}) (p = 0.48). In a combined model including age, diabetes duration and HbA_{1C}, only the correlation to age remained significant (age: p = 0.03; diabetes duration: p = 0.105; HbA_{1C}: p = 0.20).

Conclusions : Blood oxygen saturation is lower in individuals with T1D and normal AER than in healthy controls, in supine and standing position. Low baroreflex sensitivity in T1D might be explained by low saturation, suggesting impaired autonomic cardiorespiratory control. In T1D, age seems the most important factor for low saturation. Our findings suggest impaired autonomic cardiorespiratory control due to- or related to subclinical hypoxia in T1D around the clock.

O18. ASSESSMENT OF THE SKIN MICROVASCULAR BLOOD FLOW IN DIABETIC PATIENTS WITH CARDIAOVASCULAR AUTONOMIC NEUROPATHY

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Objectives : Diabetic autonomic neuropathy is the reason for early morbidity and mortality on diabetic patients. The pathology not only cardiac innervation but microvascular are presented. We estimated the parameters of skin microvascular blood flow in accordance with cardiovascular autonomic neuropathy staging in diabetic patients.

Methods : We included 76 patients with type 2 diabetes in the study (24 patients with resent-onset diabetes, 26 with diabetic sensorimotor neuropathy (SMN) and 26 with SMN and previous history of diabetic foot amputation). The SMN was diagnosed on the basis of patients complaints, anamnesis and data of clinical neurological examinations using the scale of Neuropathic Disability Score. Cardiovascular autonomic neuropathy (CAN) was detected using several cardiovascular autonomic reflex tests (CART) as a gold standard of diagnosis: the tilt-table test, a deep- breathing and Valsalva Maneuver, handgrip test, cold-stress vasoconstriction. Spontaneous arterial baroreflex was also assessed. According to the Toronto Diabetic Neuropathy Expert Group Recommendation all patients was separated on three groups: CAN 0 (all CARTs were normal), CAN 1 (possible/early CAN - one abnormal CART was presented), CAN 2 (definite/confirmed CAN –at least two abnormal CARTs were found), CAN 3 (severe/advanced CAN – in the cases of orthostatic hypotension in addition to CARTs abnormalities). Microvascular blood flow of skin at the nail roller of fingers skin was valuated at rest as well as in functional tests: with cold impact and occlusion (cuff), by method of High-frequency Ultrasonic Dopplerography using the "Minimax Doppler K" device (LLC JV "Minimax", St. Petersburg, Russia).

Results : CAN 1 was found in 8% patients with recent-onset diabetes, 42 and 21% patients with SMN and diabetic foot amputations respectively. CAN 2 was diagnosed in 27% patients with SMN and 58% patients history of diabetic foot amputations. CAN 3 in 8% and 19% cases respectively. The parameters of microvascular blood flow at rest were significantly decreased in patients with confirmed/severe CAN in comparison with early staging of CAN and patients without CAN (Vam=2.5±0.66 sm/min vs. 4.4±0.54 sm/min and 5.1±1.01 sm/min respectively; $p<0.05$). The abnormal result of cold test was detected in 94% patients with confirmed/severe CAN and 26% patients with CAN 1. The predictors of confirmed/severe CAN turned out were diabetic foot amputations in anamnesis (OR =3.2, 95% CI 0.99-7.89; $p<0.05$), severe of SMN (OR=1.2, 95% CI 1.06-1.59; $p<0.05$), parameters of microvascular blood flow (OR=-1.62, 95%CI 1.15-2.89; $p<0.05$) and abnormal cold-stress vasoconstriction (OR=3.6, 95% CI 1.15-9.26; $p<0.05$).

Conclusions : Microvascular blood flow of skin decreased progressively in patients with different staging of CAN. High-frequency Ultrasonic Dopplerography allowed separating of CAN stages. This study is necessary to continue for revealing of all method possibilities.

O19. THE RELATIONSHIP BETWEEN CARDIOVASCULAR AUTONOMIC NEUROPATHY AND CEREBRAL BLOOD FLOW IN PATIENTS WITH TYPE 2 DIABETES MELLITUS

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Introduction : Cardiovascular autonomic neuropathy (CAN) is a significant risk factor for cardiovascular morbidity, mortality and cerebrovascular disease in patients with diabetes mellitus (DM). However, an association between CAN stages and cerebral blood flow in patients with DM was not insufficiently studied.

Objectives : The aim of this study was to investigate the relationship of CAN stages and cerebral blood flow in diabetes mellitus type 2.

Methods : We examined 20 patients with type 2 DM, 6 men and 14 women with clinical symptoms of cerebrovascular disease (aged 57,8±1,99 years, duration of diabetes – 5,3±1,02 years, HbA1c – 7,8±0,28 %) (data are presented everywhere as mean+SEM). All patients were performed cardiovascular autonomic reflex (CART) tests by Ewing, bilateral extracranial duplex sonography and transcranial Doppler sonography. The diagnosis of CAN was confirmed in patients with 2 positive tests. The data analysis was performed by SPSS statistical package version 23.0 for Windows.

Results : CAN with 2 abnormal tests was diagnosed in 45% patients, 3 abnormal tests were recorded in 35 % patients. We found positive correlation between the presence of 2 abnormal CART tests with the pulsatility index (PI) of the right middle cerebral artery (MCA), (OR=0,12, p<0,05), the resistivity index (RI) of the right MCA, (OR=0,064, p<0,05) and negative correlation with the end-diastolic flow velocity (Ved) of right common carotid artery (CCA), (OR= –4,67, p<0,05). The presence of 3abnormal CART tests had positive relationship with Ved of right CCA (OR=4,68, p<0,05), Ved of left CCA (OR=6,84, p<0,05) and negative with PI of right MCA (OR= –0,12, p<0,05), PI of basilar artery (BA) (OR= –0,18, p<0,05) and RI right MCA (OR= –0,06, p<0,05).

Conclusions : We found some relationship between different CAN stages and parameters of cerebral blood flow. These data can suggest the possible role of CAN in the disturbances of cerebral blood flow in patients with type 2 DM.

O20. SYSTEMATIC REVIEW AND META-ANALYSIS ON THE PREVALENCE OF CARDIAC AUTONOMIC NEUROPATHY IN PRE-DIABETES AND METABOLIC SYNDROME

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Objectives : A number of studies have highlighted an increased prevalence of cardiac autonomic neuropathy (CAN) in patients with pre-diabetes (pre-DM) and metabolic syndrome (MetS). Considering there is an exponential rise of pre-DM and MetS worldwide, we aimed to determine the prevalence of CAN through a systematic review and meta-analysis.

Methods : A literature search was performed in multiple electronic databases. Studies were included if they displayed prevalence data for CAN in pre-DM and the MetS cohorts, were in an adult population and full-text publications. All included studies were evaluated for risk of bias. The systematic review was undertaken to the PRISMA guidelines. Random effects models were used to provide a pooled prevalence estimate.

Results : 4112 articles were retrieved; 194 full text articles were screened, 12 of which fulfilled the inclusion criteria (n=3066 pre-DM/MetS participants) (Figure 1). Six studies defined CAN using 1 abnormal autonomic function test (AFT), 6 defined CAN using > 1 abnormal AFT, 9 studies included a diabetes group and 6 studies included a NGT group. The overall CAN prevalence in the pre-DM/MetS group ranged from 0% to 57.3% with most studies showing a CAN prevalence between 10-30% (6 studies). The overall pooled prevalence of CAN in pre-DM/MetS was 27% (95%CI: 18-36), however there was very high heterogeneity amongst the pooled studies (I^2=97%) (Figure 2). The prevalence for studies defining CAN as 1 abnormal AFT (6 studies, n=2196) was 31% (95%CI: 21-42), and for studies using >1 abnormal AFT (6 studies, n=870) was 19% (95%CI: 10-27). CAN pooled prevalence was the lowest in the NGT group (n=1880) 10%, (95%CI: 3-16) (1 AFT: 14%, 95%CI=12-16, >1 AFT: 8%, 95% CI=2-13), and highest in the diabetes group (n=1669) (36%, 95% CI: 20-52) (1 AFT: 41%, 95%CI: 11-72, >1 AFT: 32%, 95%CI=21-44). All studies had a low risk of bias (1.75±0.97, out of 10).

Conclusions : There is a high prevalence of CAN in pre-DM and MetS in particular when defining CAN with a single abnormal AFT. A rising prevalence of pre-DM and MetS will therefore have a major impact on CAN prevalence globally. The early detection of CAN is vital due to its reversibility with improved prognosis where lifestyle and diet may result in remission of both CAN and pre-DM/MetS.

O20. SYSTEMATIC REVIEW AND META-ANALYSIS ON THE PREVALENCE OF CARDIAC AUTONOMIC NEUROPATHY IN PRE-DIABETES AND METABOLIC SYNDROME
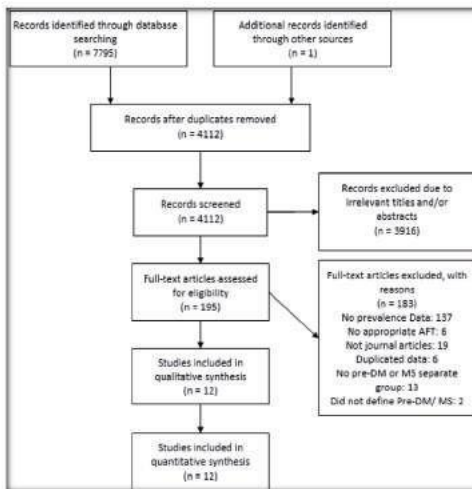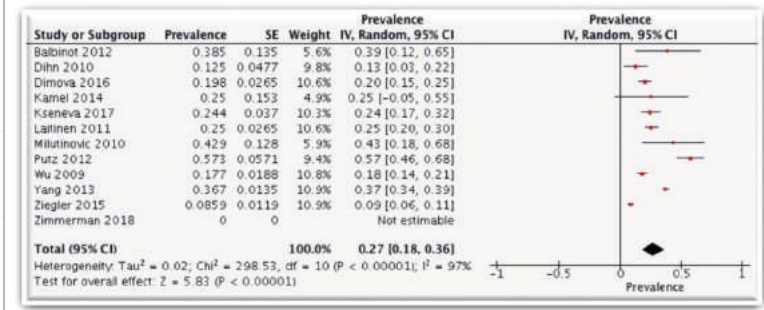

Figure 1 PRISMA flowchart

Figure 2. Forest plot of CAN Prevalence (expressed as proportion) in Pre-diabetes and MetS

Study or Subgroup	Prevalence	SE	Weight	Prevalence IV, Random, 95% CI
Balbinot 2012	0.385	0.135	5.6%	0.39 [0.12, 0.65]
Dihn 2010	0.125	0.0477	9.8%	0.13 [0.03, 0.22]
Dimova 2016	0.198	0.0265	10.6%	0.20 [0.15, 0.25]
Kamel 2014	0.25	0.153	4.9%	0.25 [-0.05, 0.55]
Kseneva 2017	0.244	0.037	10.3%	0.24 [0.17, 0.32]
Laitinen 2011	0.25	0.0265	10.6%	0.25 [0.20, 0.30]
Milutinovic 2010	0.429	0.128	5.9%	0.43 [0.18, 0.68]
Putz 2012	0.573	0.0571	9.4%	0.57 [0.46, 0.68]
Wu 2009	0.177	0.0188	10.8%	0.18 [0.14, 0.21]
Yang 2013	0.367	0.0135	10.9%	0.37 [0.34, 0.39]
Ziegler 2015	0.0859	0.0119	10.9%	0.09 [0.06, 0.11]
Zimmerman 2018	0	0		Not estimable
Total (95% CI)			**100.0%**	**0.27 [0.18, 0.36]**

Heterogeneity: $Tau^2 = 0.02$; $Chi^2 = 298.53$, $df = 10$ ($P < 0.00001$); $I^2 = 97\%$
Test for overall effect: $Z = 5.83$ ($P < 0.00001$)

O21. TOPICAL OXYBUTYNIN, A MUSCARINIC RECEPTOR ANTAGONIST, IMPROVES EPIDERMAL NERVE FIBER DENSITY AND NERVE FUNCTION IN SUBJECTS WITH TYPE 2 DIABETES

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[1] Strelitz Diabetes Center for Endocrine and Metabolic Disorders, Department of Medicine; Eastern Virginia Medical School. Norfolk, Virginia USA, [2] Department of Pathology, University of California San Diego, La Jolla, California USA, [3] Department of Pharmacology & Therapeutics, University of Manitoba, Winnipeg, Manitoba, Canada.

Objectives : Mitochondrial dysfunction has been implicated in the pathogenesis of diabetic peripheral neuropathy (DPN). We have recently shown that manipulation of mitochondrial function by antagonism of the muscarinic M1 receptor (M_1R) promotes neurite outgrowth from adult sensory neurons in vitro and protects against multiple indices of neuropathy in rodent models of type 1 and type 2 diabetes. These preclinical studies were extended to evaluate the topical administration of oxybutynin (OXY), a muscarinic receptor antagonist currently in clinical use, on subjects with type 2 diabetes (T2DM), in order to assess its efficacy against structural and functional measures of neuropathy.

Methods : In vitro studies were performed in sensory neuron cultures derived from adult control and streptozotocin-diabetic rats exposed to 1-100nM OXY prior to measuring neurite outgrowth and mitochondrial respiration (Seahorse method). Rodent studies were performed in adult male controls and db/db mice treated with vehicle or 2% OXY daily to the paw after onset of neuropathy. Paw thermal sensation was measured after 8 weeks of treatment followed by skin biopsy for intraepidermal nerve fiber density (IENFD). Subsequently, a randomized, placebo-controlled, double-blinded 20-week study of topical 4% OXY was performed in 46 human subjects with established T2DM and neuropathy. Multiple indices of neuropathy including IENFD, neuropathy scores and quality of life (Norfolk QOL-DN) were assessed at baseline and after 20 weeks of treatment.

Results : OXY significantly enhanced neurite outgrowth and mitochondrial spare respiratory capacity of sensory neurons in vitro. Topical OXY significantly reversed paw thermal hypoalgesia, and attenuated IENFD loss in diabetic mice. In human subjects, demographic characteristics were similar between the treatment groups at baseline. IENFD increased significantly ($p<0.001$) in the OXY treated subjects, along with significant improvement in neuropathy scores, pain questionnaires and Norfolk QOL DN survey (Tables 1 & 2). No improvements were seen in the placebo group.

Conclusions : Topical oxybutynin reversed structural and functional indices of established neuropathy in cultured adult sensory neurons, type 2 diabetic mice and subjects with T2DM. This proof of concept study establishes the viability of topical delivery of muscarinic receptor antagonists as a therapeutic approach to reversing established neuropathy in patients with T2DM.

O21. TOPICAL OXYBUTYNIN, A MUSCARINIC RECEPTOR ANTAGONIST, IMPROVES EPIDERMAL NERVE FIBER DENSITY AND NERVE FUNCTION IN SUBJECTS WITH TYPE 2 DIABETES

	OXY (n=23)			Placebo (n=23)		
	Baseline	**20 weeks**	**P-Value**	**Baseline**	**20 weeks**	**P-Value**
Nerve Pathology						
IENFD (Left leg skin biopsy)	1.90 ± 0.43	3.51 ± 0.70	0.001	3.18 ± 0.43	3.89 ± 0.44	0.261
Norfolk QOL-DN						
Total Score	29.39 ± 4.95	17.29 ± 3.10	0.002	21.26 ± 3.64	16.41 ± 3.13	0.113
Physical/Large Fiber function	18.39 ± 3.53	10.18 ± 2.12	0.001	13.22 ± 2.74	10.32 ± 2.30	0.155
Symptoms	5.00 ± 0.70	3.47 ± 0.61	0.078	4.22 ± 0.57	3.59 ± 0.52	0.109
Small Fiber function	2.00 ± 0.61	1.12 ± 0.38	0.264	0.55 ± 0.22	0.27 ± 0.14	0.101
Autonomic function	1.34 ± 0.34	1.00 ± 0.30	0.553	1.22 ± 0.33	0.96 ± 0.28	0.388

Data are group mean ± SEM. Within-subject analysis by Repeated Measures Multivariate Analysis of Variance (MANOVA). IENF: Intra-epidermal nerve fiber density; Norfolk QOL-DN: Quality of Life-Diabetic Neuropathy

Table 1.
Improvement in measures of nerve fiber structure and Quality of Life in T2DM subjects after 20 weeks of treatment with oxybutynin or placebo

	OXY (n=23)			Placebo (n=23)		
	Baseline	**20 weeks**	**P-Value**	**Baseline**	**20 weeks**	**P-Value**
Neuropathy Scores						
NIS Sensory Score	6.44 ± 0.79	4.39 ± 0.62	0.006	4.13 ± 0.65	3.57 ± 0.46	0.268
NIS-LL Sensory Score	11.13 ± 1.08	9.20 ± 0.85	0.098	7.74 ± 0.82	7.78 ± 0.79	0.957
NIS Total Score	8.01 ± 0.87	6.09 ± 0.76	0.049	5.94 ± 0.70	5.44 ± 0.59	0.425
MNSI-A	6.69 ± 0.62	4.58 ± 0.65	0.015	5.74 ± 0.50	5.00 ± 0.50	0.081
UENS Total Score	10.98 ±1.13	8.85 ± 0.78	0.165	8.13 ±0.93	8.34 ± 0.99	0.803
NTSS-6 Total Score	7.61 ± 1.33	5.54 ± 1.26	0.021	5.30 ± 1.06	4.01 ± 0.91	0.371
NRS - Pain feet (0-10)	2.68 ± 0.77	0.56 ± 0.39	0.003	2.55 ± 0.75	1.25 ± 0.51	0.191

Data are group mean ± SEM. Within-subject analysis by Repeated Measures Multivariate Analysis of Variance (MANOVA). MNSI-A: Michigan Neuropathy Screening Instrument Part A; NIS: Neuropathy Impairment Score; NIS-LL: Neuropathy Impairment Score - Lower Legs; NRS: Numerical Rating Scale; NTSS-6: Neuropathy Total Symptom Score; UENS: Utah Early Neuropathy Screening Instrument.

Table 2.
Improvement in measures of nerve fiber function in T2DM subjects after 20 weeks of treatment with oxybutynin or placebo

O22. EFFICACY AND SAFETY OF A PILL CONTAINING SOD, ALA, VIT. B12 AND CARNITINE AFTER 12 MONTHS OF ADMINISTRATION IN PATIENTS WITH DIABETIC NEUROPATHY

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Objectives : To investigate the efficacy and safety of a new combination of four elements (Superoxide Dismutase, Alpha Lipoic Acid, Acetyl L-Carnitine, Vit. B12) contained in one pill in Diabetic Neuropathy (DN).

Methods : In current prospective, double-blind, placebo controlled, age matched study, 85 patients with Diabetes Mellitus Type 2 (DMT2), 41 women, with mean age 64±11 years, mean duration of DM 15 years randomized in two groups: group A: n=43 received the pill with the combination of the four elements (SOD, ALA, B12, ACL) and group B: n=42 received placebo. Treatment of diabetes did not change during the 12 months of follow up.The following methods for detecting Diabetic Peripheral and Autonomic Neuropathy (DPN, DAN) used: Michigan Neuropathy Screening Instrument Questionnaire and Examination (MNSIQ and MNSIE), measurement of vibration perception threshold with biothesiometer (BIO) and Cardiovascular Autonomic Reflex Tests (CARTS) indices: mean circular resultant (MCR), Valsalva maneuver (Vals), 30:15 ratio and blood pressure response to standing (OH). Recently, a novel point-of-care sural nerve conduction device has been developed and sural nerve functions were measured using DPN Check [sural nerve conduction velocity (SNCV) and amplitude (SNAP)]. We used a pain (PS) 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 (7.2±1.2 vs 6.8±1.2% p=0.207, Vit.B12 263±100 vs 299±155 pmol/L p=0.268). The following indices decreased significantly in group A (baseline vs final): BIO 37±13 vs 16±10 (p<0.001), MNSIQ 6.6±1.6 vs 6.0±1.7 (p=0.003), QL 39.8±10.8 vs 36.2±9.8 (p<0.001), PAIN 20.6±7.9 vs 17.4±7.0 (p<0.001) and SNCV 32.5±23.8 vs 39.4±22.8 m/s (p=0.027), SNAP 6.2±5.1 vs 7.5±6.5 uV (p=0.031) improved significantly. Indices of CARTS and MNSIE did not differ significantly in group A (baseline vs final). Vit. B12 increased in group A 257.4±104.9 vs 326.0±108.8 pmol/L (p<0.001) and was unchanged in group B. We did not observe a significant change in all indices in group B (placebo group) except MCR which decreased (baseline vs final), 20.7±14.7 vs 12.5±9.1 (p=0.012). No adverse events reported in both groups.

Conclusions : In current study after 12 months from administration of the combination with the four elements in one pill in patients with DMT2 (group A), we observed an improvement in all indices of peripheral neuropathy including neurophysiological parameters, Pain and Quality of Life except CARTS and MNSIE. In group B parasympathetic function deteriorated and all other indices did not change. The pill could be helpful in the management in patients with DPN or could be a good starting point for a valid adjuvant for the treatment of pain symptoms.

O23. A CREAM FORMULATION OF TRPV1 AGONIST RESINIFERATOXIN FOR THE TREATMENT OF PAINFUL DIABETIC PERIPHERAL NEUROPATHY

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Painful Diabetic Peripheral Neuropathy (PDPN) is one of the major complications of diabetes. Currently, the centrally acting drugs such as antidepressants, anticonvulsants, opioids, and topical analgesics are used for treating PDPN. However, the use dependence and addiction potential of opioids and inefficacy of non-opioids are serious limitations. Recent research suggests that targeting Transient Receptor Potential Vanilloid 1 (TRPV1) receptor, a non-selective cation channel protein expressed in the peripheral sensory nerve terminals is an emerging option to treat pain. Blocking TRPV1 using specific antagonists induces hyperthermia in clinical trials leading to their abandonment as a therapeutic strategy. TRPV1 agonists are useful to treat pain by virtue of their ability to cause calcium influx, which subsequently leads to nerve terminal desensitization/ablation. Recently, an 8% capsaicin containing patch (Qutenza) has been approved to treat painful DPN in Europe. Since activation of TRPV1 depolarizes the nerve terminal and generates and action potential leading to pain, lidocaine, a local anesthetic is applied to numb the area before application of capsaicin patch. Here, we report the effect of an ultra-potent TRPV1 agonist, resiniferatoxin (RTX), in a topical formulation to alleviate PDPN in animal models of diabetes by inducing nerve terminal depolarization block in the short-term, which prevents pain during application and leading to nerve terminal desensitization/ablation in the long-term resulting in long lasting pain relief. RTX cream application suppressed the thermal hyperalgesia and mechanical allodynia in diabetic animals. Our data provide compelling evidence for developing RTX topical formulation as an effective replacement for the use of 8% capsaicin to treat painful conditions, which is both cumbersome and painful during application.

O24. IMPACT OF NORMALISED HBA1C AND WEIGHT LOSS ON NEUROPATHY AND OTHER MICROVASCULAR COMPLICATIONS IN TYPE 2 DIABETES MELLITUS

Tavakoli M, Ishibashi F

Objectives : To investigate the impact of normalizing HbA1c by extensive HbA1c control (EHC) on neuropathy outcome measures (NOMs), nephropathy and retinopathy in type 2 diabetes.

Methods : Detailed clinical and neurological examinations were performed in 2 cohorts of 40 uncontrolled type 2 diabetic patients (HbA1c: 9.6%) at baseline and after glycemic control (GC) with or without EHC by diet restriction and hypoglycemic agents over 4 years along with 48 controls with normal glucose tolerance (NGT) and 38 subjects with impaired glucose tolerance (IGT) only at baseline. EHC patients, controls and IGT subjects underwent oral glucose tolerance test. Glycemic variability (GV) was evaluated by standard deviation and coefficient of variation of monthly measured HbA1c levels and casual plasma glucose.

Results : In EHC cohort, HbA1c levels over four years and last 2 years improved to 6.1% and 5.8% with 7.3kg body weight reduction, and 50% and 28.9% of patients returned to IGT and NGT at endpoint. Baseline neurophysiological and corneal nerve fiber (CNF) measures were impaired in patients. Normalized HbA1c with EHC improved neurophysiological and CNF measures similar to IGT, while GC without EHC (mean HbA1c levels: 7.0%) improved only vibration perception. The mean normalized HbA1c levels by EHC determined NOM improvements. The high GV and baseline HbA1c levels compromised NOMs. Albumin excretion rate significantly decreased, while retinopathy severity and frequency insignificantly worsened on EHC.

Conclusions : Besides the strict Glycemic Control (GC) and smaller Glycemic Variability (GV), the metabolic syndrome components should be controlled for ameliorating diabetic neuropathy and retinopathy even under normal HbA1c level. Normalizing HbA1c in type 2 diabetes with short duration improves microvascular complications including neuropathy and nephropathy more effectively than standard GC but not retinopathy.

O25. EFFECT OF LATE INTERVENTION WITH MENHADEN OIL ON PERIPHERAL NEUROPATHY IN DIET-INUDCED OBESE AND TYPE 2 DIABETIC SPRAGUE-DAWLEY RATS

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Objectives : Determine the effect of dietary enrichment with menhaden oil (enriched in omega-3 polyunsaturated fatty acids; eicosapentaenoic and docosahexaenoic acids) on peripheral neuropathy in high fat fed type 2 diabetic Sprague-Dawley rats.

Methods : Rats were fed a high fat diet (45% kcal primarily lard) for 8 weeks and then treated with or without a low dose of streptozotocin in order to induce hyperglycemia. After an additional 16 weeks obese and diabetic rats were continued on the high fat diet or treated with menhaden oil (45% kcal). In addition, a control group fed a standard diet (4% kcal fat) or menhaden oil enriched diet was included. The treatment period was 20 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 : Initial studies demonstrated that vascular and neural complications of obesity and type 2 diabetes are progressive. Late intervention with menhaden oil reversed both vascular and neural damage induced by obesity and type 2 diabetes.

Conclusions : These studies further support omega-3 polyunsaturated fatty acids derived from fish oil as an effective treatment for peripheral neuropathy.

Determination	Control	Control + MO	Obese	Obese + MO	Diabetic	Diabetic + MO
	(11)	(6)	(17)	(17)	(17)	(17)
MNCV (m/sec)	58.0 ± 1.2	53.3 ± 2.1	50.5 ± 2.1[a]	53.6 ± 1.6	39.7 ± 1.1[a,b]	52.5 ± 1.7[c]
SNCV (m/sec)	37.0 ± 0.6	37.3 ± 0.8	31.0 ± 0.6[a]	36.0 ± 0.9[a]	29.8 ± 0.5[a]	34.9 ± 0.5[c]
IENF (profiles/mm)	19.5 ± 0.6	19.9 ± 1.4	14.9 ± 0.5[a]	19.1 ± 0.6[b]	13.8 ± 0.3[a]	20.1 ± 0.7[c]
Corneal nerve fiber length (mm/mm^2)	8.4 ± 0.3	8.6 ± 0.6	4.5 ± 0.2[a]	7.6 ± 0.3[b]	3.4 ± 0.2[a]	7.3 ± 0.4[c]
Cornea sensitivity (cm)	5.97 ± 0.02	5.65 ± 0.13	4.50 ± 0.09[a]	5.24 ± 0.09[a,b]	4.15 ± 0.11[a,b]	5.18 ± 0.09[a,c]
Cornea sensitivity (AUC)	57.4 ± 8.5	52.3 ± 3.8	118.1 ± 8.6[a]	87.8 ± 5.7[b]	117.1 ± 6.2[a]	87.2 ± 8.5[c]
Thermal nociception (sec)	12.3 ± 0.3	11.9 ± 0.4	20.1 ± 0.9[a]	13.2 ± 0.4[b]	20.3 ± 0.7[a]	13.1 ± 0.4[c]

Data are presented as mean ± SEM. **a** P < 0.05 compared to Control; **b** P < 0.05 compared to Obese; **c** P < 0.05 compared to Diabetic.

O26. PERIPHERAL POLYNEUROPATHY PREVALENCE IN GRADE II AND III OBESE SUBJECTS WITHOUT DIABETES BEFORE AND AFTER BARIATRIC SURGERY

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Background : Peripheral Polyneuropathy (PPN) is a diabetes complication also described in pre-diabetes and in metabolic syndrome subjects. In obese patients and after bariatric surgery (BS) it is not clear which factors are associated with PPN prevalence.

Objectives : Evaluation of PPN prevalence in grade II and III obese subjects without diabetes, before and after 6 to 18 months of BS.

Methods : In a cross-sectional study we evaluated with the Michigan Neuropathy Screening Instrument (MNSI), subjects without Diabetes Mellitus: 688 with obesity grade II and III and 586 after BS, Roux en-Y gastric bypass (RYGB) or sleeve gastrectomy (SG). The cut-point for the MNSI was ≥2.5 plus a symptom. Non metabolic causes for PPN were excluded. Fisher's exact test was used to compare the prevalence between two groups (obese and after-BS) and between two types of BS (RYGB and SG). For evaluating the association between the continuous variables and the presence of PPN Mann-Whitney test was used. Variables with $p \leq 0.2$ on univariate analysis were tested on Poisson multivariate regression.

Results : Between obese participants PPN prevalence was 20.6%, while post-BS it was 11.3% ($p<0.001$). Post-BS, there was no significative difference on PPN prevalence between the two types of surgery, 12.7% on RYGB and 10.1% on SG ($p=0.361$). In obese subjects PNP was associated with age ($p<0.001$), stature ($p=0.0.31$) and waist circumference ($p=0.022$). Post-BS, PPN was associated with weight ($p=0.028$), stature ($p<0.001$), pre-surgery weight ($p=0.002$), fasting glucose levels ($p=0.010$) and triglycerides levels ($p=0.049$). On two Poisson regression models, age ($p=0.011$, IC95% 1.050 (1.005-1.041)) and stature ($p=0.009$, IC95% 1.026 (1.006-1.047)) were independently associated with PPN in obese subjects. Stature ($p=0.007$, IC95% 1.050 (1.014-1.088)) and serum triglycerides levels ($p=0.038$, IC95% 1.007 (1.000-1.014)) were independently associated with PPN post-BS.

Conclusions : PPN prevalence was higher in grade II and III obese subjects without diabetes than in post-BS subjects. For the obese patients, each year of higher age increased the chance of PPN in 2.3% and, each cm of a higher stature increased the chance of PPN in 2.6%. Post-BS, for each cm of a higher stature the chance of PPN increased 5% and for each 1mg/dL of higher serum triglycerides levels the chance of PPN increased by 3.8%.

O27. CENTRAL BRAIN MECHANISMS THAT PREDICT TREATMENT RESPONSE IN PAINFUL DIABETIC NEUROPATHY

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Objectives : Painful diabetic polyneuropathy (DPN) poses a major treatment challenge. The management of painful DPN is inefficient as the current approach assumes that all patients respond similarly to a given drug when in fact there is a wide variability in response. The aim of this study was to explore the central mechanisms to explain the variance in treatment response.

Methods : Forty-five consecutive patients who received intravenous lidocaine treatment for painful DPN were assessed. All subjects completed a treatment efficacy questionnaire. Twenty-nine patients (responders n=14 and non-responders n=15) along with 26 healthy controls subsequently underwent multimodal brain magnetic resonance (MR) imaging to acquire T1 weighted anatomical and resting state functional MRI data (3T, Achieva, Phillips Healthcare).

Results : There was no significant difference in age (p=0.53), pain duration (p=0.89), diabetes duration (p=0.19) and clinical parameters of neuropathy (TCNS, p=0.16 and NTSS-6, p=0.61) between responders and non-responders to intravenous lidocaine treatment. Neither was there a difference in the use of concurrent neuropathic pain treatments. Non-responders to intravenous lidocaine had significantly lower mean S1 cortical volumes and mean number of vertices compared to responders and healthy controls (ANOVA p=0.02 and 0.02 respectively). There was no significant difference in S1 cortical volumes or vertices between responders and healthy controls. There was significantly greater resting state functional connectivity in lidocaine responders between the insula cortex [F(4)(13)=10.33; p-FDR=0.01] and the orbital frontal cortex [T(20)=3.88; p-FDR=0.02] and amygdala [T(20)=3.65; p-FDR=0.02] on the right (Figure 1). Similarly, on the left, there was significantly greater functional connectivity between the insula cortex [F(4)(13)=6.46; p-FDR=0.04] and the anterior cingulate gyrus [T(20)=4.04; p-FDR=0.01], orbital frontal cortex [T(20)=3.90; p-FDR=0.01] and nucleus accumbens [T(20)=3.50; p-FDR=0.02].

Conclusions : These results provide, to the best of our knowledge, the first assessment of the central mechanisms of treatment response in painful DPN. Within the CNS key sensorimotor areas showed decreased grey matter density (S1 cortex) and reduced insula functional connectivity that may also contribute to treatment response. These central mechanisms could serve as a possible Central Pain Signature which could be used to predict treatment response. This supports the idea of a mechanism-based, individualised therapy for patients with painful DPN.

O27. CENTRAL BRAIN MECHANISMS THAT PREDICT TREATMENT RESPONSE IN PAINFUL DIABETIC NEUROPATHY
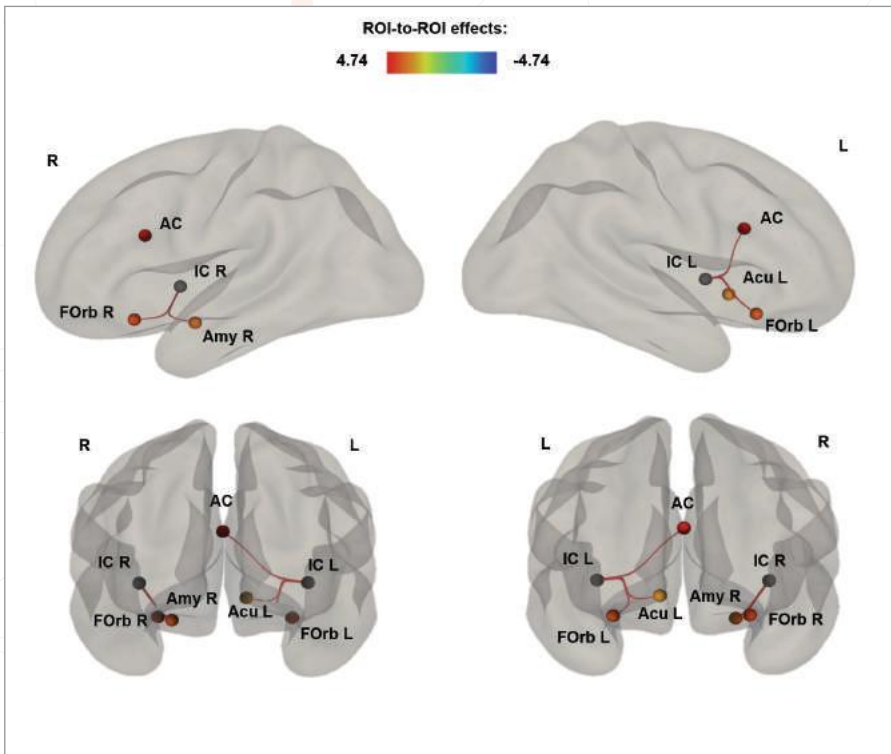

Figure 1.
Anterior, posterior, left, right and superior view of bilateral insular cortices resting-state functional connectivity in responders > non-responders to intravenous lidocaine treatment. Red to blue = positive to negative Z-scores . R, right; L, left; ACU, nucleus accumbens; IC, insula cortex; Amy, amygdala; AC, anterior cingulate gyrus; FOrb, orbital frontal cortex. Check this is z scores.

O28. PANCREATIC EXOCRINE INSUFFICIENCY AND AUTONOMIC NEURONAL DYSFUNCTION IN DIABETES – A PILOT STUDY

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Objectives : The reported prevalence of pancreatic exocrine insufficiency (PEI) in diabetes mellitus (DM) varies between 14-74%. Also, the aetiology is contentious, with autonomic neuropathy being an important hypothesis. We aimed to establish the prevalence of PEI in DM using the faecal elastase-1 (FE-1) assay as screening test and the mixed ^{13}C-triglyceride (^{13}C-MTG) breath test for confirmation. Furthermore, in a sub-group, we aimed to compare cardiac autonomic function in DM patients with vs. without PEI.

Methods : One hundred thirty-three consecutive type 1 or type 2 DM patients without known exocrine pancreatic disorders were recruited from the out-patient clinics of Haukeland University Hospital (Bergen) and Aalborg University Hospital (Denmark).
An FE-1 value <200 µg/g was used as screening cut-off for PEI and patients with FE-1 values below this level were referred for a ^{13}C-MTG breath test. Patients from Bergen with low FE-1, and a matched group with normal FE-1 were further investigated in terms of cardiac autonomic function.

Results : Faecal samples were returned by 102 patients, 13% with low FE-1. Insulin use, type 1 DM, and DM duration were associated with low FE-1. Stool habits were unaffected by low FE-1. Twelve out of 13 patients with low FE-1 performed the breath test, all were normal. Results of cardiac autonomic function tests are listed in Table 1.

Conclusions : The prevalence of PEI (based on FE-1) was lower than in previous studies. Further, there was a discrepancy between FE-1 and the breath test. Patients with low FE-1 showed signs of impaired cardiac autonomic function. Although not conclusive, our data support a hypothesis of diabetic autonomic neuropathy being a risk factor for PEI.

Table 1.

Resting HRV	Cases (n=8)	Controls (n=13)	p-value
Mean HR	59.2 (52.7-63.6)	65.7 (54.7-68.2)	NS
SDNN	31.1 (27.6-34.7)	49.3 (28.2-70.1)	NS
RMSSD	16.9 (13.5-22.6)	25.8 (18.8-44.6)	0.05
Total Power	299 (173-364)	427 (264-1880)	NS
LF Norm	74.7 (61.9-84.8)	66.6 (45.7-84.5)	NS
HF Norm	25.4 (15.2-38.1)	38.8 (16.1-53.7)	NS
LF/HF	3.0 (1.7-5.7)	1.6 (0.9-5.2)	NS
Baroreflex	Cases (n=8)	Controls (n=13)	p-value
SD of HR	2.3 (2.1-4.2)	5.1 (3.6-6.8)	0.02
Maximal variance of HR	5.9 (5.2-11.6)	16.6 (1.8-22.4)	0.01
Mean variance of HR	5.0 (3.7-9.2)	10.4 (9.2-19.3)	0.02
E/I ratio	1.1 (1.1-1.1)	1.2 (1.2-1.4)	0.02

All values as median (1st quartile-3rd quartile) unless otherwise indicated. NS = not significant.

O29. HAPTICS FOR EVALUATION OF TOUCH DYSFUNCTION IN TYPE 1 DIABATES MELLITUS

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Objectives : Touch is a mechanical sense responding to different types of skin deformations. Tactile dysfunctions, mostly in lower limbs, are a frequent symptom in diabetic patients with peripheral neuropathy. The evaluation of tactile dysfunction includes clinical tests like biothesiometry and monofilament tests. 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 dysfunctions of upper limbs, in type 1 diabetic patients (DM1).

Methods : 12 DM1 patients (HbA1c < 9.5%) and 8 healthy control subjects (C) comparable in age and gender were enrolled. Patients underwent neurological assessment with monofilament and vibratory perception (VP) of upper and lower limbs using biothesiometry. Patients were divided in two groups based on VP alterations (VP- and VP+). Tactile sensitivity has been evaluated in all subjects using a mechatronic device that produced highly precise motion and vibration stimuli. In a forced-choice protocol, subjects contacted the movable surface of the device with their bare fingertip and reported the perceived speed. The protocol was replicated with and without masking vibrations. We used a general linear model to fit participants' responses and quantified their precision by means of the Just Noticeable Difference (JND). The higher the JND, the worse the tactile sensitivity. Multivariable linear regressions were used to test for differences in JND in VP- and VP+ with respect to C.

Results : In patients, mean HbA1c was equal to 7.8% +/- 0.76 (mean +/- SD). None of the patients tested positive in the monofilament test. Without masking vibrations, the JND was significantly lower in C than in VP+ group (estimated difference = 0.77 +/- 0.34, p = 0.04). With masking vibrations, the JND was significantly lower in C with respect to VP+ group (difference = 0.77 +/- 0.26, p = 0.009). Difference between C and VP- was not significant with and without masking vibrations.

Conclusions : To the best of our knowledge this is the first study evaluating tactile dysfunction in DM1 with haptic technology. Tactile sensitivity at the fingertip was significantly lower in patients with reduced vibration sensitivity in lower limbs with respect to controls. In future work it will be possible to extend this method for lower limbs and introduce haptics in clinical tests for the evaluation of peripheral diabetic neuropathy.

O30. DYSFUNCTION IN THE SUBTYPES OF PERIPHERAL NERVE FIBRES AND THEIR RELATION TO THE FOOT PLANTAR PEAK PRESSURE REGISTERED BY WALKING SENSORS IN DIABETIC PATIENTS

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Objectives : Diabetes has been associated with the development of abnormally high pressures under the feet and ulceration has been considered to be a problem in this condition. In order to examine further relationship between different subtypes of peripheral nerve fibres alterations and different dynamic measurements of plantar pressure peaks.

Methods : We have studied 21 patients with DM1-2 of both genders with a mean evolution time of 12 years ±5, glycosylated haemoglobin (HbA1c) 8.8 ±7 Body Mass Index 28 ±4. Subject were divided in groups without neuropathy (N), with alterations of 1 sensory fibre for the vibration perception threshold on both feet (PNAB) and with alteration of 2 or more small and large peripheral sensory nerve fibres on both feet (PNABH). The neurological examination was performed with the Quantitative Sensory testing NerveCheck Master (NCM) and Neuropathy Disability Score (NDS).Using the footwear instrument with sensors (F-scan, insole sensor system), walking the same path 4 times, the pressure measurements were obtained in Newton/m2. The registers when walking resulted from the pressure (T) and pressure means plus the Body Mass Index (TBMI) in the 1st, 2nd metatarsal and 1st phalanges of each foot.The Peak Plantar Pressures *(PPP)*, Pressure Time Integral *(PTI)* and the Peak Pressure Gradient *(PPG)* were examined *Statistics by analysis of Anova single factor (AST) and t-student (t-s).*

Results : *AST and t-s to PPP* on the left and right foot,measuring T and TBMI in groups: N, PNAB, and PNABH (NS). *AST analysis to PTI* on the left foot measuring T and TBMI in groups: N, PNAB, PNABH were (NS) but nevertheless right foot measuring T has been (0.05)* not so TBMI (NS). Groups: N, PNAB and PNABH *t-s analysis to PTI* on the left foot measuring T in comparison group N vs. PNAB P-value (0.03)* and TBMI in group N vs. PNABP (NS); Right foot measuring T group N vs. PNAB (NS); PNAB vs. PNABH P-value has been (0.03)*.*AST analysis to PMG* on the left foot measuring T and TBMI in groups: N, PNAB, PNABH (NS), unlike right foot measuring T (0.009)* and TBMI (0.01) in groups: N,PNAB and PNAB. *t-s analysis to PMG* on the Right foot measuring T group N vs. PNAB P-value (0.009)* and N vs. PNABH P-value (0.01)* TBMI in group N vs.PNABH (NS); Right foot measuring T group N vs. PNAB (NS); PNAB vs. PNABH P-value (0.03)*,TMBI group N vs. PNAB P-value (0.004)* and N vs. PNABH P-value (0.02)*.

O30. DYSFUNCTION IN THE SUBTYPES OF PERIPHERAL NERVE FIBRES AND THEIR RELATION TO THE FOOT PLANTAR PEAK PRESSURE REGISTERED BY WALKING SENSORS IN DIABETIC PATIENTS

Conclusions: It seems that with only dysfunction of the VPT it is already possible to distinguish alterations in the PTI,however the incorporation of the dysfunction in other nerve fibres makes more evident the alteration of the plantar pressure but in the parameter of gradients. It is interesting to note in particular,the observation of the increased PPG,increasing in concordance with the highest dysfunction that occurs in the peripheral nerves, highlighting the dominant foot. These data emphasize the importance of being vigilant to the loss of the sensitivity that happens in the pathogenesis of diabetic neuropathic foot injuries and suggest that only the pressure peaks are not direct cause of the ulceration. Furthermore, the pathogenic role of high plantar pressures is crucial in the presence of alterations of peripheral nerve fibres. Need to be considered that it is a small sample size and it should be extended on number of subjects to draw definitive conclusions.

O31. PERIPHERAL DIABETIC NEUROPATHY EARLY DIAGNOSIS – SOMETHING OLD THAT SHOULD ALWAYS BE CONSIDERED SOMETHING NEW

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Objectives : A very frequent complication of diabetes mellitus (DM) which requires a complex management is represented by diabetic peripheral neuropathy (DPN). The importance of an early diagnosis even in case of a multifactorial approach with metabolic control, tight blood pressure control and an lipid profile in targets is emphasized by the high risk of development into ulceration or amputation and increase in the mortality rate.

Methods : We included 136 patients, with signed informed consent, admitted in a six month period, in NIDMNMD "N. C. Paulescu" and analysed their clinical and paraclinical data using Excel and SPSS software.

Results : The group with assessed QST consisted of males 61.03% and females 38.97%, with an average age of 55.97±15.2 years. They presented type 1 DM 22.79%, type 2 DM 30.88% and insulin-treated type 2 DM 46.32%, with a mean HbA1c of 9.64%±2.49% and a mean duration of DM of 11.94 years. The DM complications are DPN 68.38%, retinopathy 27.94%, chronic kidney disease (CKD) 25.74%, atherosclerotic diseases 38.24%.

DPN diagnosis positively correlates with age $p=0.031$, BMI $p<0.0001$, CKD $p=0.01$, albumin to creatinine ratio $p=0.049$, retinopathy $p=0.001$, DM duration $p<0.001$ and type 2 DM $p=0.007$. This brings new data by integratively approach the DPN and assessing the patient as a whole – comorbidities, DM complications and clinical and paraclinical profile.

Conclusions : QST are underused, despite it's highly availability and useful information provided. DPN frequently associates with microvascular complications, such as CKD and retinopathy, so, despite the risk for amputation and ulceration, the early diagnosis is the key for a proper case management.

Key-Words : Quantitative sensory testing, diabetes mellitus, diabetic peripheral neuropathy, HbA1c.

O32. KEY TO THE SENSORY PARADOX OF PAINFUL DIABETIC NEUROPATHY

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Loss of pain sensitivity to heat and burning spontaneous pain are characteristic features of painful diabetic neuropathy (PDN). This phenomenon could be explained, if different types of small diameter fibers located at different depths are responsible for the loss of pain sensitivity and generation of spontaneous pain, respectively. In fact, partially depleted and retracted epidermal polymodal C- and Aδ-fibers are likely responsible for the loss of pain sensitivity to heat; whereas, subepidermal, less-depleted, mechano-insensitive C (CMi) fibers are likely mediate spontaneous pain (1-2). Activation thresholds of CMi-fibers are the highest among nociceptors, when stimulated by non-fiber type-selective contact or radiant heat or electrical current. Thus, CMi-fibers are not accessible by these sensory assays. It is the likely reason why sensory assays have not demonstrated any correlation with diabetic pain states (3, 4). CMi-fibers, which are silent in healthy subjects and are found to be abnormally spontaneously active in diabetic patients with painful vs.painless neuropathy. This spontaneous activity is so far the only clinical sign correlated with peripheral neuropathic pain (2, 3, 6, 7). Interestingly, in humans, pigs and likely some primates, activation of CMi fibers are solely responsible for inducing axon reflex neurogenic flare. (8,9)

Diode Laser heating (DLss), which has been demonstrated to selectively activate A-δ or C fibers has been applied to PDN patients as well as to healthy controls (10-12). Compared to electrical simulation, DLss induced heat is fiber specific and primarily activate heat sensitive TRPV1 positive nerve endings in the skin. These nerve endings are responsible for peripheral neuropathic pain.

The electrical stimulation currently used for inducing of the flare are not selective and activates both axon and free nerve endings. The contact or radiant heat activates CMi fibers at the temperatures higher than the pain-threshold stimulation of C-polymodal fibers. Activation of CMi-fibers can be assessed by measuring neurogenic flare response to DLss, as CMi-fibers are solely responsible for this.

Nine PDN patients and 21 healthy subjects were tested. The stimulus intensity that induced threshold-level Aδ-fiber-mediated pain was roughly two times higher in diabetic patients when compared to healthy controls. However, C-fiber-evoked pain thresholds were similar in both groups. The energy necessary to activate CMi-fibers was assessed by induction of neurogenic flare response and was found to be below the energy necessary to induce pain.

The ability of DLss to preferentially activate CMi-fibers may explain abnormally low C-fibers pain thresholds in patients with painful diabetic neuropathy as they have few epidermal polymodal fibers but deeper CMi-fibers may be relatively intact and sensitized (13, 14). Traditional sensory testing assays are not fiber-type selective and CMi fibers have the highest thresholds of all nociceptors when stimulated by surface heat or electrical current. Therefore, these assays do not provide an adequate biomarker for painful neuropathy. I propose that DLss-based assay may allow to explain the paradox that some diabetic patients exhibit loss of thermal pain sensitivity, yet complain of spontaneous pain.

O32. KEY TO THE SENSORY PARADOX OF PAINFUL DIABETIC NEUROPATHY

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O33. PREDICTION OF FUTURE NEUROPATHY ONSET USING CORNEAL CONFOCAL MICROSCOPY: A LONGITUDINAL MULTINATIONAL CONSORTIUM STUDY

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Objectives : Corneal Nerve Fibre Length (CNFL) reasonably identifies the presence of neuropathy in patients with T1D and T2D. In this longitudinal diagnostic study, we aimed to determine its ability to predict future neuropathy.

Methods : Among 998 participants with diabetes, we examined the 387 who did not have neuropathy at baseline and who had follow-up in a 5-centre multinational consortium study. Participants underwent corneal nerve quantification and clinical and electrophysiological examination for neuropathy at baseline and in scheduled follow-up. Predictive validity and diagnostic thresholds were determined using time-dependent receiver operating characteristic (ROC) curves that accounted for censoring, and used baseline and time-updated CNFL. Estimates were derived in the T1D subcohort and validated in the T2D subcohort.

Results : The 387 participants had mean follow-up of 4.8y (interquartile range 3-7y). 288 had T1D (baseline mean age 35±17y and A1c 8.2±1.5%) and 99 had T2D (baseline age 59±8y and A1c 7.3±1.1%). New onset neuropathy occurred in 85 participants (22%; incidence rate 5.05 events per 100 person years). The crude area under the ROC curve (AUC) for CNFL was 0.64 (95% CI 0.56-0.73, p=0.001) in the T1D derivation set, which was confirmed in the T2D validation set (AUC 0.69, 95% CI 0.57-0.81, p=0.002). In the combined cohort, time-dependent ROC curves were generated for 2, 4, 6, and 8 years; AUC ranged from 0.67 to 0.71 for baseline CNFL, and 0.66 to 0.68 for time-updated CNFL. The optimal diagnostic threshold for baseline CNFL was 14.1mm/mm^2 (sensitivity 67%, specificity 63%, 1likelihood ratio (LR) positive 1.8, LR negative 0.5, Cox proportional hazard rate ratio 2.79, p<0.001).

Conclusions : CNFL showed modest but statistically significant predictive validity. Though its utility may be limited as a diagnostic tool in estimating risk for individual patients, it could play a role in identifying higher-risk groups of individuals for inclusion in clinical research and trials.

O34. CORNEAL CONFOCAL MICROSCOPY IDENTIFIES EARLY AND DEFINITE CARDIAC AUTONOMIC NEUROPATHY

Shazli Azmi[1], Maryam Ferdousi[1], Alise Kalteniece[1], Georgios Ponirakis[2], Ioannis Petropoulos[2], Uazman Alam[3], Andrew Marshall[1], Nathan Efron[4], Rayaz A Malik[2].

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Objectives : Cardiac Autonomic Neuropathy (CAN) is an independent risk factor for mortality, therefore early recognition is key to prevent progression. Autonomic function tests are not widely available and cannot be performed in patients on beta-blockers. We have previously shown the utility of corneal confocal microscopy (CCM) to identify advanced diabetic autonomic neuropathy. We now aim to assess its utility to identify early CAN.

Methods : 148 patients with type 1 and type 2 diabetes mellitus of 15.9±1.3 years duration and 48 age-matched controls (57.2±1.1 v 55.4±1.7, NS) underwent cardiac autonomic function tests and CCM. CAN was graded according to the Toronto Autonomic Diabetic Neuropathy Consensus Panel.

Results : CAN was absent in 17%, early in 16% and definite in 67% of patients with DM. There was no significant difference in deep breathing heart rate variability (DB-HRV), E:I ratio, valsalva ratio or CCM in patients without CAN compared to controls. However, compared to controls there was a reduction in DB-HRV in patients with early and definite CAN (28.2±1.9 v 28.3±2.2 v 22.2±1.6$^{(p<0.05)}$ v 12.9±0.7$^{(p<0.0001)}$). E:I ratio and valsalva ratio were progressively reduced in patients without, early and definite CAN. E:I ratio (1.3±0.03 v 1.2±0.02$^{p<0.005}$ v 1.0±0.006$^{p<0.005}$); Valsalva ratio (1.4±0.05 v 1.2±0.01$^{p<0.05}$ v 1.1±0.01$^{p<0.005}$).

Compared to controls CNFD (35.6±1.0 v 30.5±1.3 v 24.01±1.0$^{(p<0.05)}$ v 22.1±0.7$^{(p<0.05)}$) CNBD (84.6±5.5 v 79.6±8.3 v 62.1±6.3$^{(p<0.05)}$ v 44.7±2.2$^{(p<0.05)}$) and CNFL (28.2±1.3 v 26.1±0.8 v 24.3±1.3$^{(p<0.05)}$ v 20.2±0.6$^{(p<0.05)}$) showed a progressive reduction in patients without, early and definite CAN. CNFD (22.2±0.7 v 24.01±1.02 p=0.05), CNBD (44.7±2.2 v 62.1±6.3, p=0.03) and CNFL (20.2±0.6 v 24.3±1.2, p=0.02) were further reduced in definite compared to early CAN.

DB-HRV correlated with CNFD (r=0.5, p<0.0001), CNBD (r=0.3, p=0.001) and CNFL (r=0.3, p=0.002) and E:I ratio showed a weak correlation with CNFD (r=0.2, p=0.013), CNBD (r=0.2, p=0.04) and CNFL (r=0.2, p=0.024).

Conclusions : CCM identifies early CAN and worsens with severity of CAN. It may act as an objective surrogate marker of CAN.

O34. CORNEAL CONFOCAL MICROSCOPY IDENTIFIES EARLY AND DEFINITE CARDIAC AUTONOMIC NEUROPATHY

	Control	No CAN	Early CAN	Definite CAN
CNFD	35.6±1.0^	30.5±1.3	24.01±1.02*	22.1±0.7*
CNBD	84.6±5.5^	79.6±8.3	62.1±6.3*	44.7±2.2*
CNFL	26.1±0.8^	28.2±1.3	24.3±1.3*	20.2±0.6*
DB-HRV	28.2±1.9^	28.3±2.2	22.2±1.6*	12.9±0.7***
E:I ratio	1.3±0.01	1.3±0.03	1.2±0.02**	1.0±0.006**
Valsalva ratio	1.4±0.03	1.4±0.05	1.2±0.01*	1.1±0.01**
OH (%)	0	0	0	2

^p<0.0001 Control vs Diabetes Mellitus
*p<0.05, **p<0.005, ***p<0.0001 No CAN vs Early CAN, Early CAN vs Definite CAN

O35. CORNEAL NERVE AND KERATOCYTE DENSITY ARE REDUCED IN SUBJECTS WITH IMPAIRED GLUCOSE TOLERANCE WHO DEVELOP TYPE 2 DIABETES

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Objectives : Corneal keratocytes are stromal cells involved in corneal nerve regeneration. We have previously shown a progressive reduction in keratocyte density (KD) with increasing severity of diabetic neuropathy and an increase in KD and corneal nerves in T1DM patients after simultaneous pancreas and kidney transplantation. There are no data on KD in subjects with impaired glucose tolerance (IGT).

Methods : 26 subjects with IGT and 21 age-matched controls (61.3±2.1 v 57.6±2.4, NS) underwent corneal confocal microscopy and neuropathy assessments at baseline. Glycaemic status was re-assessed after 3 years using an oral glucose tolerance test (OGTT). Stromal KD (no/mm^2) and sub-basal corneal nerve fibre density (CNFD) (no./mm^2), branch density (CNBD) (no./mm^2) and length (CNFL) (mm/mm^2) were quantified.

Results : Subjects with IGT had a significantly lower CNBD (64.5±6.6 v 96.8±4.4, P<0.0001), CNFL (23.9±1.2 v 28.9±0.89, P=0.004) and KD (297.8±12.2 v 405.5±9.1, P<0.0001) compared to controls. A repeat OGTT at 3 years showed that 6 subjects with IGT had reverted to normal glucose tolerance (NGT), 11 remained IGT and 9 had developed type 2 diabetes (T2DM). KD at baseline was higher in subjects with IGT who reverted to NGT vs those who remained IGT and those who progressed to T2DM (341.5±21.4 vs 306.6±23.0 vs 245.5±20.3, NS). Furthermore, KD (245.5±20.3 vs 318.3±16.8, P=0.01), CNBD (44.0±5.2 v 75.4±8.8, P=0.01) and CNFL (21.4±1.7 v 25.3±1.5, P=0.03) were significantly lower, with no difference in CNFD (28.0±2.9 v 30.6±2.0, NS), NDS (3.2±0.9 v 3.1±0.9, NS), cold perception threshold (27.5±2.6 v 25.7±0.9, NS), warm perception threshold (37.9±2.2 v 40.3±1.0, NS) or PMNCV (44.2±0.9 v 45.4±1.3, NS) in subjects with IGT who did and did not progress to T2DM.

Conclusions : Reduced keratocyte density, CNBD and CNFL are associated with the progression of subjects with IGT to T2DM. CCM provides prognostic value to identify subjects at high risk of developing T2DM.

O36. 10-YEAR FOLLOW-UP OF CARDIAC, AUTONOMIC AND SENSORY FUNCTIONS IN YOUNG TYPE 1 DIABETIC PATIENTS

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Background : The detailed characteristics of the progression of cardiac and neuronal complications are not documented appropriately in symptom-free, young type 1 diabetic patients.

Objectives : The aim of our study was to manage a 10-year follow-up of sensory and cardiac functions in type 1 diabetic patients.

Methods : 20 type 1 diabetic patients (age: 28.4±1.5 years, duration of DM: 14.0±1.8 years, HbA1c: 8.1±0.4%; BMI: 23.2±0.7; mean±SE) without sensory or cardiac symptoms were involved in the study. Autonomic neuropathy (AN) was assessed by cardiovascular reflex tests (CRT-s). The peripheral sensory function was detected by Neurometer. Cardiac morphology and functions were measured with conventional and Doppler echocardiography. The tests were done in 2008 and were repeated in 2018.

Results : The most sensitive parasympathetic CRT, the heart rate response to deep breathing correlated negatively with the duration of DM and the systolic RR at the first tests (breathing-duration: r=-0.55, p<0.05; breathing-systolic RR: r=-0.64, p<0.05). BMI correlated with both the systolic RR (r=0.61, p<0.05) and the diastolic RR (r=0.47, p<0.05). The results of 2 parasympathetic CRT-s worsened during the 10-year follow-up (breathing: 25.1±2.5 vs 18.1±1.6 beats/min., p<0.05 and Valsalva ratio: 1.74±0.09 vs 1.24±0.05 beats/min, p<0.05). The current perception thresholds (CPT) increased at the upper and lower extremities at 2000 Hz stimulating frequency (CPT at median nerve at 2000 Hz: 1.28±0.2 vs 2.68±0.3 mA p<0.01; CPT at peroneal nerve at 2000 Hz: 3.16±0.4 vs 4.44±0.4 mA, p<0.05). The duration of late atrial diastolic filling (A dur) increased (A dur: 0.12±0.04 ms vs 0.13±0.04 ms p<0.05), while the velocity of the mitral annulus (E') decreased (E': 16.3±0.6 cm/s vs 13.1±0.6 cm/s p<0.01). Both the left atrial volume and the LV muscle mass seriously increased (left atrial volume: 32.1±2.7 ml vs 44.2±3.1 ml p<0.01, LV mass: 148.5±11 g vs 171.1±10 g p<0.05).

Conclusions : A silent progression of parasympathetic autonomic and peripheral sensory neuropathy together with cardiac morphologic and functional alterations is proven during 10 years in young, symptom-free type 1 diabetic patients. Strategies should be implemented to prevent or slow down the progression of these complications, including glycaemic control and the management of risk factors, especially hypertension for young type 1 diabetic patients.

O37. OBSTRUCTIVE SLEEP APNOEA AND CARDIAC AUTONOMIC NEUROPATHY IN PATIENTS WITH TYPE 1 DIABETES: A CROSS-SECTIONAL STUDY

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Objectives : Obstructive sleep apnoea (OSA) is associated with sympathetic activation in the general population. However, little is known about the relationship between OSA and cardiac autonomic function in patients with Type 1 diabetes (T1D). Previous studies have shown a high prevalence of OSA in patients with T1D despite the absence of obesity, suggesting factors other than obesity might contribute to OSA in these patients, such as cardiac autonomic neuropathy (CAN). We aimed to assess the relationship between OSA and CAN in patients with T1D.

Methods : Adults with T1D without known OSA or end stage renal disease were recruited from a single secondary diabetes centre in the UK. OSA was defined as an apnoea hypopnea index (AHI) ≥ 15 or an AHI 5-14.9 with excessive daytime sleepiness (based on Epworth Sleepiness Scale (ESS) ≥ 11). The AHI was measured using polygraphy (ApneaLink Air, Resmed, USA). CAN was defined as >= 2 abnormal tests (E/I, Valsalva, & 30:15 ratios, or postural drop in blood pressure). Cardiac autonomic reflex tests and heart rate variability were assessed using ANX 3.0 (ANSAR inc, Philadelphia, PA).

Results : 42 patients were included (men 24%, insulin pumps 69%, mean (SD) age 46.8 (12.6), diabetes duration 30.9 (13.1), median [IQR] BMI 26.1 [23.0 - 29.2], Hb1Ac 8.1% [7.3 – 8.7]). 57.1% (n=24) had AHI >=5 and OSA prevalence was 36% (n=15), Patients with and without OSA had similar age, gender, diabetes duration, and Hb1Ac. Patients with OSA had higher BMI (28.7 (25.0 - 32.4) vs 25.1 (22.6 – 28.1), p=0.047).
CAN prevalence was 33.3% (n=14). CAN was more common in patients with OSA vs without OSA (60% (n=9) vs. 18.5% (n=5), p=0.01) which remained significant after adjusting for age, sex, BMI, and diabetes duration (Nagelkerke R^2=0.37; OR 6.97; 95% 1.18 – 41.29; p=0.033). AHI was also associated with CAN after similar adjustments (Nagelkerke R^2=0.42; OR 1.30; 95% 1.03 – 1.63; p=0.024). Patients with OSA and T1D had lower frequency and time domain parameters compared to patients with T1D only (Table 1).

Conclusions : CAN is associated with OSA in patients with T1D. OSA is associated with sympathetic and parasympathetic withdrawal. Whether OSA has an impact on diabetes-related outcomes such as hypoglycaemia and vascular disease remain to be examined. CAN might contribute to the development of OSA in patients with T1D in the absence of obesity, but longitudinal studies are needed.

O37. OBSTRUCTIVE SLEEP APNOEA AND CARDIAC AUTONOMIC NEUROPATHY IN PATIENTS WITH TYPE 1 DIABETES: A CROSS-SECTIONAL STUDY

1. Frequency-domain		OSA+	OSA-	
		Mdn [IQR]	Mdn [IQR]	P-value
Lfa[a]	Baseline	0.54 [0.18 - 0.9]	0.99 [0.53 - 2.27]	**0.01**
	Deep Breathing	1.07 [0.36 - 1.7]	1.02 [0.54 - 2.5]	0.35
	Valsalva	14.96 [1 - 38.01]	46.56 [22.93 - 67.31]	**0.01**
	Standing	0.77 [0.32 - 2.66]	1.73 [0.64 - 7.25]	0.09
Rfa[a]	Baseline	0.31 [0.09 - 0.57]	0.82 [0.35 - 2.75]	**< 0.01**
	Deep Breathing	12.06 [0.88 - 22.14]	14.8 [10.71 - 40.41]	0.06
	Valsalva	0.73 [0.28 - 2.54]	4.98 [2.06 - 8.81]	**< 0.01**
	Standing	0.29 [0.11 - 1.65]	0.52 [0.19 - 1.53]	0.24

2.Time-domain		OSA+	OSA-	
		Mdn [IQR]	Mdn [IQR]	P-value
sdNN[b]	Baseline	22 [13 - 29.75]	33.5 [26 - 40]	**< 0.01**
	Deep Breathing	53 [23.5 - 68.25]	68 [56.25 - 97.5]	**0.03**
	Valsalva	58 [27 - 88.75]	93.5 [73.25 - 116]	**0.01**
	Standing	34 [15.25 - 43.5]	39.5 [27.25 - 52.5]	**0.05**
pNN50	Baseline	0.5 [0 - 1]	1.5 [1 - 8.75]	**< 0.01**
	Deep Breathing	14 [0.75 - 27.75]	24 [14 - 33]	**0.04**
	Valsalva	8 [2.25 - 17.5]	19.5 [8.25 - 23.5]	**0.02**
	Standing	0.5 [0 - 1.75]	1 [0 - 2]	0.28

Table 1.
Heart Rate Variability (HRV) response in T1D patients with obstructive sleep apnoea (OSA+) versus T1D patients without obstructive sleep apnoea (OSA-) to deep breathing, Valsalva, and standing manoeuvres

Lfa: Low Frequency area; Rfa: Respiratory Frequency area; sdNN: sample difference of beat to beat; pNN50: percent of consecutive beat-to-beat intervals that are greater than 50 milliseconds long (%); Mdn: Median; IQR: Interquartile Range.
a: measured in beats per minute^2/Hz; b: measured in milliseconds

O38. CORNEAL NERVE FIBRE LOSS IS RELATED TO THE SEVERITY OF PAIN AND QUALITY OF LIFE IN PATIENTS WITH PAINFUL DIABETIC NEUROPATHY

Alise Kalteniece, Maryam Ferdousi, Shazli Azmi, Andrew Marshall, Andrew JM Boulton, Handrean Soran, Rayaz A Malik.

Objectives : Corneal confocal microscopy (CCM) has been utilized to identify small nerve fibre damage in diabetic peripheral neuropathy (DPN). We have assessed whether CCM can detect loss of small nerve fibres in patients with DPN in relation to the severity of pain and quality of life (QoL).

Methods : 113 patients with diabetes and 38 healthy controls underwent assessment of symptoms of neuropathy, depression and anxiety and QoL (SF-36, SFN-SIQ, pre-R-ODS and HADS). Based on the visual analogue scale (VAS) patients were divided into four groups: no pain (VAS 0-4) (n=43), mild pain (VAS 5-44) (n=34), moderate pain (VAS 45-74) (n=16) and severe pain (VAS 75-100) (n=20).

Results : There was a progressive reduction in corneal nerve fibre density (CNFD), branch density (CNBD) and length (CNFL) in DPN patients with none, mild, moderate and severe pain compared to controls (all $P<0.005$). Vibration perception threshold (VPT) was increased and peroneal nerve conduction velocity (PMNCV) was reduced in all groups ($P<0.005$) compared to controls, but was not related to the severity of painful DPN. The number of symptoms in SFN-SIQ was significantly higher in severe ($P<0.0001$) and moderate ($P=0.01$ and $P<0.0001$) compared to mild and no pain. SF-36 was significantly reduced in severe ($P=0.005$ and $P<0.0001$) and moderate ($P=0.001$ and $P<0.0001$) compared to mild and no pain. Pre-R-ODS demonstrated a significant effect on all aspects of daily life in mild, moderate and severe pain groups compared to no pain. The anxiety score was significantly higher in patients with severe ($P=0.02$ and $P<0.0001$) and moderate ($P=0.005$ and $P<0.0001$) pain compared to mild and no pain and the depression score was significantly higher in severe ($P=0.001$), moderate ($P<0.0001$) and mild ($P=0.005$) pain compared to no pain. There was a negative association between severity of pain and CNFD (R=-0.4, $P<0.0001$), CNBD (R=-0.3, $P=0.001$) and CNFL (R=-0.4, $P<0.0001$). The average SF-36 score had a positive association with CNFD (R=0.3, $P=0.01$), CNBD (R=0.3, $P=0.005$) and CNFL (R=0.3, $P=0.003$).

O38. CORNEAL NERVE FIBRE LOSS IS RELATED TO THE SEVERITY OF PAIN AND QUALITY OF LIFE IN PATIENTS WITH PAINFUL DIABETIC NEUROPATHY

	Controls (n=38)	No pain (n=43)	Mild (n=34)	Moderate (n=16)	Severe (n=20)
HbA1c (%)	5.5 ± 0.05	7.4 ± 0.2*	7.3 ± 0.1*	8.4 ± 0.4*^"	8.0 ± 0.4*
CNFD (no./mm^2)	33.6 ± 1.1	23.5 ± 0.9*	20.7 ± 1.1*	19.2 ± 2.4*^	14.5 ± 2.1*^"
CNBD (no./mm^2)	92.3 ± 5.02	56.7 ± 4.5*	45.5 ± 4.4*	49.4 ± 9.5*	29.8 ± 5.8*^$
CNFL (mm/mm^2)	26.8 ± 0.8	22.6 ± 0.9*	20.4 ± 1.1*	18.2 ± 2.1*^	13.1 ± 1.9*^"$
PMNCV (m/s)	46.6 ± 0.6	38 ± 1.1*	38.9 ± 1.2*	39.8 ± 1.9*	34.1 ± 2.4*^"$
VPT (V)	7.6 ± 1.4	24.0 ± 1.8*	21.9 ± 1.8*	24.6 ± 3.2*	24.3 ± 3.1*
SFN-SIQ (0-39)	-	5.1 ± 0.6	9.2 ± 0.7^	13.8 ± 2.5^"	17.8 ± 2.2^"
SF-36 (0-100)	-	77 ± 2.6	55.1 ± 3.4^	32.7 ± 3.6^"	36.1 ± 7.1^"
Depression score (0-21)	-	3.7 ± 0.5	6.1 ± 0.6^	9.5 ± 0.9^"	8.3 ± 1.3^
Anxiety score (0-21)	-	4.1 ± 0.4	6.6 ± 0.6^	10.1 ± 1.1^"	9.5 ± 1.4^"

All data presented as mean ± SE. *P<0.005 compared to controls, ^P<0.005 no pain, "P<0.005 compared to mild pain, $P<0.005 compared to moderate pain.

Conclusions : This study shows a gradual reduction of corneal nerve fibres and quality of life in patients with increasing severity of painful diabetic neuropathy and a relationship between corneal nerve loss with the severity of pain and QoL in patients with painful diabetic neuropathy.

POSTER
ABSTRACT

P1. OBSTRUCTIVE SLEEP APNOEA IS ASSOCIATED WITH INCREASED RISK OF INCIDENT PERIPHERAL NEUROPATHY AND FOOT DISEASE IN PATIENTS WITH TYPE 2 DIABETES: A POPULATION-BASED MATCHED CONTROLLED COHORT STUDY

Nicola J Adderley, Anuradhaa Subramanian, Konstantinos Toulis, Krishna Gokhale, Neil Thomas, Christopher Sainsbury, Krishnarajah Nirantharakumar, Abd A Tahrani.

Objectives : Our group has previously shown associations between obstructive sleep apnoea (OSA) and diabetes peripheral neuropathy (DPN) and diabetes foot disease (DFD) in patients with Type 2 diabetes (T2D) in cross-sectional studies. However, the direction of the relationship was not clear and longitudinal studies are lacking. Hence, we aimed to determine risk of DPN and DFD in patients with T2D who subsequently develop OSA compared to patients with T2D who do not develop OSA.

Methods : An age-, sex-, body mass index (BMI)- and diabetes duration-matched retrospective cohort study was performed using data from the Health Improvement Network, a UK database of routinely collected primary care patient records. Study period was 1st January 2005 to 1st May 2017. Participants aged 16 and over with T2D were included. Exposed participants were those who developed OSA after their diabetes diagnosis; unexposed participants were those with T2D but without OSA. Outcomes were DPN and DFD. DFD was defined as the diagnosis of foot ulcer, gangrene or amputation. DPN and DFD were identified using Read codes.

Results : 4,007 adults with T2D and a subsequent diagnosis of OSA and 11,557 matched controls without OSA were included. The median follow-up duration was approximately 3 years. The exposed cohort were at increased risk of developing DPN (adjusted HR 1.61, 95% CI 1.27-2.04; p<0.001) and DFD (adjusted HR 1.50, 95% CI 1.23-1.84; p<0.001) after adjustment for age, sex, BMI, smoking, social deprivation score, hypertension, lipid lowering drugs, antihypertensives, antiplatelets, insulin, ethnicity, diabetes duration, HbA1c, eGFR, and albuminuria status.

Conclusions : Patients with T2D who go on to develop OSA are at increased risk of DPN and DFD compared to patients with type 2 diabetes who do not develop OSA. Whether OSA treatment reduces the incidence of DPN and DFD requires future RCTs.

P2. EFFECT OF FENOFIBRATE TREATMENT IN PATIENT WITH DIABETIC PERIPHERAL NEUROPATHY AND HYPERTRIGLYCERIDEMIA IN PATIENTS WITH TYPE 2 DIABETES IN GEORGIA

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Objectives : Diabetic peripheral neuropathy (DPN) is one of the common complication of type 2 diabetes (T2DM). About 60% to70% of all people with diabetes will eventually develop DPN. The cause of diabetic neuropathy is multifactoical, including diabetes duration (DD), poor glycemic control, vascular and autoimmune factors. Hypertriglyceridemia is a typical lipid disorder in patients with poorly controlled T2DM. Fenofibrate is a derivate of fibric acid that is used to treat lipid disorders.

The Aim of this study was to show the effect of fenofibrate therapy in patient with T2DM, DPN and hypertriglyceridemia

Methods : In total, 62 T2DM patients with DPN and diagnosed hypertriglyceridemia comprised a Study Group/SG (33 men /29 women, mean age 56±5 yrs, DD varied from 5 to 10yrs). Age, sex and DD match 50 diabetic patients with mildly eleveated triglyceride (TG) levels and without diagnosed DPN were used as controls (CG). HbA1c in SG and CG was 8,1±1,2% and 7,7±1,1%, respectively. According to current Guidelines following neuropathy tests to assess DPN were performed in the all patients: 10-g monofilament test, tip-term/temperature test, vibration test with the 128-Hz tuning fork, prick tests and neurological examination with Sudoscan (a non–invasive method for the assessment of the small fiber function, Impeto Medical, France). In SG patients results of all neurological tests (monofilament, tip-term/temperature, vibration tests) were positive, Sudoscan examination revealed presence of mild small fiber neuropathy. In CG patients all listed above tests, except Sudoscan, were negative, while Sudoscan revealed small fiber damage in 60% of patients. Serum TG levels in SG patients were 299± 45mg/dl; while in CG patients TG level were 160±30mg/dl. All patients were receiving oral hypoglycemic agents (OHAs). The SG patients were treated with fenofibrate+diet for 6 months, while CG patients received only dietary recommendations. Treatment with OHAs continued.

Results : Six months post study initiation TG levels in SG patients reduced and were within the normal range (150±30mg/dl); results of neurological examinations improved in 64,5% of cases (40 patients). TG levels in CG remained unchanged, and neuropathy tests (monofilament, tip-term/temperature tests) were positive in approx., 35% of CG patients.

Conclusions : This study shows that fenofibratehas neuroprotective actions can improve patient's condition through prevention of endothelial call demage and inflammation. Though TG are not the only factor that influences neuropathy progression in T2DM with .sub-optimal glycemia control. It is necessary to continue the study and assess the effect of fenofibrates in patients with mild TG elevation, who already have small fiber damage that is detected by Sudoscan.

P3. VARIATION IN DIABETES PERIPHERAL NEUROPATHY (DPN) PREVALENCE AND LACK OF AGREEMENT BETWEEN NEUROPAD, SUDOSCAN, VIBRATION PERCEPTION THRESHOLD AND THE MICHIGAN NEUROPATHY SCREENING INSTRUMENT IN DIAGNOSING DPN IN PATIENTS WITH LONGSTANDING TYPE 1 DIABETES

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Objectives : Diabetes peripheral neuropathy (DPN) is common in patients with Type 1 diabetes (T1D). Currently available tools to diagnose DPN vary in its ability to detect large vs small fibre neuropathy. Hence the prevalence of DPN might vary according to the method used. In this cross-sectional study we aimed to assess the prevalence of DPN in patients with longstanding T1D based on Neuropad, Sudoscan, vibration perception threshold (VPT) and the Michigan Neuropathy Screening Instrument (MNSI). We also aimed to compare the agreement between these methods

Methods : Adults with T1D without known OSA or end stage renal disease were recruited from a single secondary diabetes centre in the UK. Neuropad test was classified as normal if there was a total change in the colour of the plaster, while patchy or no change was considered abnormal. Sudoscan test was interpreted in line of the paper by Vinik et al. (2015) based on ethnicity. MNSI was considered abnormal if MNSI questionnaire scored more than 7 or MNSI examination scored ≥ 2.5. VPT was measured using a neurothesiometer (Scientific Laboratory Supplies Limited, Nottingham, UK) with an average of three measurements ≥ 15 volts on either great toe considered abnormal.

Results : 42 patients were included (Caucasian 95%, men 24%, insulin pumps 69%, mean (SD) age 46.8 (12.6), diabetes duration 30.9 (13.1), median [IQR] BMI 26.1 [23.0 - 29.2], Hb1Ac 8.1% [7.3 – 8.7]). The prevalence of DPN was 60% (n=25), 36% (n=15), 14% (n=6), 60% (n=25) based on Neuropad, Sudoscan, VPT and MNSI respectively.

There was poor agreement in detecting DPN between the examined methods.

Out of 25 patients with abnormal Neuropad, 56% (n=14), 16% (n=4), 60% (n=15) had abnormal Sudoscan, VPT, and MNSI respectively. Out of 15 patients with abnormal Sudoscan, 93% (n=14), 20% (n=3), 67% (n=10) had abnormal Neuropad, VPT, and MNSI respectively.

P3. VARIATION IN DIABETES PERIPHERAL NEUROPATHY (DPN) PREVALENCE AND LACK OF AGREEMENT BETWEEN NEUROPAD, SUDOSCAN, VIBRATION PERCEPTION THRESHOLD AND THE MICHIGAN NEUROPATHY SCREENING INSTRUMENT IN DIAGNOSING DPN IN PATIENTS WITH LONGSTANDING TYPE 1 DIABETES

Out of 25 patients with abnormal MNSI, 20% (n=5), 60% (n=15), 40% (n=10) had abnormal VPT, Neuropad, and Sudoscan respectively.

Out of 6 patients with abnormal VPT 83% (n=5), 50% (n=3), 67% (n=4) had abnormal MNSI, Sudoscan, and Neuropad respectively.

Conclusions : The prevalence of DPN vary considerably depending on the methods used. There was lack of agreement between the methods used to detect DPN, even methods that rely on small fibre function (Neuropad and Sudoscan) lacked agreement in detecting DPN. MNSI detected a DPN prevalence which would be consistent with the published literature in a population with long standing T1D. There need to be further clarity regarding the place and interpretation of newly developed methods to detect DPN.

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P4. CORNEAL CONFOCAL MICROSCOPY AND NOT OCULAR COHERENCE TOMOGRAPHY DETECTS DIABETIC PERIPHERAL NEUROPATHY IN TYPE 1 DIABETES

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Corneal confocal microscopy (CCM) is a non-invasive ophthalmic technique proven to accurately detect diabetic peripheral neuropathy (DPN). OCT biomarkers of neurodegeneration including reduced retinal nerve fibre layer (RNFL) thickness has been demonstrated in patients with DPN.

Objectives : To determine the ability of CCM and OCT surrogate biomarkers to detect DPN in subjects with type 1 diabetes (T1D).

Methods : Subjects with T1D (n=30) without neuropathy (n=13) and DPN (n=17) were quantified using neuropathy disability score (NDS), diabetic neuropathy symptom score (DNS), McGill VAS, vibration perception threshold (VPT) and sural nerve conduction velocity (SNCV) and amplitude (SNAmp), cold perception (CT) and warm threshold (WT). Corneal nerve morphology, namely corneal nerve fibre density (CNFD), branch density (CNBD) and fibre length (CNFL) were quantified. Putative OCT biomarkers of DPN, namely RNFL, ganglion cell layer (GCL), inner nuclear layer (INL), central retinal thickness (CRT) and choroidal thickness were determined. Additionally, OCT angiography (OCTA) was undertaken to assess the fovea avascular zone (FAZ) area.

Results : Comparing T1D without neuropathy to DPN: There was no significant difference in age (44.4±13.3 vs 51.7±12.4 years, P=NS), duration of diabetes (14.2±12.0 vs 26.7±13.9 years, P=NS), BMI (26.4±4.2 vs 28.8±6.0 kg/m^{2}, P=NS), total cholesterol (4.2±1.2 vs 4.4±1.0 mmol, p=NS), systolic blood pressure (130±15 vs 138±25mmHg) and eGFR(81.6±14 vs 56.8±18 ml/min,p=NS) between both groups. HbA1c (65.9±14.2 vs 75.2±14.6 mmol/mol, p=0.09) and triglycerides (1.1±0.4 vs 1.5±1.0, p=NS) were higher in DPN. Although they did not reach significance. NDS (0 ± 0 vs 5.8 ± 4.1, p<0.0001), NSP (1.6 ± 1.9 vs 11.1 ± 6.5, p<0.0001), VAS (1.31±2.5 vs 5.11±3.5, p=0.0035), VPT (9.4±2.4 vs 32.8±14.0 volts, p<0.001), WT (37.2±2.5 vs 44.1±4.8°C, p<0.001) were all higher in DPN. CT (26.8±1.9 vs 13.9±9.6°C, p<0.001), SNCV (50±5.1 vs 39.5±9.3 m/s) and SNAmp (8.2±3.3 vs 3.6±2.9 mV) were lower in DPN. Evaluation of CCM showed a lower CNFD (18.84±6.24 vs 9.78±3.83 no/mm^{2}, p<0.001), CNBD (26.33±13.39 vs 9.15±6.22 no/mm^{2}, p<0.001), CNFL (9.30±1.78 vs 5.89±1.70 no/mm^{2}, p<0.001) in DPN with no difference in OCT measures including RNFL (25.1±2.3 vs 23.8±2.6μm, p=NS), GCL (38.7±5.2 vs 35.2±4.9μm, p=NS), INL (35.4±3.5 vs 34.9±2.7μm, p=NS), CRT (280.3±23.5 vs 277.5±27.0μm, p=NS) and choroidal thickness (265.3±53.7 vs 257.7±68.3, p=NS). The FAZ area on OCTA examination was no different in controls compared to DPN (0.19±0.09 vs 0.53±0.36, p=NS).

Conclusions : CCM detects DPN in T1D prior to putative retinal biomarkers on OCT. CCM merits wider applicability and to be utilised in the diagnosis and screening of DPN in clinical practice.

P5. CCM DEMONSTRATES INCREASED CORNEAL LANGERHANS CELLS IN PATIENTS WITH LADA COMPARED TO TYPE 1, TYPE 2 DIABETES AND HEALTHY SUBJECTS

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Objectives : Langerhans cells (LC) are antigen presenting dendritic cells in the cornea. Both animal and human studies have shown increased LC density in diabetes mellitus (DM) compared to healthy controls and an association with diabetic neuropathy (DN). However, there are no data comparing LC density in type 1 diabetes (T1D), type 2 diabetes (T2D) and latent autoimmune diabetes in adults (LADA). We assessed LC density in T1D, T2D, LADA and healthy subjects and its association with corneal nerve morphology using corneal confocal microscopy (CCM).

Methods : 17 patients with T1D (age 53.0±8.2 yrs), 21 patients with T2D (age 58.5±7.4 yrs), 16 patients with LADA (age 51.5±13.1 yrs) and 14 control subjects (age 57.1±10.8 years) underwent a detailed assessment of neuropathy and CCM. Total LC density (no/mm^2), corneal nerve fibre density (CNFD) (no./mm^2), branch density (CNBD) (no./mm^2) and length (CNFL) (mm/mm^2) were quantified.

Results : LC density was significantly increased in T1D, T2D and LADA compared to healthy controls (66.9±63.4 (P=0.01) vs 62.7±76.1 (P=0.03) vs 119.3±115.1 (P=0.001) vs 26.1±41.4). There was no difference between T1D and T2D, but LC density was further significantly increased in LADA compared to T1D (p=0.04) and T2D (p=0.01).

There was a significant reduction in CNFD (20.5±7.8 vs 22.3±8.5; vs 18.6±7.8 vs 27.2±6.0 respectively; p=0.02), CNBD (21.3±9.7 vs 39.0±22.1 vs 21.9±11.4 vs 36.5±13.9 respectively; p=0.001) and CNFL (12.9±3.4 vs 14.2±3.9 vs 12.1±3.4 vs 15.9±3.4 respectively; p=0.026) between T1D, T2D, LADA and healthy controls. There was no significant correlation between LC and CCM measures with diabetes duration, BMI, HbA1c and lipids.

Conclusions : This study reports increased LC density in patients with T1D, T2D and LADA, with the greatest increase in LADA compared to T1D and T2D patients, indicative of on-going immune mediated nerve damage in diabetes, particularly in patients with LADA.

P6. NATIONAL TRENDS IN LOWER EXTREMITY AMPUTATION IN SINGAPORE FROM 2008 TO 2017

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Objectives : This study aimed to examine nation-wide trends in lower extremity amputation (LEA) in Singapore from 2008 to 2017. LEA is one of the most common as well as preventable end-stage complications of diabetes. Therefore, LEA rates in patients with diabetes are often used as an indicator for quality of long-term diabetes care. In the past decade, Singapore's healthcare system has put greater emphasis on strengthening chronic disease management in primary care and we hypothesized that these may be reflected in LEA incidence over the same period.

Methods : Data from The Ministry of Health Singapore's administrative database was used in our study. LEAs, excluding traumatic and tumour related LEAs, were identified using the Ministry of Health Table of Surgical Procedures (TOSP) from all public hospitals in Singapore, recorded between 1 January 2008 and 31 December 2017. Incidence rates were calculated for the population with diabetes, the population without diabetes and the entire population.

Results : Between 2008 and 2017, the rates of major LEA per 100,000 people with diabetes declined by 39%, while the rates of minor LEA remained stable. LEA rates in the non-diabetes population were 65 to 100 times lower, but showed similar trends, with a 46% decline in major LEA and stable rates of minor LEA (Figure 1). In the whole population, rates of diabetes related minor LEA increased over time, mirroring the rise in diabetes prevalence, while rates of diabetes related major LEA remained steady. Rates of non-diabetes related LEA remained low and stable throughout this period (Figure 2).

Conclusions : Rates of major LEA in people with and without diabetes have declined in the past 10 years, suggesting better primary care and management of risks. However, rates in people with diabetes remain substantially higher than in the non-diabetic population, and diabetes related LEAs now contribute to a larger proportion of LEAs in the population due to increasing diabetes prevalence.

P6. NATIONAL TRENDS IN LOWER EXTREMITY AMPUTATION IN SINGAPORE FROM 2008 TO 2017
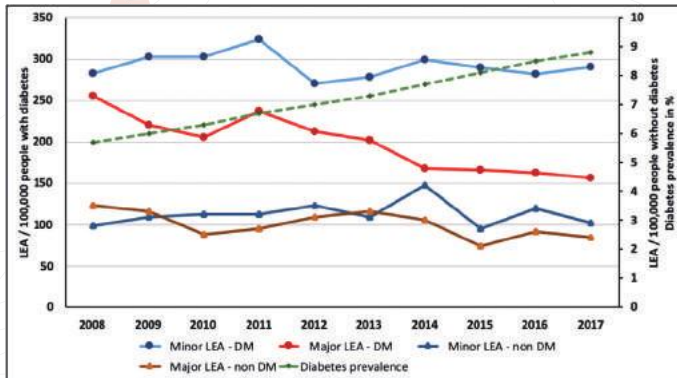

Figure 1.
Trends in rates of major and minor lower extremity amputations (LEA) in people with and without diabetes, Singapore 2008 - 2017
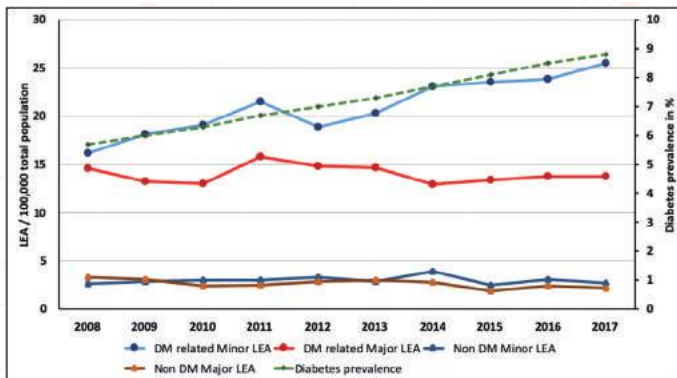

Figure 2.
Trends in rates of major and minor lower extremity amputations (LEA) in the whole population, Singapore 2008 – 2017

P7. CORNEAL KERATOCYTE DENSITY IMPROVES IN ASSOCIATION WITH CORNEAL NERVE FIBRE REGENERATION IN SUBJECTS WITH MORBID OBESITY AFTER BARIATRIC SURGERY

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Objectives : Obesity and metabolic syndrome increase the risk of peripheral neuropathy.[1] Corneal Confocal Microscopy (CCM) can detect early sub-clinical nerve damage[2] Corneal stromal keratocytes, mesenchymal cells of neural crest origin[3], may play a role in nerve regeneration[4]
The aim of this study was to assess changes in corneal keratocyte density (KD) and corneal nerve morphology after bariatric surgery in subjects with morbid obesity.

Methods : 22 obese subjects (age- 48.8 ± 18 years, BMI – 49.56 ± 9.2, 17 with diabetes) underwent CCM, measurement of serum cholesterol, HbA1c, HDL, LDL, IL-6, CRP and neuropathy assessments before and 12 months after bariatric surgery. CCM metrics© (University of Manchester) was used to quantify corneal nerve fibre length (CNFL) (mm/mm^2), corneal nerve fibre density (CNFD) (no./mm^2), corneal nerve branch density (CNBD) (no./mm^2) and keratocyte density (no./mm^2) from the anterior, middle and posterior stroma. 17 aged matched controls (age-54.2 ± 13 years, BMI - 28 ± 5.1) also underwent the same protocol at baseline only.

Results : CNFL (26.8 ± 5.1 vs 29.8 ± 5.8 p<0.001), CNBD (74.2 ± 36.45 vs 96.6 ± 22.1 P<0.001) and anterior (491.091 ± 97.6 vs 676.466 ± 124.450 P<0.001), middle (318.123 ± 61.600 vs 406.799 ± 45.850 P<0.001) and posterior (321.873 ± 69.200 vs 391.542 ± 52.67 P<0.001) keratocyte densities were significantly reduced in obese subjects compared to controls. 12 months after bariatric surgery there was a significant improvement in BMI (49.56 ± 9.2 vs 34.09 ±7.1, P<0.001), HDL (0.92 ± 0.23 vs 1.17 ± 0.18 P=0.014), CRP (7.42 ± 7.54 vs 1.75 ± 1.60, P=0.022). There was a significant increase in CNFL (26.8 vs 31.1 P<0.001), (CNBD 74.2 vs 90.77 P<0.001), (CNFD 19.9 vs 22.33 P<0.001), anterior KD (491.091 vs 554.602, P=0.049), Mid KD (318.123 vs 343.09, P<0.01) but no change in posterior KD (321.873 vs 358.386, P=0.15).

P7. CORNEAL KERATOCYTE DENSITY IMPROVES IN ASSOCIATION WITH CORNEAL NERVE FIBRE REGENERATION IN SUBJECTS WITH MORBID OBESITY AFTER BARIATRIC SURGERY

Conclusions : There is evidence of early small fibre damage and reduced keratocyte density in obese subjects with diabetes. Bariatric surgery leads to weight reduction and an improvement in glycemic status, lipids and inflammation, which was associated with an improvement in keratocyte density and adjacent corneal nerve regeneration.

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P8. OBSTRUCTIVE SLEEP APNOEA IS ASSOCIATED WITH PAINFUL PERIPHERAL NEUROPATHY AND WORSE QUALITY OF LIFE IN PATIENTS WITH LONGSTANDING TYPE 1 DIABETES

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Objectives : Obstructive sleep apnoea (OSA) is common in patients with type 1 diabetes (T1D). However, the associations of OSA and painful diabetes peripheral neuropathy (PDPN) and quality of life (QOL) in patients with longstanding T1D are unknown. The aim of this study was to assess the relationship between OSA and PDPN and QOL in patients with T1D.

Methods : Adults with T1D without known OSA or end stage renal disease were recruited from a single secondary diabetes centre in the UK. OSA was defined as an apnoea hypopnea index (AHI) ≥ 15 or an AHI 5-14.9 with excessive daytime sleepiness (based on Epworth Sleepiness Scale (ESS) ≥ 11). The AHI was measured using polygraphy (ApneaLink Air, Resmed, USA). PDPN was assessed using the Short Form McGill Pain Questionnaire 2 (SF-MPQ-2), and QOL was assessed using the EQ-5D-5L questionnaire.

Results : 42 patients were included (men 24%, insulin pumps 69%, mean (SD) age 46.8 (12.6), diabetes duration 30.9 (13.1), median [IQR] BMI 26.1 [23.0 - 29.2], Hb1Ac 8.1% [7.3 – 8.7]). 57.1% (n=24) had AHI >=5 and OSA prevalence was 36% (n=15), Patients with and without OSA had similar age, gender, diabetes duration, and Hb1Ac. Patients with OSA had higher BMI (28.7 (25.0 - 32.4) vs 25.1 (22.6 – 28.1), p=0.047).
The prevalence of OSA was 36%. Patients with OSA and T1D had higher total mean pain score (0.64 [0.5 - 2.05] vs 0.23 [0.05 - 0.64]; p<0.01) and neuropathic pain score (1.5 [0.5 - 2.67] vs 0 [0 - 0.67]; p<0.01) compared to patients with T1D without OSA. Patients with OSA and T1D had lower QOL compared to those with T1D only (EQ-5D-5L Scale: 75% [60 - 85] vs 86% [80 - 90]; p<0.01; EQ-5D-5L Index: 0.77 [0.74 - 0.85] vs 1 [0.85 - 1]; p<0.01).
After adjusting for age, sex, BMI, diabetes duration and HbA1c the association between OSA and neuropathic pain score remained significant (Nagelkerke R^2=0.66; OR 7.59; 95% 1.40 – 41.04; p=0.02). The association between OSA and total mean pain score became borderline following adjustment (Nagelkerke R^2=0.48; OR 4.21; 95% 0.92 – 19.34; p=0.06).
After similar adjustment, EQ-5D-5L scale (Nagelkerke R^2=0.64; OR 0.86; 95% 0.76 – 0.98; p=0.02), and EQ-5D-5L index (Nagelkerke R^2=0.67; OR 0.00; 95% 0.00 – 0.07; p=0.02) remained significantly associated with OSA showing that OSA was associated with worse QOL.

Conclusions : OSA is associated with PDPN and worse quality of life in patients with long standing T1D. Whether OSA treatment can improve pain and quality of life needs to be examined in a randomised controlled trial.

P9. IMPAIRED CURRENT PERCEPTION, THERMAL PERCEPTION, AND NERVE CONDUCTION VELOCITY IN GLUCOSE-RESPONSIVE ATP-SENSITIVE POTASSIUM CHANNEL DEFICIENT MICE

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Objectives : Glucose-responsive ATP-sensitive potassium (K_{ATP}) channels in pancreatic beta cells are metabolic sensors that determine glucose-responsive membrane excitability in the regulation of insulin secretion. In addition to the role in beta cells, the physiological role of K_{ATP} channels has been proven in the central nervous system. The K_{ATP} channel is an octameric protein consisting of two subunits: the pore-forming inward rectifier K+ channel member Kir6.1 or Kir6.2, and the sulfonylurea receptor SUR1 or SUR2. In central nervous systems, glucose responsive neurons share the same molecular composition Kir6.2 and SUR1 with beta cell. Here we investigated functional roles of K_{ATP} channel and potential effects of K_{ATP} channel modulators in peripheral nervous systems (PNS).

Methods : The expressions of Kir6.1, Kir6.2 and SURs in the PNS were determined with RT-PCR, immunohistochemistry (IHC) and western blotting (WB). *Kir6.2-/-* mice (KO) and wild type mice (WT) were used in this study. In 4-24 weeks old mice, current perception thresholds (CPTs), thermal plantar test (TPT) and motor and sensory nerve conduction velocities (MNCV and SNCV, respectively) were evaluated. Dorsal root ganglia (DRG) neurons derived from wild WT were cultured with or without K_{ATP} channel closer: glibenclamide, glimepiride or gliclazide for 24h. Additionally, DRG neurons were cultured with or without K_{ATP} channel opener nicorandil diazoxide. The neurons were immunostained with an anti-neurofilament M antibody to evaluate neurite outgrowths.

Results : RT-PCR, IHC and WB revealed the expression of Kir6.2 in the PNS. Expressions of Kir6.1 and SURs in the PNS were confirmed with RT-PCR. CPTs in KO were significantly increased compared with these in WT, indicating hypoalgesia (2000Hz: WT 146.7±37.0 μA, KO 335.4±100.0, $p < 0.0005$; 250Hz: WT 74.6±5.8, KO 202.6±179.3, $p < 0.05$; 5Hz: WT 86.3±17.4, KO 159.8±84.6, $p < 0.05$). In TPT, paw withdrawal latencies were delayed in KO compared with these in WT (WT: 6.1 ± 1.3 s, KO: 11.1 ± 5.3, $p < 0.05$). SNCVs but MNCVs in KO were significantly delayed (MNCV: WT 42.0±6.7 m/s, KO 50.6±12.4, $p = 0.11$, SNCV: WT 38.4±6.8, KO 25.0±2.6, $p < 0.005$). The neurite outgrowths of DRG neurons was remarkably

P9. IMPAIRED CURRENT PERCEPTION, THERMAL PERCEPTION, AND NERVE CONDUCTION VELOCITY IN GLUCOSE-RESPONSIVE ATP-SENSITIVE POTASSIUM CHANNEL DEFICIENT MICE

reduced in the presence of glibenclamide and glimepiride (glibenclamide 43.5±9.8% using the control as 100%, p <0.0001; glimepiride 27.4±15.8%, p < 0.05). However, gliclazide significantly promoted neurite outgrowth (148.1±7.2%, p < 0.05). KATP channel opener nicorandil promoted neurite outgrowth (274.5±30.3%, p < 0.0001).

Conclusions : KO mice, which deficient a function of K_{ATP} channel, showed impaired sensory functions. These results suggest that K_{ATP} channels could have physiological functions in the PNS. K_{ATP} channel modulators, gliclazide and nicorandil, might have neuroprotective effects in the PNS.

P10. RELATIONSHIP BETWEEN CEREBRAL HEMODYNAMICS, SYSTEMIC ENDOTHELIAL FUNCTION AND RETINAL MICROVASCULAR DENSITY IN TYPE 2 DIABETES MELLITUS

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Objectives : Cerebral and retinal small vessels have similar vascular structure, and the blood–brain barrier is structurally similar to the blood-retinal barrier. Several clinical studies have shown that retinal microvascular abnormalities are closely related to cerebral small vessel disease, suggesting that retinal microvascular abnormalities could be an imaging marker for cerebral vascular disease.
Few data are available on the relationship between the functional changes of vascular retinal district and the cerebral haemodynamics and systemic endothelial function. Our aim is to explore the association between cerebral vasomotor reactivity (VMR), flow mediated dilation (FMD) and microvascular retinal blood flows changes in well-controlled and uncomplicated type 2 diabetes (DM2) mellitus patients.

Methods : Well-controlled 15 DM2 patients (HbA1c 6.6 ±0.7), without diabetic retinopathy and any vascular complications were consecutively recruited. Optical coherence tomography angiography (OCTA) imaging was performed, measuring parafoveal and foveal vessel density in the deep capillary plexus (DCP) and superficial capillary plexus (SCP) with automated quantification software. Cerebral vascular function was evaluated by VMR and systemic endothelial function by FMD and shear rate FMD.

Results : A significant decrease of foveal vessel density was found in DCP and SCP of DM2 patients compared to normative data for age (28.5 ± 4.6% versus 32.0± 6.2%; 28.5 ± 4.6 versus 32.8 ±5.2, respectively p < 0.001). No significant difference was found in SCP and DCP parafoveal vessel density between droups. A negative correlation between VMR and DCP parafoveal density and VMR and SCP foveal density was found (r -0.460, p 0.03, -0.597 p 0.003, respectively). No association with FMD and FMD shaer rate has been observed.

Conclusions : These OCTA findings suggest that foveal capillary nonperfusion is an early process in DM2-related retinal changes. There is a relationship between retinal vascular density and cerebral hemodynamics, but not with systemic endotelial function, suggesting that the retina may represent a "window" on cerebral vascular function in type 2 diabetes.

P11. RETINAL NEURODEGENERATION IN PEDIATRIC PATIENTS WITH TYPE 1 DIABETES MELLITUS

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Objectives : Retinal neurodegeneration (RN) has been considered an early marker of diabetic retinopathy (DR), preceding vascular damage. Few data are available between the pediatric population with type 1 diabetes mellitus (DM1) regarding the early structural or functional signs of RN and whether these changes may represent an early marker of DR or neuropathic damage. Moreover, the role of glycemic control and daily glucose variability (GV) on early RN is still not clarified. The aim of our study are to evaluate the structural and functional alteration of neuroretina and the impact of the GV on neuroretina in pediatric DM1 subjects without any complication.

Methods : 24 patients with DM1 (ages 10-20 years) and 17 healthy subjects (C) comparable in age were enrolled. All subjects underwent an Optical Coherence Tomography, measuring subfoveal macular neuroretinal layers thickness of inner and outer nasal (N)/temporal (T)/superior (S)/inferior (I) quadrants. The functional study was obtained by multifocal electroretinogram analysis, measuring the amplitude density (RAD) and implicit time (IT) from 4 concentric annular retinal regions (rings, R1-R4). Metabolic control was evaluated by glycated hemoglobin (HbA1c), and indexes of GV.

Results : RNFL-S-inner thickness was significantly reduced in the DM1 group compared to C (mean difference, md=1.53; p=0.046), together with T, N, I outer plexiform layer (OPL) (md=2.33; p=0.04; md=1.22; p=0.01; md=1.37; p=0.03 and md=1.5, p=0.03 respectively). Also N outer nuclear layer (ONL) (md= 14,24, p=0.04) was reduced in DM1. IT in R2 and R4 was significantly increased in the DM1 group compared to C (md=-2,58 ms; p=0.046 and md=-3,23 ms; p=0.005; respectively). A negative correlation between OPL-T and Low Blood Glucose Index (LBGI) (r=-0.522, p=0.031) and between ONL-N and mean amplitude of glycemic excursions (MAGE) (r=-494, r=0.04) were observed in DM1 patients. No association with HbA1c has been observed.

Conclusions : Very early morphological and functional alterations of the neuroretina are already present in pediatric DM1 patients without both vascular retinopathy and neuropathy, supporting the hypothesis that RN occurs early in the course of diabetes. Glycemic variability seems to play a pathogenic role in the morphological abnormalities of neurosensory retina in DM1 pediatric population. A longitudinal evaluation is needed to identify whether the damage to the neuroretinal nerve is a predictor marker of diabetic neuropathy.

P12. EVALUATION OF THE DIAGNOSIS OF ELASTOGRAPHY ON THE TIBIAL NERVE AND THE SUBCUTANEOUS PLANTAR FOOT OF DIABETIC PATIENTS WITH DYSFUNCTION OF DIFFERENT SUBTYPES OF PERIPHERAL NERVES FIBRES

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Objectives : To evaluate the diagnostic method of Elastrography (ELY) to detect structural alterations of rigidity on the tibial nerve and subcutaneous cellular tissue at the anterior plantar support point on diabetic patients type 1-2, together with dysfunction in different types of peripheral sensory nerve fibres.

Methods : 21 patients with DM12 of both genders with a mean evolution time of 12 years ±5, glycosylated haemoglobin (HbA1c) 8.8 ±7 Body Mass Index 28 ±4. Subjects were divided in groups; without neuropathy (N), with alteration of 1 sensory nerve fibre for vibration perception threshold on both feet (PNAB) and with alteration of 2 or more small and large peripheral sensory nerve fibres on both feet (PNABH). The neurological examination performed was done with Neuropathy Disability Score (NDS) and Quantitative Sensory Testing NerveCheck Master (NCM). Tibial Nerves (TN) and Subcutaneous Cellular Tissue (SCT) were measured on the retromalleolar region with longitudinal section of the stiffness on both feet on 3 points at each end A/B of the TN and SCT. Compression resistance is expressed as a percentage (the less percentage the greater rigidity). Statistics by analysis of Anova single factor and t-student.

Results : Anova single test of left and right TN elastography measured elasticity index in the points A/B, in groups: N, PNAB and PNABH has not significant differences (NS). However t- student analysis of the SCT point B measured on the right foot between N / PNAB P-value (0.01); PNAB / PNABH P-Value (NS); N / PNABH P-value (0.007) has determined significant correlation in relation to degree of dysfunction and diversity of peripheral subtypes of nerve fibres altered (PNAB).

Conclusions : The tibial nerve stiffness based on mean ± deviation standard using longitudinal section elasticity index was not shown any significant differences in groups with PNA. In particular, it is interesting to note the observation of the increased SCT stiffness in one of the biomechanical support points of the right foot, points predominating in the lesions of diabetic foot. The combination of ELY, NCM and NDS, could be useful as an early indicator that the SCT together with PNA, has reduced its protective physiological function in the face of the mechanical impact and as a defensive barrier tissue against environmental injuries. It should be considered that it is a sample of small size to draw final conclusions.

P13. PREVALENCE AND CLINICAL CHARACTERISTICS OF DIABETIC PERIPHERAL NEUROPATHY IN TYPE 2 DIABETES: RESULTS FROM A NATIONAL HEALTH INSURANCE SERVICE–NATIONAL SAMPLE COHORT, 2006-2015

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Objectives : To determine the prevalence and clinical characteristics of diabetic peripheral neuropathy in patients with type 2 diabetes in Korea.

Methods : From the target population a representative sample cohort of 1,021,208 participants was randomly selected, comprising 2.1% of the total eligible Korean population in 2006, and followed until 2015. Strata were constructed by age group, sex, eligibility status and income level. During the follow-up period, the cohort was refreshed annually by adding a representative sample of newborns. Data source: NHIS-NSC: National Health Insurance Service–National Sample Cohort. Definition of diabetic peripheral neuropathy (DPN): i) Diagnosed with DPN (ICD-10 codes E10.4, E11.4, E12.4, E13.4, and E14.4). ii) Diagnosed with DPN (ICD-codes G59.0, G63.2, and G99.0). iii) Receiving a prescription for DPN drugs and DM drugs.

Results : From 2006 to 2015, the prevalence of DPN in diabetic patients over the age of 30 years and older was 24.5%- 21.2%. DPN medication was administered in 68% to 69% of DPN patients. Drug therapy was prescribed for up to 90% mono therapy, dual combination treatment for up to 10%, and triple combination treatment for up to 1%. Prescribed medications for DPN from 2006 to 2015 were α-lipoic acid (54.7% to 43.2%), anticonvulsant drugs (21.7% to 36.8%), tricyclic antidepressants (21.3% to 12.6%), serotonin-norepinephrine reuptake inhibitors (0.3% to 5.5%), γ-linoleic acid (2.3% to 1.9%). Persistency for pharmacological treatment of DPN was 30.0%- 48.5%, and the rate of persistency was increasing over time.

Conclusions : The prevalence of DPN patients is about a quarter of those with diabetes, and medication is about 70 percent, and most medications are administered with mono therapy.

P14. THERAPEUTICAL APPROACH IN DIABETIC NEUROPATHY – DATA FROM THE 2016 CLUJ-NAPOCA FOLLOW-UP COHORT OF THE QoL-DN ROMANIA STUDY

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Objectives : The aim of this study was to evaluate what percentage of the patients included in the 2016 follow-up of the QoL-DN Romania study (Quality of life in patients with diabetic neuropathy in Romania), with a diagnosis of diabetic peripheral (DPN) in their medical file have received pathological-orientated and/or symptomatic treatment.

Methods : In the current analysis, 375 patients (52.7% from the initial Cluj-Napoca cohort of 711 subjects) with identified medical records were included. 2 subjects with inadvertences of reported age in 2012 and 2016 were excluded. Also, 31 deceased patients were excluded from this evaluation. The study was conducted in the Center for Diabetes, Nutrition and Metabolic diseases Cluj-Napoca, from March 2016 to December 2016. Statistical evaluations of the results of this study were done using Microsoft Excel 2013. The data were summarized as mean or median.

Results : In 2016, 244 subjects had the DSPN diagnosis in their medical records and all of them were treated with pathogenetic-orientated or symptomatic therapy. Of the 131 subjects without a diagnosis of DPN, 12 (9.2%) were receiving Benfotiamine, 2 subjects alpha-lipoic acid and 1 subject tricyclic antidepressants.

Conclusions : In our analysis, all the patients diagnosed with DPN were receiving treatment for this condition. Despite not having a DSPN diagnosis in their medical records, 15 subjects (4%) of the total cohort were receiving drugs that are also used in the DSPN management.

P14. THERAPEUTICAL APPROACH IN DIABETIC NEUROPATHY – DATA FROM THE 2016 CLUJ-NAPOCA FOLLOW-UP COHORT OF THE QoL-DN ROMANIA STUDY

Parameter	Mean	Interval (min-max)	STDEV
Age (years)	65.39	26-89	±9.59
BMI (kg/m^2)*	31.55	18.82-58.46	±6.01
WC (cm)**	110.02	77-160	±19.20
Age of DM (years)	17.67	6-49	±6.43
Age of DPN (years)***	7.86	2-37	±4.20
A$_1$c (%)****	7.88	4.48-12.6	±1.45

Table 1.
The general characteristics of the study population; *Data were available for 202 subjects; **Data were available for 55 subjects; ***Data available for 235 subjects; ****Data available for 271 subjects; STDEV=standard deviation, WC=waist circumference, DM=diabetes mellitus, DPN=distal symmetric polyneuropathy, A1c= glycated hemoglobin

DPN diagnosis in the medical file in 2016				
	Yes		No	
Treatment	No. of subjects	Percentage (%)	No. of subjects	Percentage (%)
	244	100	131	100
Benfotiamine	154	63	12	9.2
alpha-lipoic acid	78	32	2	1.5
Gabapentin	10	4.1	0	0
TCA	2	0.9	1	0.8

Table 2.
The characteristics of the DPN treatment in 2016; TCA= tricyclic antidepressants

P15. CLINICAL CHARACTERISTICS OF DIABETIC PERIPHERAL NEUROPATHY IN TYPE 2 DIABETES: RESULTS FROM A NATIONAL HEALTH INSURANCE SERVICE–NATIONAL SAMPLE COHORT, 2015

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Objectives : Diabetic peripheral neuropathy is a common complication of diabetes. To investigated the clinical characteristics of diabetic peripheral neuropathy(DPN) in patients with Type 2 diabetic mellitus in Korea.

Methods : From the target population a representative sample cohort of 1,021,208 participants was randomly selected, comprising 2.1% of the total eligible Korean population in 2006, and followed until 2015. Strata were constructed by age group, sex, eligibility status and income level. During the follow-up period, the cohort was refreshed annually by adding a representative sample of newborns. Data source: NHIS-NSC: National Health Insurance Service–National Sample Cohort. We conducted a clinical analysis of diabetic patients and DPN patients in 2015 among cohort subjects.

Results : According to the analysis, DPN patients showed that older age, being female, high alcohol intake, low physical activity, low body mass index, high waist circumference, high fasting glucose, the presence of cardiovascular diseas, a history of cerebrovascular accident, or peripheral arterial disease, the presence of hypertension or dyslipidemia, treatment with an oral hypoglycemic agent or insulin, a history of foot ulcers and amputation of foot and higher hospitalization than diabetic patients.

Conclusions : The tibial nerve stiffness based on mean ± deviation standard using longitudinal section We suggest that DPN patients need attention in treating elderly people, poor life style habits, high co-morbidities and complications, and high hospitalization rates.

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P16. PREVALENCE OF CARDIAC AUTONOMIC NEUROPATHY AND HYPERTRIGLYCERIDEMIA IN OBESSE PATIENTS BY SUDOSCAN

Ana Kopaleishvili.

Background : Sudomotor function is used to assess the peripheral autonomic system. Measurement of Electrochemical Skin Conductance (ESC) based on the electrochemical reaction between the chloride ions in sweat and stainless steel plate electrodes is a simple, non-invasive and quick method, which is used to assess sweat gland function. There is evidence that several factors, including age, sex, BMI, and glycemic status influence sweat function.

Objectives : Our aim was to study correlation between BMI and prevalence and severity of CAN.

Methods : Participant were 75 patients/pts (not having any major illness or chronic addiction). Based on their BMI patients were divided into three groups: Group 1 (Gr.1) - 28 pts (16 males/12 females, mean age 45±6.0 yrs) with BMI <25kg/m², Groups 2 (Gr.2) - 25 pts (15 males/10 females, mean age 43±4.9 yrs) with BMI 25-30kg/m² and Groups 3 (Gr.3) -22 pts (16 males/6 females, mean age 44±5.3 yrs) with BMI >30kg/m². Following tests and analysis were performed in all the patients: Sudoscan test, HbA1c, fasting plasma glucose, BMI, LDL-C, triglycerides (TG), systolic and diastolic blood pressure (SBP/DBP). According to Sudoscan results neuropathy is defined as : 1) no neuropathy >70 (feet) / >60 (hands); 2) moderate neuropathy 50-70 feet/ 40-60 hands; 3) severe neuropathy <50 (feet) / <40 (hands). CAN was defined according to CAN risk score: <30 - no risk of CAN; ≥30 - at risk of CAN. There was no significant difference in sex and age, between the groups.

Results : Prevalence of moderate or severe neuropathy, both DPN and CAN was higher in Gr.3 patients with the highest BMI : (no neuropathy - 4pts/18%; moderate neuropathy - 10pts/45%; severe neuropathy - 8pts/36%; CAN - <30 - 8pts /36%; ≥30 - 14pts/63%), than in Gr.1 (no neuropathy - 20pts/71%, moderate - 6pts/21%, severe- 2pts/7%; CAN - <30 in 22pts/78%; ≥30 - 6pts/21%) and Gr.2 (no neuropathy - 7pts/28%, moderate - 12pts/48%, severe- 6pts/24%; CAN - <30 in 14pts/56%; ≥30- 11pts/44%). BMI was the highest in Gr.3 (32.7±2.4 kg/m²,) compared to Gr.1 (23.2±1.8 kg/m²,) and Gr.2 (27.9±1.3 kg/m²,). There was no statistically significant difference in fasting plasma glucose, TG , SBP/DBP between Gr.1 and Gr.2. Fasting plasma glucose was higher in Gr.3 compared in Gr.1 (76.0±8.1mg/dl vs 99.8±7.0mg/dl, p=0.03); TG and LDL-C were higher is Gr.3 compared to Gr.1 (TG - 1.48±0.2mmol/l vs 2.99±0.7mmol/l, p=0.04; LDL-C - 2.0±0.4mmol/l vs 3.99±0.9mmol/l, p=0.04), SBP and DBP was higher in Gr.3 compared in Gr.1 (118±1.2mmHg vs 127±2.2mmHg, p=0.000; 75±2.3mmHg vs 84±3.6mmHg, p=0.03, respectively).

Conclusions : Overall prevalence of CAN was higher in obese patients than in those with normal BMI or overweight. Obesity affects autonomic nervous system and may cause various complications associated with this condition. Sudoscan is easy, non-invasive and quick method to detect CAN in early stage. Further studies are necessary to approve this findings.

P17. INTEREST OF SLOW BREATHING TEST TO EVALUATE THERAPEUTIC EFFICACY AND ADHERENCE TO CONTINUOUS POSITIVE AIRWAY PRESSURE TREATMENT IN TYPE 2 DIABETES AND OBESE PATIENTS WITH OBSTRUCTIVE SLEEP APNOEA SYNDROME

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Objectives : We previously showed that the slow breathing test (SLBT) is a fast and inexpensive investigation for the detection of obstructive sleep apnoea syndrome (OSAS), and, compared to the gold standard polysomnography, offers good performances. We here tested in patients with OSAS whether SLBT was able to evaluate the efficacy of continuous positive airway pressure (CPAP) treatment and the patients compliance to this treatment.

Methods : In 36 patients, 26 with type 2 diabetes (age 59.5±10.9 yrs, BMI 34.9±3.0 kg/m^2, HbA1c 7.8±1.4%) and 10 nondiabetic obese (age 53.6±15.0 yrs, BMI 39.3±4.2 kg/m^2, HbA1c 5.5±0.4%), with evidence of OSAS on polysomnography, still treated, treated in the past with CPAP or who never utilized CPAP, we performed the SLBT consisting of 5 minutes of breathing at a frequency of 6 cycles/min. If patients developed apnoeas and/or hypopneas during the 10 minutes post-SLBT, the test was considered positive. All patients had performed two times, at least one year apart, the SLBT and Epworth Sleepiness Scale (ESS): 20 patients performed two times SLBT during treatment; in 5 patients, first SLBT before and the second one during treatment; in 6 patients both tests were performed without treatment; 5 patients were without treatment but had utilized CPAP in the past.

Results : Regarding SLBT, 12 patients were positive to both tests and 4 became positive (group 1), while 11 were negative to both tests and 9 patients became negative (group 2). Among the 16 patients of group 1, 7 were no longer using CPAP, 5 had poor adherence to treatment (< 5 hours/night) and only 4 patients had good adherence to treatment (> 5 hours/night) while among the 20 patients of group 2, all but one had good adherence to treatment (p=0.025). Regarding the second ESS, it remained or became negative in 70% of the patients in group 2 and 68% of the patients in group 1 (p=0.722). In group 2, BMI decreased at the time of the second SLBT (36.6±0.8 kg/m^2 pre, 35.0±1.3 kg/m^2 post, p=0.087), while it did not change in group 1 (35.7±2.1 kg/m^2 pre, 36.2±2 kg/m^2 post, p=0.768).

Conclusions : In diabetic and obese patients with OSAS, the SLBT may be used as a follow-up test to assess the efficacy of therapy with CPAP and is more accurate than ESS. Good adherence to treatment is associated with a trend towards BMI reduction.

P18. RELATIONSHIP BETWEEN THE SURVEY OF THE AUTONOMIC SYMPTOMS SCORE AND NORFOLK QOL-DN QUESTIONNAIRE IN ROMANIAN PATIENTS WITH DIABETES

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Objectives : The aim of this study was to assess the association between the Survey of the Autonomic Symptoms (SAS) score and autonomic score subscale of Norfolk Quality of Life (QoL) questionnaire, used previously for screening diabetic neuropathy (DN) in Romanian patients.

Methods : Patients with diabetes followed for at least 6 years (enrolled in previous Norfolk QoL-DN study) were evaluated in this study from 2018 at Podiatry Clinic from Cluj-Napoca, Romania. All patient responded to the self-administered Norfolk QoL-DN questionnaire and were investigated with SAS - a questionnaire with 11 questions for women or 12 questions for men with Yes/No answers for evaluating symptoms most frequently present in autonomic DN. Diabetic peripheral neuropathy (DPN) was assessed with Michigan Neuropathy Screening Instrument clinical examination (MNSIe).

Of 174 patients included in this study, 9 (5.2%) patients had type I diabetes, 165 (94.8%) had type II diabetes; 89 (51.1%) were male; with mean age: 66.68±8.69years and mean diabetes duration of 16.03±6.92years. According to MNSIe 104 (59.8%) patients had DPN (MNSIe≥2.5).

P18. RELATIONSHIP BETWEEN THE SURVEY OF THE AUTONOMIC SYMPTOMS SCORE AND NORFOLK QOL-DN QUESTIONNAIRE IN ROMANIAN PATIENTS WITH DIABETES

Results : Norfolk QoL-DN total score and all of its subscales, SAS score, SAS-total symptom impact (TIS) score and its subscales except sexual and urinary dysfunction were statistically significantly positive correlated with MNSIe score (r between 0.221 and 0.429, p≤0.003). SAS score, SAS-TIS and its subscales except sexual dysfunction were positively statistically significantly correlated with total QoL-DN score and all of its subscales (Table).

Conclusions : Norfolk QoL-DN questionnaire's autonomic item had good correlation with SAS-TIS score, with orthostatic and gastrointestinal dysfunction, but was less correlated (acceptable) with SAS score, sudomotor, vasomotor, urinary dysfunction, and not significantly correlated with sexual dysfunction.

Coefficients of Pearson correlation between SAS score and Norfolk QOL-DN Total and Subscale Scores in Romanian Patients with Diabetes Mellitus.

Pearson coefficient of correlation	Total QoL-DN	PFLF	Symptoms	ADLs	Autonomic	SFN	Mortality risk score
SAS score	0.613**	0.591**	0.496**	0.371**	0.473**	0.336**	0.615**
SAS-TIS score	0.661**	0.611**	0.572**	0.429**	0.617**	0.325**	0.658**
Orthostatic	0.448**	0.403**	0.401**	0.292**	0.556**	0.144	0.464**
Sudomotor	0.493**	0.455**	0.445**	0.328**	0.426**	0.233*	0.469**
Vasomotor	0.528**	0.494**	0.437**	0.347**	0.356**	0.377**	0.523**
Sexual dysfunction	-0.011	-0.007	-0.074	0.079	-0.028	-0.042	0.031
Gastrointestinal dysfunction	0.516**	0.462**	0.495**	0.274**	0.545**	0.313**	0.505**
Urinary dysfunction	0.351**	0.348**	0.267**	0.228*	0.352**	0.061	0.354**

Quality of life (QOL); Diabetic Neuropathy (DN); Physical Functioning/ large-fiber neuropathy (PFLF); Activities of daily living (ADL); Small fiber neuropathy (SFN); Survey of the Autonomic Symptoms (SAS); Total Symptom Impact (TIS); * 0.001≤p<0.05; ** p<0.001.

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P19. DIASTOLIC BLOOD PRESSURE RESPONSE TO HANDGRIP TEST AND ECHOCARDIOGRAPHIC PARAMETERS OF LEFT VENTRICULAR HYPERTROPHY – A RETROSPECTIVE ANALYSIS

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Objectives : Diagnosis of cardiovascular autonomic neuropathy (CAN) is still based on the standard cardiovascular autonomic reflex tests (CARTs). However, new guidelines do not recommend the diastolic blood pressure response to handgrip exercise being performed. In our previous study, an inverse relationship between handgrip test abnormality and the presence of hypertension was established. Furthermore, the association between hypertension and left ventricular hypertrophy is well known carrying risk of cardio- and cerebrovascular morbidity and mortality.
Aim of the present study was to assess the associations between the handgrip test and echocardiographic parameters in diabetic patients.

Methods : Our study involved 83 patients with diabetes (mean age: 62.9±11 years; 43.9% male; 9.7% with type 1 diabetes; 91.4% with hypertension; HbA_{1c}: 7.5±1.5%; BMI: 31.3±4.6 kg/m^2). Cardiovascular autonomic neuropathy was assessed by the CARTs, and all patients underwent echocardiography examination as well.

Results : CAN was confirmed in 38 cases (46.3%), handgrip test was abnormal in 31 patients (37.8%). Significant correlations between diastolic blood pressure response to handgrip test and left ventricular end-systolic (r=0.247 p<0.05) and end-diastolic (r=0.304 p<0.05) diameters were found. Diastolic blood pressure elevation showed an inverse proportion to the E/Ea value (feature of left ventricular compliance), but the correlation did not reach statistical significance (r=-0.346 p=0.06). No correlations with posterior wall thickness (r=0.125, p=0.35), left ventricular outflow tract velocity time integral (LVOT-VTI) and maximal velocity trough left ventricular outflow tract (LVOT-vmax) (r=0.429, p=0.12 and r=0.322, p=0.36) could be proven.

Conclusions : There are significant correlations between diastolic blood pressure response to handgrip test and left ventricular end-systolic and end-diastolic diameters. Our data provide more evidence on the association between the handgrip test and hypertension as well as hypertension-related end-organ damage.

P20. A CLINICAL SCREENING SCORE FOR THE RISK OF DIABETIC CARDIOVASCULAR AUTONOMIC NEUROPATHY IN TYPE 2 DIABETES

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Objectives : A practical approach to the wide under diagnosis of diabetic cardiovascular autonomic neuropathy (CAN) might consist in reducing the burden of a universal screening by identifying the patients at major risk as the candidates for CAN screening. This study was aimed at developing a suitable scoring system for CAN risk based on suggestions from literature and the associations between CAN and clinical variables observed in an unselected population with type 2 diabetes.

Methods : One hundred and six participants with type 2 diabetes (age 63±9 years, duration 11±8 years, HbA1c 7.1±1.4%, 70 males, 40 insulin-treated), free from conditions affecting autonomic function and beta-blockers treatment, underwent standard cardiovascular reflex tests (CARTs).

Results : Confirmed CAN based on 2 abnormal CARTs, present in 11.3% of participants, was associated in univariate logistic regression with retinopathy (P=0.0002), insulin treatment (P=0.0035), HbA1c ≥8% (P=0.0136), microalbuminuria (P=0.0153), resting heart rate ≥80 bpm (measured as the average heart rate obtained from two 10 second resting ECG recordings in lying position) (P=0.0259), and with lack of physical activity (P=0.04). A risk score was built, based on the strength of univariate associations and multivariate analysis, by giving a score of 3 to the presence of retinopathy, 2 to insulin treatment, 1 to HbA1c ≥8%, 1 to microalbuminuria, 1 to basal heart rate ≥80 bpm, and 1 to the absence of physical activity (range of this risk score: 0-9). This CAN risk score was associated with confirmed CAN (P<0.0001), was related to CARTs (deep breathing: rho: -0.43, P<0.0001; lying to standing: -0.24, P=0.0147; overall CARTs score: rho=0.47, P<0.0001), and showed a high diagnostic accuracy for both confirmed CAN and CAN [including confirmed and early CAN (based on ≥1 abnormal CART)]. The table shows the area under the ROC curve (AUC), sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV), and Likelihood Ratio Positive (LR+) and Negative (LR-) of CAN risk score at the cut-off of 4.

	AUC	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)	LR+	LR-
Confirmed CAN	0.89±0.049	83.3	74.5	29.4	97.2	3.26	0.22
CAN (early and confirmed)	0.84±0.052	77.8	77.3	41.2	94.4	3.42	0.29

Table. Diagnostic characteristics of CAN risk score for confirmed and early CAN.

Conclusions : This risk score for CAN (the first compared to the gold standard diagnosis of CAN), based on clinical variables, microangiopathic complications and resting heart rate, can be easily obtained in clinical practice and, if confirmed in a further validation study, may help in identifying individuals with type 2 diabetes at a higher risk of CAN to be referred for CARTs performance.

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P21. THE ASSOCIATION BETWEEN ELECTROCHEMICAL SKIN CONDUCTION AND NORFOLK QOL-DN QUESTIONNAIRE IN ROMANIAN PATIENTS WITH DIABETES

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Objectives : The aim of this study was to assess the association between electrochemical skin conduction (ESK) measured with Sudoscan (Impeto Medical, France) and scores measured with self-administered Norfolk Quality of Life (QoL) questionnaire, previously used for screening diabetic neuropathy (DN) in Romanian patients with diabetes.

Methods : In this study from 2018, 172 patients with diabetes, part of a prospective study started in 2012 were included. The patients were evaluated at the Podiatry Clinic from Cluj-Napoca, Romania. All patients responded to the self-administered Norfolk Quality of Life (QoL) questionnaire and were investigated with SUDOSCAN a device that allows non-invasive evaluation of sudomotor function. SUDOSCAN can be used also for early screening of autonomic cardiac neuropathy (CAN). Peripheral DN was assessed with Michigan Neuropathy Screening Instrument clinical examination (MNSIe).

Of 172 patients, 9 (5.2%) patients had type I diabetes, 163 (94.8%) had type II diabetes; 87 (50.6%) were male; with mean age: 66.55±8.64years and mean diagnosed diabetes age of 16.11±6.91 years. According to MNSIe 103 (59.9%) patients had peripheral DN (MNSIe≥2.5).

P21. THE ASSOCIATION BETWEEN ELECTROCHEMICAL SKIN CONDUCTION AND NORFOLK QOL-DN QUESTIONNAIRE IN ROMANIAN PATIENTS WITH DIABETES

Results : Significantly low ESK values (measured in microSiemens - µS) for both foot and hands were found in patients with peripheral DN compare with patients without peripheral DN (Table). The QoL total score and all subscales were significantly higher (high scores means worst QoL) in patients with peripheral DN (Table).
ESK foot value was significantly correlated with total QoL-DN score (r=-0.155, p=0.043), symptoms score (r=-0.167, p=0.029), activities of daily living (ADL) score (r=-0.166, p=0.029) and mortality risk score (r=-0.163, p=0.033). ESK hand value was significantly correlated with total QoL-DN score (r=-0.271, p<0.001), physical functioning/ large-fiber neuropathy (PFLF) score (r=-0.260, p=0.001), symptoms score (r=-0.203, p=0.008), activities of daily living score (r=-0.329, p<0.001) and mortality risk score (r=-0.276, p=0.002). Risk of CAN was significantly correlated with total QoL-DN score (r=0.232, p=0.002), PFLF score (r=0.226, p=0.003), symptoms score (r=0.232, p=0.002), and mortality risk score (r=0.234, p=0.002)..

Conclusions : Patients who have high Norfolk QoL-DN questionnaire scores (worst QoL) are likely to have a low level of ESK, both of them indicating the presence of DN.
Electrochemical Skin Conduction and QOL differences in between patients with and without DPN shown in SUDOSCAN evaluations (Mean ± SE), respectively, Norfolk QOL-DN Total and Subscale Scores (Mean ± SE) in Romanian Patients with Diabetes Mellitus.

Parameters	ROF	Without DPN (MNSIe<2.5) (n=69)	With DPN (MNSIe≥2.5) (n=103)	p
SUDOSCAN Foot value (µS)	-	77.45±0.77	71.05±1.40	0.001
SUDOSCAN Hand value (µS)	-	70.55±1.23	64.51±1.47	0.004
SUDOSCAN CAN risk score	0-100%	33.52±1.06	38.55±0.87	<0.001
SUDOSCAN Diabetic Nephropathy risk score	0-100%	59.41±1.71	52.11±1.18	<0.001
Total QOL-DN score	-4-136	8.99±1.40	26.17±2.33	<0.001
PFLF	-4-56	4.87±0.95	15.52±1.51	<0.001
Symptoms	0-32	2.52±0.30	5.43±0.44	<0.001
ADLs	0-20	0.72±0.32	2.44±0.40	0.002
Autonomic	0-12	0.77±0.15	1.53±0.20	0.006
SFN	0-16	0.10±0.05	1.25±0.24	<0.001
Mortality risk score	-4-72	4.91±0.90	15.35±1.32	<0.001

Standard errors (SE); Range of scores (ROF); Normative data (ND); Quality of life (QOL); Diabetic Peripheral Neuropathy (DPN); Autonomic cardiac neuropathy (CAN); Physical Functioning/ large-fiber neuropathy (PFLF); Activities of daily living (ADL); Small fiber neuropathy (SFN)

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P22. THE ASSOCIATION BETWEEN SKIN AUTOFLUORESCENCE AND NORFOLK QOL-DN QUESTIONNAIRE IN ROMANIAN PATIENTS WITH DIABETES

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Objectives : The aim of this study was to assess the association between advanced glycation endproducts (AGE) evaluated by autofluorescence of the skin (SAF) measured by AGE Reader (Groningen, The Netherlands) and the quality of life (QoL) in patients with diabetic neuropathy (DN) measured using self-administered Norfolk QoL-DN questionnaire in Romanian patients with diabetes.

Methods : A transversal study was performed in 2018, in which 174 patients with diabetes were included. All patients had been followed at least 6 years before as participants in an initial study started in 2012. The self-administered Norfolk QoL-DN questionnaire was applied and SAF was measured three times (in arbitrary units- AU) at forearm using the AGE Reader (Groningen, The Netherlands). The mean SAF was considered for this study. Clinical examination, section of Michigan Neuropathy Screening Instrument (MNSIe) was used for assessing peripheral DN.
Of 174 patients, 9 (5.2%) patients had type I diabetes, 165 (94.8%) with type II diabetes; 89 (51.1%) were male; mean age of 66.68±8.69years and mean diagnosed diabetes age of 16.03±6.92years. According to MNSIe, 104 (59.8%) patients had peripheral DN (MNSIe≥2.5).

Results : Statisticaly significant higher values of SAF were found in patients with peripheral DN (2.60±0.06 AU) than in patients without peripheral DN (2.25±0.07 AU), p<0.001.
SAF was significantly correlated with total QoL-DN score (r=0.155, p=0.041), physical functioning/ large-fiber neuropathy (PFLF) score (r=0.153, p=0.044), activities of daily living (ADL) score (r=0.168, p=0.027), mortality risk score (r=0.162, p=0.033) and with MNSIe score (r=0.305, p<0.001).

Conclusions : Patients who have high Norfolk QoL-DN questionnaire scores (worst QoL) are likely to have a high level of SAF, both of which might indicate the presence of peripheral DN.

P23. RESISTANT TO TREAT DIABETIC FOOT IN TYPE 1 DIABETIC PATIENT WITH RHEUMATHOID ARTHRITIS AND HALLUX VALGUS DEFORMATION: A CASE REPORT

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Case report : 51 year old female T1DM patient complained at the emergency room on the left leg pain accompanied by swelling, foot redness and ulcer between 3rd-4th fingers, which appeared 3 months ago, also unstable glycaemia. Patient's medical history documented 33 years (yrs) of T1DM, lastly treated with insulins: insulinum glarginum (Lantus) and insulinum lispro (Humalog) (under the scheme: long-acting insulin 18 U twice a day; short-acting insulin 12-12-12 U), and a history of rheumatoid arthritis (RA) (26 yrs), treated with methylprednisolone sufficiently to poor enough with standard doses of 4 mg bid. Diabetic complications: retinopathy (>26 yrs), polyangioneuropathy (22 yrs), nephropathy (7 yrs), hypoglycemic episodes (~once a month). Physical examination: disturbed vibratory and tactile sensation, weak pulse of a. dorsalis pedis bilaterally, deformed left foot fingers and chronic trophic ulcer with pus between 3rd-4th fingers; Lab: CRP 13,7 mg/l, erythrocyte sedimentation rate 35 mm/h, HbA1c% 7,9%. Left foot X-ray revealed foot fingers destruction and HV deformation; patient was hospitalized. Ulcers' bacterial culture showed Streptococcus aureus sensitive to oxacillin, intravenous oxacillin 2g and oral metronidazole 500 mg/d. were administered. Decision to perform left foot fingers amputation from 2nd to 5th finger was made shortly after osteomyelitis was diagnosed. Despite the successful amputation, 4 months later patient required another partial amputation of right foot 2nd finger due to recurrent ulcer. Even though after amputations, patient's feet care was performed regularly by the diabetologist nurse, pressure relieving methods for feet and orthopedic shoes were assured, patient still suffered from repeating ulcers in feet, especially in left foot in the HV area where, according to a patient, orthopedic shoes put the most pressure. Patient's hospitalizations became regular not only due to poor glycaemic control and rheumatoid arthritis but also due to non-healing ulcers in feet. Following another hospitalization due to trophic ulcer in HV area and after one more percutaneous transluminal angioplasty (3rd in 5 years), decision to perform HV surgery was made by DF console after 4 years since last amputation. Arthrodesis of the right hallux with 2 Kinker wires was performed successfully and the healing process required 2 yrs of weekly/monthly visits to diabetologist nurse for wound clearing, necrotizing/keratosis masses removal till patient completely recovered. It is noted, that ulcers in left foot did not appeared since.

Conclusions : Resistant to treat DF ulcers may appear for DM patients with additional health conditions, especially those with arthropathies, such as RA and HV deformation, causing DF overload with pressure for bony feet structures. Inappropriately adapted footwear may be the reason for such-alike injuries for HV patients with DF.

P24. ETHNIC DIFFERENCES IN INSULIN SENSITIVITY BETWEEN FILIPINO IMMIGRANT WOMEN AND KOREAN RESIDENTS IN KOREA: FILIPINO WOMEN'S DIET AND HEALTH STUDY

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Objectives : Due to the globalization of Korea, the number of immigrants to Korea is increasing. Studying immigrants is important not only because immigrants are becoming an integral part of the Korean population, but also to provide an opportunity to estimate the contribution of ethnicity in the development of diabetes mellitus. We aimed to compare lifestyle and biochemical markers related to glucose metabolism among immigrated Filipino women and native Korean women, and to investigate the cause of the differences in the two groups.

Methods : Baseline data of 461 participants from the Filipino women's diet and health (FiLWHEL) study were matched with data from participants of the Korea National Health and Nutrition Examination Survey (KNHANES) by age and body mass index (BMI). The homeostatic model assessment (HOMA) for insulin resistance (HOMA-IR) and β-cell function (HOMA-β) values were calculated and compared between the two groups.

Results : Native Korean women had a higher fasting plasma glucose than immigrated Filipino women after adjusting for age and BMI. Also, HOMA-β was lower in native Korean women than immigrated Filipino women. However, HOMA-IR was not significantly different between native Korean women and immigrated Filipino women. In conditional logistic regression analysis, the odds ratio of the impaired fasting glucose (IFG) group was 2.68 for Korean women compared with Filipino women (95% CI = 1.60-4.48) after adjusting for age, BMI, smoking, alcohol, education, and marital status. For insulin resistance and β-cell dysfunction, the odds ratios were 0.66 (95% CI = 0.45-0.97) and 3.50 (95% CI = 2.35-5.20), respectively, for Korean women compared with Filipino women after adjusting for age, BMI, smoking, alcohol, education, and marital status. When we performed covariance analysis (ANCOVA) in the IFG group, the least square mean of HOMA-β was significantly different between Korean women and Filipino women. However, the least square mean of HOMA-IR did not show a significant difference between Korean women and Filipino women.

Conclusions : Our findings showed that native Korean women had a higher fasting plasma glucose after adjusting for age and BMI. Also, native Korean women had lower HOMA-β than immigrated Filipino women. Therefore, lower HOMA-β value might be associated with higher fasting plasma glucose in native Korean women.

P25. TYPE 2 DIABETIC PATIENTS WITH PERIPHERAL NEUROPATHY DISPLAY AN INCREASED RISK OF DEVELOPING HYPERTENSION

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Objectives : Arterial stiffness, a measure of macrovascular damage predictive of poor cardio-vascular outcomes, is strongly related to type 2 diabetes (T2D) and hypertension (HT). We previously showed that, in normotensive T2D patients, peripheral neuropathy (PN) is associated with increased arterial stiffness independently of HT. Some epidemiological studies suggest that HT is a risk factor of PN. The aim of the present study was to examine whether normotensive T2D patients with PN were exposed to an increased risk of developing hypertension and to evaluate the role of arterial stiffness in this risk.

Methods : In our previous study, we included 447 T2D patients. Among this population, 66% were hypertensive and 53% displayed a PN. Of 150 normotensive patients, we followed-up 80 T2D patients for 8.9±2.7 years. Arterial stiffness was measured by carotid-femoral pulse wave velocity (PWV), and PWV values above the 90th percentile age- and blood pressure-adjusted reference range were considered as pathological. PN was diagnosed by clinical criteria (according to Toronto consensus) and patients were considered HT if treated by anti-hypertensive drugs or if blood pressure was ≥140/90 mmHg.

Results : During the follow-up, 41 out of the 80 patients developed HT, more often in PN+ group as compared to PN- one (20/28=71.4% vs 21/52=40.4%, p=0.008), independently of the class of PWV (abnormal PWV: 7/15=46.7% vs normal PWV: 13/26=50% p=0.837). Patients were separated in two groups according to the development or not of HT. At baseline the two groups were similar for duration of diabetes, BMI, HbA1c, PWV class, prevalence of nephropathy and diabetic retinopathy, and the duration of follow-up. The patients who developed HT were older (57.9±7.8 vs 54.2±11.3 years, p=0.003), with a greater proportion of men (63.4% vs 38.5%, p=0.026). A multivariate analysis confirmed the association between PN and HT development, independently of age, gender and PWV class (OR: 3.910; 95% CI: 1.086-14.079; p=0.037).

Conclusions : In T2D patients, PN is associated with arterial stiffness. T2D patients with PN show an increased risk of developing HT independently of arterial stiffness. PN could contribute to arterial stiffness and to the development of HT by promoting media calcifications and altering vascular tonus.

P26. LESIONS OF THE SMALL FIBERS OF THE AUTONOMIC NERVOUS SYSTEM AND GRADATION OF THE DIABETIC FOOT RISK IN PATIENTS WITH DIABETES

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Objectives : Foot lesions are a common, serious and costly complication of diabetes. The examination of the foot allows the evaluation of the diabetic foot risk according to the international classification ranging from grade 0 to grade 3. The sweat glands are innervated by the small fibers C of the autonomic nervous system and the evaluation of the plantar sudoromotor function allows detection and follow-up of peripheral vegetative neuropathy. Our objective was to evaluate the association between the grade of diabetic foot risk and a marker of the severity of small fiber neuropathy estimated by a non-invasive, objective, rapid and quantitative method.

Methods : 647 patients from two diabetology departments and including, 503 patients with type 2 diabetes and 89 with type 1, had gradation of the risk for diabetic foot in the course of the treatment and a Sudoscan test allowing assessment of sudoromotor function of the feet through measurement of the electrochemical skin conductance (ESC, µS). Thresholds for ESCs were : <70µS: neuropathy; <50 µS severe neuropathy. In addition Sudoscan test was performed in 276 obese patients without neuropathy.

Results : The characteristics of the patients were: 42% of women, age: 57 ± 14 years, HbA$_{1c}$: 8.0 ± 1.6%. Feet ESC decreased significantly with grade; grade 0: 72 µS [20]; grade 1: 65 µS [21]; grade 2: 60 µS [32]; grade 3: 28 µS [23] (results expressed in median [inter-quartile], p <0.0001 Kruskal-Wallis test) (Figure). The feet ESC were <70 µS in 44% of patients of the whole population with grade 0 (asymptomatic), while it was in 47 % of patients with type 2 diabetes and in 31 % of patients with type 1 diabetes. In addition, the feet ESC were <50 µS in 15% of patients of the whole population with grade 0, while it was in 16 % of patients with type 2 diabetes and in 6 % of patients with type 1 diabetes In patients with type 2 diabetes, among the patients' characteristics, there was no association with BMI, beta-blockers or tobacco, but ESC <50 µS were more frequent in patients with a history of severe hypoglycemia in the patient during the previous year (39 vs. 17%) (p = 0.0013).

Conclusions : This study revealed a link between the neuropathy of the small fibers of the autonomic nervous system and the gradation of the diabetic foot risk carried out during the treatment, confirming the clinical interest of Sudoscan. This work needs to be completed on a larger population and by studying the possible predictive character of the neuropathy of small fibers on the development of future lesions of the foot.

P26. LESIONS OF THE SMALL FIBERS OF THE AUTONOMIC NERVOUS SYSTEM AND GRADATION OF THE DIABETIC FOOT RISK IN PATIENTS WITH DIABETES
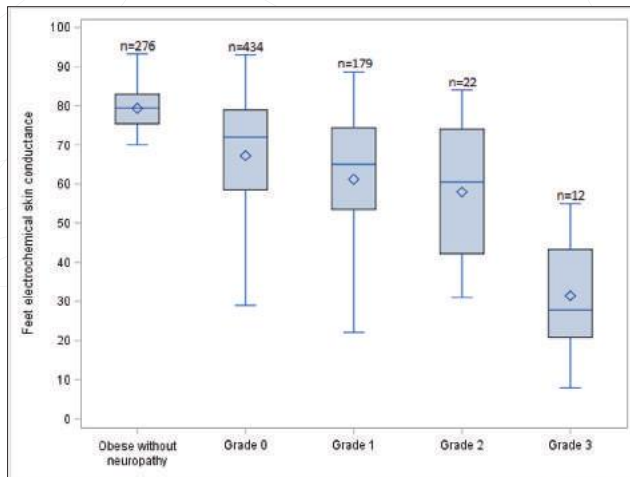

Figure 1.
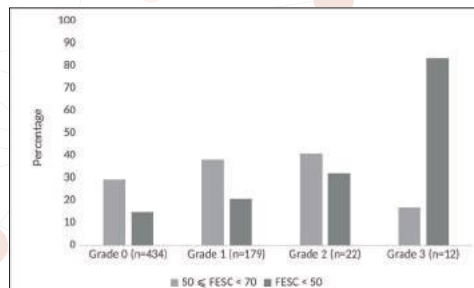Feet Electrochemical Skin Conductances according to grade of diabetic foot risk

Figure 2.
Percentages of patients with small fiber neuropathy according to grade of diabetic foot risk

P27. THE MICROBIOME IN THE SKIN OF THE FOOT, DIABETIC PERIPHERAL NEUROPATHY, PLANTAR SUBCUTANEOUS STIFFNESS AND PEAK PRESSURE GRADIENT, RISK FACTORS TO PROMOTE INFECTIONS AND WOUNDS: NEW DIAGNOSTIC OBJECTIVES TO PREVENT WOUNDS AND INFECTIONS

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Objectives : Examine diabetic patients (DM 1,2) without clinically evident skin infections, the possible inter-relationships between subtypes of peripheral nerves fibres alteration (SPNA), abnormally high pressures under the feet, stiffness of subcutaneous tissue (SCT) and microbiome skin conditions, as possible factors that could predispose overall to chronic neuropathic ulcers and/ or recurrent infection in the skin.

Methods : 21 subjects DM1,2 both genders, evolution time of 12 years + - 5, glycosylated haemoglobin (HbA1c) 8.8 + -7 Body Mass Index (BMI) 28 + -4. Groups without neuropathy (N), 1 vibration perception threshold altered (VPT) on both feet (PNAB) and 2 or more SPNA on both feet (PNABH). SPAN was detected by Quantitative Sensory testing NerveCheck Master (NCM) and Neuropathy Disability Score (NDS). Footwear instrument with sensors (F-scan, insole sensor system), 4 measured pressure in Newton, during walking pressure (T), pressure/body mass index (TBMI) in both 1st, 2nd metatarsal and 1st phalanges (MET). Peak plantar pressures (PPP), Pressure time Integral (PTI) and Peak pressure gradient (PPG) were examined. The subcutaneous cellular tissues (SCT) were measured in the retromalleolar region with longitudinal section of the stiffness wax expressed as % on both feet, with 3 points at each end A/B of the SCT. Likewise, no localized infectious pathologies were detected in the lower limbs assessed by C-reactive protein, absence of leukocytosis, cutaneous normality of temperature and by Wood's lamp. Analysis of microbiome skin from interdigital folds of toes of the feet and heel to identified bacterial by Genomic DNA PCR amplification of the V4 region of bacterial 16S rRNA genes. For each Amplicon quantitation, pooling, and pyrosequencing. *Statistics by analysis de correlacion linear de Pearson*.

Results : Proportional correlation group N 1st metatarsal right A in T and TBMI. PNAB reverse correlation 1st metatarsal left at point B T. Finally, PNABH left inverse correlation at A for PPP, PTI, TBMI TBMI, TBMI TBIMMI respectively and right at A for PTI at T and TBMI and at B for all values, PPP, PTI and PPG both in T and TBMI (table 1) . The microbiome diversity between the N and PNAB groups was not significant, while PNABH shown reduced diversity. There are significant differences in the correlation between the increased rate of Staphylococcus in PNABH in relation to PNAB and N (0.001), in addition to a significant decrease in the rate of Corynebacterium and Acinetobacter of the PNABH Group in relation to PNAB and N. The latter groups have shown increased of Lactobacillus in relationship to PNABH group.(table 2).

P27. THE MICROBIOME IN THE SKIN OF THE FOOT, DIABETIC PERIPHERAL NEUROPATHY, PLANTAR SUBCUTANEOUS STIFFNESS AND PEAK PRESSURE GRADIENT, RISK FACTORS TO PROMOTE INFECTIONS AND WOUNDS: NEW DIAGNOSTIC OBJECTIVES TO PREVENT WOUNDS AND INFECTIONS

Conclusions : These data emphasize the importance of inter-relationships between SPNA, abnormally PPP, PTI and specially PPG in diabetic patients who have STC high pressures under the feet, stiffness of subcutaneous tissue stiffness in SCT and microbiome skin conditions, as possible factors that could predispose overall to chronic neuropathic ulcers and / or recurrent infection in the skin. Moreover, the pathogenic role of high plantar pressures is crucial in the presence of established clinical neuropathy diverse and partially distinct microbial community in 3 skin compartment. Should be considered that it is a sample of small size to draw final conclusions. Limitation of this study is that, although commonly used in microbiome, the V4 region of the 16S rRNA gene does not allow differentiation between Staphylococcus aureus and other Staphylococcus species found on skin, such as Staphylococcus epidermidis.

P28. NORMAL HIGH HbA1c IS A RISK FOR ABNORMAL PAIN THRESHOLD IN A GENERAL JAPANESE POPULATION

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Objectives : Diabetic polyneuropathy (DPN) is a slowly progressive sensory predominant neuropathy characterized by a distal "dying back" type. In this type of neuropathy, small fibers in the distal foot are often first to be affected. The symptom of DPN may be apparent even in prediabetes like impaired glucose tolerance. It is unsettled, however, whether marginal glucose intolerance is implicated in the onset and progression of small fiber dysfunction. In this study, we explored the relationship between glycated hemoglobin levels (HbA1c) and pain sensation in a general Japanese population.

Methods : A population-based study of 894 individuals (352 men, 542 women; average age 53.8±0.5 years) and 55 subjects with impaired fasting glucose (IFG) in the 2017 Iwaki project were enrolled in this study. Blood chemistry and urinalysis were measured. Individuals with diabetes were excluded. Relationships between pain threshold for intraepidermal electrical stimulation (PINT) and parameters associated with metabolic syndrome were statistically examined.

Results : PINT was elevated with increasing of age in female but not in male. Average PINT (mA) was increased in IFG subjects (n=55, 0.20±0.03) compared to normoglycemic/non-IFG subjects (n=894, 0.15±0.11) (p<0.01). It was comparable between IFG and a group of normal high HbA1c (5.9-6.4%). Univariate linear regression analyses showed no influence of gender, triglyceride or cholesterol on the value of PINT. In contrast, there were significant correlations between PINT and serum HbA1c (ß = 0.120, p <0.001). Adjustments for the multiple clinical measures confirmed positive correlation of PINT with HbA1c (ß = 0.075, p=0.049).

Conclusions : Subjects with normal high HbA1c exhibited an elevated PINT in a non-overt diabetic Japanese population which may be useful for the screening of subclinical DPN.

P29. WHAT ELSE (COULD THERE BE), BEYOND A FOOT ULCER

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Objectives : People with diabetes who develop foot ulcers are at more risk of dying prematurely than those without the wounds, according to a study published in the November 2012 edition of *Diabetologia*. Diabetic foot infections in the presence of peripheral neuropathy and/or vascular compromise can have devastating results in the patient's overall treatment. Ulcers have a better chance of healing if they're cared for by a specialized team. According to our experience, dermatologists and oncologists should be part of this team.

Methods : In our outpatient clinic, 30 type 2 diabetes patients are examined daily, 5 days per week. On average, among them, each day 7 patienst with foot ulcers receive a regular once weekly treatment. Patients with ulcers are visited until the ulcer heals. We estimate, that 91 foot ulcers are examined each month. We calculate that in 2016, 1092 foot ulcers were regularly seen by our team, which consists of 3 diabetologists and 6 nurses. This year, there were 2 foot ulcers, that deserved our special attention and were referred to dermatologists and later to oncologists. Here we present their course of treatment.

Conclusions : A differential diagnosys is important in case of nonspecific signs and course of foot ulcer treatment, a malignant disease might be underlying, promptly recognised and succcesfully treated.

Abstract of the course of treatment No1
A 69 years old T2D patient with absent protective sensation and perserved blood supply presented with a foot ulcer under the head of 5th MT bone on L foot on Sept 20th, 2016, whithin 2 weeks of the begining. After a week, because of suspected exsofitic growth, observed on a small part of the ulcer surface, she was referred to excision in order to obtain a histological diagnosis. Instead of performing the excision, the surgeon referred the patient to a vascular surgeon, as a normal, obvious ulcus pedis sin.
On October 14th, we observed a 0,2 x 0,3 cm wide subcheratotic haematoma on the median ulcer edge and on November 4th, some pigmentations appeared on the ulcer edge and she was referred to a dermatologist. On November 25th, an excision was performed and malignant melanoma was histologically confirmed: Breslow 2,6 with 5 mitoses per square mm, removed tightly in healthy. On December 21st, she was visited at oncologic clinic, there were no suspicious formations on and around the scar, no popliteal or inguinal nodes were present. A reexcision of the ulcer layer was performed with a biopsy of the sentinelle node. 2 metastases were identified, 2 and 3 mm wide, located under the capsule and in parenchima, respectively. No capsular overgrowth was detected. The indication for surgical treatment of inguinal and retroperitoneal nodes was confirmed and done. PET/CT analysis for distant metastases of melanoma was performed and the patient was included in EAGLE study. 6 L inguinal nodes were removed and a consequent inflammation was heald with a combinaton

P29. WHAT ELSE (COULD THERE BE), BEYOND A FOOT ULCER

of two antibiotics. Due to a lymphoedema, treatment continued with physiotherapy and L leg bandaging. She comes regularly to our clinic. According to dermatologic guidelines, a visit each 6 months is mandtory during the first 5 yers after the melanoma diagnosis.
On April 19th, the apperance of scar on L foot and in L inguinum is normal. A slihgt edema of L leg is present.

On April 19th, the apperance of scar on L foot and in L inguinum is normal. A slihgt edema of L leg is present.

Abstract of the course of treatment No2
A 90 years old T2DM patient came to our clinic on January 21st, 2016. Since November, she was observing a haematoma on distal phalange of 3rd toe on R foot. A vascular surgeon confirmed haematoma caused by shoe pressure and concomittant threatment with anticoagulant therapy for chronic atrial fibrillation. The treatment began and continued until August 17th 2018, when she was reffered to dermatologist because of a suspicious exofitic growth on the surface of the shallow wound on whole 3rd toe. A biopsy was performed and malignant melanoma confirmed, an infiltrate was already present on metatarsum of R foot. An inguinal node of the size of a walnut was present on right side. The patient was reffered to oncology department, where MTP amputation on 3rd toe and limphadectomy were performed in October 2018. Both wounds healed per secundam. At her last visit in oncology clinic on April 19th, all performed laboratory analyses were assessed as normal.

P30. PREULCERATIVE LESIONS IN DIABETIC INPATIENTS IN LATIN AMERICAN HOSPITALS

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Neuropathy is one of the most prevalent chronic complications of diabetes mellitus (DM) and the main cause of diabetic foot (DF). Its clinical manifestations include pain and sensitivity alteration, although it may be asymptomatic. Sensory neuropathy may cause foot ulceration by making feet insensitive, and motor neuropathy may cause muscle atrophy which leads to bone deformities and potential preulcerative lesions. These clinical changes predict the occurrence of DF ulcers.

Objectives : The purpose of this study was to describe the prevalence of preulcerative lesions in diabetic inpatients in Latin American hospitals and relate them to patients' characteristics.

Methods : This transversal study consisted of analyzing data from inpatients during one day in September and October 2017. Medical records were reviewed and inpatients were asked about personal data. All feet were examined in diabetic patients by physicians and classified using Wagner´s score, looking for ulcers (>=Wagner 1) or preulcerative lesions (Wagner 0); the last included structural bone deformities or calluses that constituted a risk for further ulcers. Chi squared, t test and Wilcoxon Mann-Whitney were used for analyzing variables.

Results : Data from 11357 inpatients in 135 health centers of 9 Latin American countries were analyzed. The prevalence of DM was 18.6% (CI 95%; 17.9-19.3). The prevalence of preulcerative lesions (W0) was 51.5% and the prevalence of ulcers (W>=1) was 27.8%. Only 20.7% of patients with DM had no lesions. Table 1. DF was the reason for admission in 3.7% of all inpatients and 20% of those with DM. Considering all diabetic inpatients, those with preulcerative lessions (W0), were little younger than patients with lesions >=Wagner 1 (W1), with a median age of 62 years vs 63 years(p<0.005). Duration of DM was shorter in patients with preulcerative lesions than in patients with ulcers W>=1 (p<0.001) Table 2. W0 patients had history of amputations in 5.9% of cases, while W>=1 patients in 36.8% (p<0.001) Table 3. Patients in W0 group had been hospitalized during less days than those in W>=1 group (p<0001).

Conclusions : Prevalence of W0 lesions was 51.5% and prevalence of W>=1 lesions was 27.8% in our study, which means that half of DM patients had deformities consistent with the presence of motor and/or sensitive neuropathy, which increase the risk of foot ulcers. Shorter evolution of DM in W0 group reflects the chronology of events and the importance of diagnosis at this stage. Only 20.7% of inpatients with DM appeared to have no feet at risk, but it´s probable that if we had used a method of screening for sensitive neuropathy, the proportion of patients with increased risk should also have risen.

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P30. PREULCERATIVE LESIONS IN DIABETIC INPATIENTS IN LATIN AMERICAN HOSPITALS

Country	Health centers n(%)	Patients with DM n	Prevalence of preulcerative lesions Wagner 0 n (%)	Prevalence of DF grade Wagner >=1 n (%)
Total	**135**	**2115**	**1090 (51,5)**	**587 (27,8)**
Argentina	114 (77,0)	1210	653 (54)	303 (25,0)
Bolivia	5 (3,7)	39	18 (46,2)	11 (28,2)
Chile	2 (1,5)	121	32 (26,4)	40 (33.1)
Ecuador	1 (0,7)	8	4 (50)	4 (50,0)
Mexico	11 (8.1)	307	197 (64,2)	81 (26,4)
Nicaragua	1 (0,7)	7	4 (57,1)	2 (28,6)
Peru	7 (5.2)	316	125 (39,6)	114 (36,1)
Uruguay	1 (0,7)	52	45 (86,5)	7 (13,5)
Venezuela	3 (2,2)	55	12 (21.8)	25 (45,5)

DM= Diabetes mellitus DF=Diabetic foot

Table 1.

Diabetes prevalence and diabetic foot rate among inpatients in Latin America
Data from 11357 inpatients. *DM=diabetes mellitus*

Wagner grade	Gender* f/m n(%)	p	Type 2 diabetes n(%)*	Patients n (%)	Median duration of DM (years)	p
0	527(49.3) /543(50.7)	<0.001	994 (92.3)	1053 (65,1)	10,8	<0,001
>=1	219(38,0)/358(62.0)		540(93.5)	565 (34,9)	14,3	

Duration time of DM in Wagner 0 lessions are statistically different from Wagner >=1 lessions. Data from 1618 patients.
* Data from 1647 patients. *P=ns*

Table 2.

Median duration time of DM in different Wagner´s grade

Wagner grade	Total (n)	Age	p	Minor amputation n(%)	p	Major amputation n(%)	p
W0	1069	62	<0.005	35 (3,3)	<0,001	28 (2,6)	<0,001
W>=1	577	63		139 (24,1)		73 (12,7)	
total	1646			174 (10,6)		101 (6,1)	

Data from 1646 patients

Table 3.

Age and amputation history in patients with preulcerative lessions (W0) or ulcers classified as Wagner 1 grade or more (W>=1)

P31. CLASSIFYING PAIN SCORES USING MAGNETIC RESONANCE IMAGING IN PAINFUL DIABETIC NEUROPATHY

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Objectives : We have demonstrated altered brain structure and functional connectivity which could serve as a possible Central Pain Signature (CPS) for painful DN. The challenge now is to apply this potential biomarker at an individual level so that it can be used for diagnostic purposes. To this end, we used machine learning approaches to clinically validate the CPS model by assessing if it can accurately classify painful DN patients with high and low pain scores

Methods : 53 patients with painful DN underwent detailed clinical and neurophysiological assessments. The NTSS-6 questionnaire was used to quantify pain severity and high pain was defined as pain scores > 7. All subjects underwent 3D, T1 weighted and RS functional MRI brain scan (3T, Achieva, Phillips Healthcare). We used machine learning algorithms [support vector machines (SVM)] to differentiate pain severity based on RS functional connectivity and structural/volume data. Different machine learning algorithms [support vector machines (SVM), random forest, logistic regression and ADABoost] with multiple feature selection techniques [recursive feature elimination (RFE) principle component analysis (PCA) and weighted feature selection] was used to differentiate pain severity based on RS functional connectivity and structural/volume data. All classifiers were hyperparameter tuned and a nested cross validation method applied to determine the accuracy (sensitivity and specificity) and thresholded using a bootstrap test (q<0.05; FDR-corrected).

Results : There was no age or gender difference (p > 0.05) between high and low pain groups. The SVM classifier was able to classify painful DN patients based on their pain intensity with 94% accuracy (AUC 0.98). The positive and negative predictive values were 0.80 and 1.00 respectively. The F1 scores for predicting high pain and low pain were 0.89 and 0.96 respectively. The brain regions identified as the best classifier parameters were the left and right postcentral gyri, thalami, and anterior and posterior cingulate cortices.

Conclusions : This proof-of-concept study demonstrates that a simple, 15-minute MR brain scan can accurately classify painful DN patients according to pain intensities. The brain regions identified may serve as specific targets for future drug trials as modulation of activation in these target areas may provide evidence that a compound has target engagement or is attenuating nociceptive processing. These findings serve as important data for neuroimaging as an objective, non-invasive biomarker in painful DPN opening a new area for further research.

P32. VALIDATION OF THE SIMPLE DIAGNOSTIC CRITERIA OF DIABETIC POLYNEUROPATHY IN JAPAN

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Objectives : The simple diagnostic criteria (SDC) proposed by Diabetic Neuropathy Study Group in Japan has been widely accepted in our country. However, the diagnostic ability has not yet been fully validated. In the present study, we examined the usefulness of SDC in diagnosis of diabetic polyneuropathy (DPN).

Methods : We evaluated admitted 114 diabetic subjects who were diagnosed as DPN employing three independent decision rules consisting SDC: physical signs and symptoms (PHY), nerve conduction study (NCS), or coefficient of variation of RR interval (CV_{R-R}) on electrocardiogram (CVRR).

#1. PHY rule: satisfied any two or more of following three items: the presence of symptoms considered to be due to DPN, the decrease or disappearance of bilateral Achilles tendon reflexes, and decreased vibration in the bilateral medial malleoli.
#2. NCS rule: one or more nerve conduction abnormalities in two or more nerves out of 12 peripheral nerves.
#3. CVRR rule: less than 2% of CV_{R-R}
The diagnostic accuracy was evaluated using the NCS rule as the reference standard.

Results :
1. Ninety-six subjects (84.2%) diagnosed as DPN. The proportions of DPN were 37.7% for PHY, 74.6% for NCS, and 43.9% for CVRR.
2. The diagnostic accuracy of PHY and/or CVRR.

	Sensitivity (%)	Specificity (%)	Positive Predictive value (%)
PHY	44.7	82.8	88.4
CVRR	49.3	72.4	84.0
PHY and CVRR	65.9	62.1	83.6

Conclusions : Diagnosis by NCS showed the highest prevalence. The sensitivity of PHY was improved by a combination with CVRR. DPN can be identified effectively utilizing SDC.

P33. THE SEVERITY OF PERIPHERAL NEUROPATHY AND INCIDENCE OF OTHER DIABETIC COMPLICATIONS IN DIABETES NEUROPATHY CENTER OF UNIVERSITY OF DEBRECEN

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Objectives : The prevalence of diabetes mellitus is significantly increasing worldwide. Distal sensory polyneuropathy (DSPN) is the most common and earliest detectable microvascular compication in diabetes mellitus. Due to its diverse clinical appearance and atypical symptoms, DSPN is often recognized in an advanced stage.

Methods : In our study the data of 431 patients who were examined using the NEUROMETER® between 2014 and 2018 at the Diabetes Neuropathy Center of University of Debrecen were processed and the correlations between cardiovascular and microvascular complications, laboratory parameters and the severitiy of DSPN were investigated.

Results : The average age of patients was 63.4 years, 62 % were women and 92 % had type 2 diabetes. The average duration of diabetes was 13.7 years. Cardiovascular disease was diagnosed in 42 % of patients. The incidence of retinopathy was 12 %, that of persistent microalbuminuria was 16 %. Despite DSPN complaints neuronal damage waas not detectable in 19 %; in the examined patients 49% had mild, 19 % had moderate and 13 % had severe neuropathy. Diabetes-related neurological damage was more serious both in presence of diabetic retinopathy (p<0.001) and microalbuminuria (p<0.001). The incidence of these microvascular complications and the severity of DSPN showed a significant positive correlation (p<0.001). There was no correlation between the severity of peripheral neuropathy and the development of cardiovascular diseases. Based on our investigation we have not found any correlation between the progression of DSPN and cardiovascular complications, although the progression of diabetic neuropathy indicated the development of other microvascular diseases.

Conclusions : Peripheral neurological examination using the NEUROMETER® is appropriate for controlling the DSPN status and the establishment of severity of neuropathy determines the quality of life in diabetic patiens. Among these patients the risk of cardiovascular disease may be assessed by Ewing's tests for autonomic nervous system function.

P34. THE PREVALENCE OF DIABETIC PERIPHERAL NEUROPATHY AMONG THE FUTSAL PLAYERS PARTICIPATING IN THE DIAEURO 2015 CHAMPIONSHIP

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Objectives : To assess the prevalence of diabetic peripheral neuropathy (DPN) among futsal players participating in the 2015 edition of the European Futsal Championship for people with diabetes (DiaEuro).

Methods : In this cross-sectional study were included 139 amateur/professional futsal player, from 15 European and Central Asia countries. The evaluation was made base on the data extracted from the standard medical certificate completed by each player's diabetologist. The official participation criteria were: age ≥ 18 years old, a diagnosis of diabetes and no other severe comorbidities that could contraindicate this type of sport.

Results : Of 139 subjects, 129 (92.8%) had type 1 diabetes, 9 (6.47%) had type 2 diabetes and 1 (0.72%) had latent autoimmune diabetes of adulthood. 8 players were on oral medication and 132 (94.96%) were under insulin treatment as follows: 100 (71.94%) on a basal bolus regimen, 31 (22.3%) on insulin pump and one person (0.72%) on mixed insulin. Regarding the diabetes microvascular complication, 13 (9.35%) individuals were diagnosed with DPN, 8 (5.75%) with retinopathy and 6 (4.31%) with nephropathy. Furthermore, only one subject out of the 13 with DPN received treatment with alpha-lipoic acid for his condition.

Conclusions : In our analysis of 139 amateur/professional futsal players with diabetes, we found a prevalence of 9.35% of DPN. To our knowledge, this is the largest study to evaluate the prevalence of DPN in a distinct population of amateur/professional futsal players with diabetes.

Parameter	Interval (min-max)	Mean	STDEV
Age (years)	18 - 52	26.69	±7.54
Diabetes duration (years)[*]	1 – 34	11.16	±7.29
Last A_1c (%)[**]	5.1 -10.8	7.48	±1.07
BMI (kg/m²)[*]	18.36 – 44.47	24.37	±3.29

Table.
The general characteristics of the study population; *Data were available for 138 subjects; **Data were available for 122 subjects; STDEV=standard deviation; A1c= glycated hemoglobin; BMI=body mass index

P35. CHARCOT-FOOT IN A 25 YEARS OLD PATIENT WITH TYPE 1 DIABETES – CASE REPORT

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Type 1 diabetes mellitus, diabetic neuropathy, hypothyreosis, urinary tract infection combined with renal abscess, foot ulcer and Charcot-foot were recorded in the 25 years old female patient's medical history.

The patient was admitted to our department due to very high blood glucose levels. In the last few years, her HbA1c levels were 10-13 %. The last HbA1c value was 13%. Some months previously, , insulin glargin was changed for an increased dose of insulin degludec. After that she had more hypoglycemic episodes and the presence of the Somogyi effect could be proven by her blood glucose data.

In 2017 December, she suffered a stab wound on her sole, and thus started using her right foot in an abnormal manner. In 2018 February, her right ankle became swollen and in May a foot X-ray showed fractured calcaneus and deformed talus. Due to these lesions, her foot arch has collapsed. CT showed extensive bone destruction in the calcaneus, osteolytic nodules and disorganized joints, as the consequences of Charcot-foot.
Neuropathy tests showed hypaesthesia in case of the right foot, as well as a medium-grade cardiovascular autonomic neuropathy.

During our observation her blood glucose results decreased and became more stable as a result of reduction of the dose of insulin degludec. A ten days long alpha-lipoic acid infusion treatment was applied. She tried to rest her right leg and her orthosis was in progress. Furthermore, parenteral pamidronate therapy was recommended.
Our case demonstrates that long term poor glycaemic control might contribute to diabetic neuropathy and the development of Charcot foot, even in young patients with type 1 diabetes mellitus. Moreover, we have to teach our patients about the early and severe microvascular complications of diabetes as neuropathy, foot ulcers and Charcot-foot.

P36. INDEPENDENTLY ASSOCIATION OF PERIPHERAL POLYNEUROPATHY WITH SERUM HIGH-DENSITY LIPOPROTEIN (HDL) CHOLESTEROL AFTER BARIATRIC SURGERY: A COHORT STUDY

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Background : The most common neurological complication reported after bariatric surgery (BS) is peripheral polyneuropathy (PPN). However, there is poor evidence about the incidence of PPN post BS.

Objectives : To evaluate incidence of PPN in non-diabetic severe obese subjects after laparoscopic bariatric surgery (LBS) and to seek for the presence of risk factors already described for diabetic PPN and serum levels of vitamin B12.

Methods : In this prospective cohort study, 322 obese non-diabetic subjects undergoing LBS were evaluated for PPN by using the Michigan Neuropathy Screening Instrument (MNSI) before and after 6 months of LBS. They were divided according to presence (+) or absence (−) of PPN on baseline. Patients with non-metabolic causes of PPN were excluded.

Results : The prevalence of pre-LBS PPN was 21.4% and decreased to 8.7% post-LBS. Evaluation of the PPN (+) group (n = 69), showed an incidence of post-LBS PPN of 20.3% (n = 14). In the PPN (−) group (n = 253), the incidence of post-LBS PPN was 5.5% (n = 14) and it was independently associated with lower serum levels of high-density lipoprotein cholesterol (HDL-C) (p = 0.001). The PPN risk increased from 7.4 to 8.6% at each 1 mg/dL decrease in HDL-C.

Conclusions : Prevalence of PPN decreased 6 months after LBS. New cases of PPN appeared post-LBS and they were independently associated with low HDL-C serum levels.

P37. MAGNESIUM PREVENTS CARBONYL STRESS-MEDIATED NEURONAL DAMAGE VIA UPREGULATION OF INTRACELLULAR GLUCOSE METABOLISM: A BACK-TRANSLATIONAL APPROACH

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Objectives : The lack of effective treatments for diabetic sensorimotor polyneuropathy (DSPN) demands the search for new strategies to combat or prevent the condition. We previously showed that serum magnesium (Mg^{2+}) strongly interacts with plasma methylglyoxal-dependent nerve dysfunction in type 2 diabetes patients. Here we aimed to assess under experimental conditions the cellular mechanisms of both hypomagnesemia-mediated methylglyoxal (MG) formation and Mg^{2+} supplementation in preventing neuronal injuries induced by carbonyl stress.

Methods : Human neuroblastoma cells (SH-SY5Y) and primary mouse neuronal cells were used to characterize cellular pathways of increased/decreased methylglyoxal formation. Downregulation of specific proteins was performed using siRNA transfection. Cells and cell lysates were assessed using immunofluorescence, quantitative Western blot analyses, cell viability assays, and ELISA. CellTiter-Glo® Luminescent Cell Viability Assay was used to measure ATP concentration.

Results : Mg^{2+} supplementation attenuated the neurotoxic effect of MG treatment in SH-SY5Y cells and resulted in a higher neurite count and neurite average lengths ($P<0.0001$). The protective effect against MG neurotoxicity was Mg^{2+} specific, because supplementation with the divalent cations zinc (Zn^{2+}) or manganese (Mn^{2+}) had no effect on neurite count (untreated: 0.95±0.09 [mean±SD]; MG: 0.82±0.06; MG/Mg^{2+}: 1.03±0.06; MG/Zn^{2+}: 0.82±0.10; MG/Mn^{2+}: 0.84±0.04 neurites/cell) or neurite average lengths (untreated: 31.7±5.6 [mean±SD]; MG: 25.2±1.9; MG/Mg^{2+}: 34.4±4.1; MG/Zn^{2+}: 25.3±3.2; MG/Mn^{2+}: 24.7±2.9 μm). Characterization of protein extracts revealed that the protective effect of Mg^{2+} supplementation was due to a reduction of detrimental methylglyoxal-mediated protein modifications ($P<0.05$). Further analyses revealed, that Mg^{2+} had no effect on protein modifications mediated by supplemented methylglyoxal but reduced the intracellular formation of methylglyoxal by more than 80% ($P=0.002$). The decreased formation of intracellular methylglyoxal-mediated protein modifications was mainly due to increased glycolysis resulting in reduced concentration of triosephosphates, the primary source of methylglyoxal formation. Mg^{2+} supplementation resulted in enhanced ATP production by more than 80% in SH-SY5Y and more than 100% in primary mouse neuronal cells (both $P<0.0001$).

Conclusions : Magnesium supplementation induced upregulation of intracellular glucose metabolism and reduced the intracellular formation of methylglyoxal. Since all thiamine-dependent enzymes involved in glucose metabolism require magnesium as a cofactor, magnesium and thiamine co-treatment merits further investigation in DSPN.

P38. A1C VARIABILITY IS ASSOCIATED WITH DIABETIC PERIPHERAL NEUROPATHY IN ADULTS WITH TYPE 1 DIABETES PARTICIPATING IN POZNAN PROSPECTIVE STUDY (PoProStu)

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Objectives : Despite great progress in the diagnosis and treatment of type 1 diabetes (T1D) diabetic neuropathy is still common complication of diabetes. Glycemic variability (GV) is regarded to be related to the development of late diabetic complications. The aim of our study was to investigate the association between A1c variability and diabetic peripheral neuropathy (DPN) in a prospective observation of T1D patients treated equally from the beginning with intensive functional insulin therapy - Poznan Prospective Study (PoProStu).

Methods : The study included 81 T1D subjects (51 men), aged 33 (IQR: 29-38) years, diabetes duration 10 (9-11) years (ClinicalTrials.gov identifier: NCT01411033) observed prospectively during 10-years follow-up period. End point was the development of DPN diagnosed based on clinical diagnosis of probable neuropathy. GV was computed as mean A1c, standard deviation (SD-A1c) and coefficient of variation (CV-A1c) of all A1c measurements from 10 years of the observation. Only patients who were present at 4 follow-up visits together with at least ten A1c measurements during these 10 years were taken into the final analysis.

Results : At follow-up complete data on A1c variability has been obtained from 37 patients (24 men), aged 43 (39-48) years, diabetes duration 20 (19-21) years. DPN was diagnosed in 8 subjects (22%). Median number of A1c measurements was 15 (13-21). Data on GV from 10-years observation were: mean A1c 7.75 (7.05-8.12)%, SD-A1c 0.63 (0.50-0.76)% and CV-A1c 0.08 (0.06-0.09). Patients with DPN in comparison to subjects without DNP had: higher mean A1c 8.56 (7.39-10.59) vs 7.2 (7.0-7.9)%, p=0.003; higher SD-A1c 0.86 (0.72-1.14) vs 0.54 (0.49-0.68)%, p=0.0008 and higher CV-A1c 0.09 (0.08-0.15) vs 0.08 (0.06-0.09)%, p=0.04. In multivariate regression analysis mean A1c and SD-A1c were associated with DPN: OR 2.95, 95%CI: 1.56-5.56, p<0.001 and OR 0.17, 95%CI: 0.05-0.64, p=0.007 respectively, independently from age and gender.

Conclusions : A1c variability is positively associated with diabetic peripheral neuropathy in long-term observation of type 1 diabetic subjects and might play a future role in clinical risk assessment.

P39. IS ALPHA LIPOIC ACID HYPE OR HOPE FOR CARDIOVASCULAR AUTONOMIC NEUROPATHY? – A CASE REPORT

Camelia Larisa Vonica[1] , Fitărău Maria-Antonia[2], Kiss Alexandra Timea[2], Norina Alinta Gavan[3].

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Objectives : Cardiovascular autonomic neuropathy (CAN) is considered to be one of the major chronic complications of diabetes mellitus (DM). In its initial stages is reversible, but frequently it is lately diagnosed and becomes an important predictor for higher morbi-mortality and a negative factor for life quality.

Methods : 63-year-old male with a 12-year history of well controled type 2 DM presented to our clinic with complaints of decreased exercise tolerance, blurred vision when standing up and toe numbness. He was 1,75m, 90 kylograms, 29 kg/m^2 BMI and an HbA1c of 5.9% with oral medication. Firstly, the Toronto clinical neuropathy scoring system was applied in order to diagnose and evaluate the severity of diabetic peripheral neuropathy (DPN). The next step was investigation of sudomotor function with SUDOSCAN through measurement of electrochemical skin conductance (ESC) of hands and feet. Further, Ewing's cardiovascular reflex tests including diastolic blood pressure (BP) upon sustained handgrip, heart rate response (HRR) to Valsalva maneuver, HRR to deep breathing, HRR and decrease in systolic blood pressure upon standing up, had been performed to assess CAN. It is worth mentioning that screening test for peripheral arterial disease (PAD) using Ankle-Brachial Index were in normal ranges.

Results : The Toronto clinical neuropathy score was 1 point and showed the absence of DPN. SUDOSCAN results illustrated moderate reduction of ESC suggesting peripheral sudomotor dysfunction and the CAN risk score (CANRS) was 40, raising high suspicion for CAN. Finally, CAN diagnosis, defined as 2 abnormal results of Ewing's cardiovascular reflex tests was confirmed. After 3 months of treatment with 600 mg of Alpha lipoic acid once a day, the patient was reevaluated, through SUDOSCAN and Ewing tests and the evolution was favourable, considering the new CANRS 31 and ESC increased their values.

Conclusions : CANRS evaluated by SUDOSCAN should be used for early screening of CAN, because of its good diagnotic efficacy and less timeconsuming compared to Ewing tests. Nonetheless, patients at high suspicion for CAN should undergo Ewing test for CAN confirmation. Alpha lipoic acid has demonstrated a good efficacy in reducing the signs and symptoms of CAN in DM.

P39. IS ALPHA LIPOIC ACID HYPE OR HOPE FOR CARDIOVASCULAR AUTONOMIC NEUROPATHY? – A CASE REPORT

	SUDOSCAN				
Before	**CONDUCTANCES**	**FEET SCORE**	**HANDS SCORE**	**CANRS**	**NEPHRO Score**
alpha	LEFT	82 μS	51 μS		
lipoic	RIGHT	80 μs	61 μS	40	63
acid	EWING TESTS				
treatment	**HRR-deep breathing**	**HRR-Valsalva**	**HRR-Tilt test**	**BP handgrip**	**BP standing up**
	2	1.11	1.02	51	0
	SUDOSCAN				
After	**CONDUCTANCES**	**FEET SCORE**	**HANDS SCORE**	**CANRS**	**NEPHRO Score**
alpha	LEFT	63 μS	53 μS		
lipoic	RIGHT	67 μs	61 μS	31	63
acid	EWING TESTS				
treatment	**HRR-deep breathing**	**HRR-Valsalva**	**HRR-Tilt test**	**BP handgrip**	**BP standing up**
	3	1.08	1.01	35	7

Table 1.
Results of SUDOSCAN and Ewing tests before and after Alpha lipoic acid treatment

P40. PERIPHERAL NERVE PRESERVATION OF METFORMIN COMPARE TO ALPHA LIPOIC ACID (ALA) IN STZ/HFD INDUCED MILD DIABETIC RATS

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Objectives : The association of metformin with diabetic peripheral neuropathy is unclear until now. Therefore, we investigated whether metformin gave beneficial or harmful effect on the peripheral nerves in diabetes in the respect of diverse neuronal parameters of small and large nerve fibers.

Methods : Animals were divided into 4 groups (n=7-10) according to the intervention as follows: Normal, diabetes (DM), DM+metfomin (100mg/kg), and DM+alpha lipoic acid (ALA) (100mg/kg). After 12 weeks, diverse sensory thresholds of mechanical, heat, and pressure stimuli were assessed. Repeated sensory tests and biochemical parameters including of vitamin B12 and oxidative stress and immunohistochemistry comparison of peripheral nerves were performed at 24 weeks.

Results : At 24 weeks, glucose levels of animals were 102.5±7.4, 311.8±50.78, 251.3±42.3, and 289.1±59.49 (normal, DM, DM with metformin, and DM with ALA, respectively). Both DM with metformin and DM with ALA groups showed less sensitive thresholds for von frey monofilament at 12 weeks and showed less blunted response at 24weeks compared with DM group (P<0.05). At 24 weeks, both DM with metformin and DM with ALA groups showed less sensitive thresholds compared with DM group (P<0.05). Quantitative comparisons of peripheral nerve by intraepidermal nerve fiber density (IENFD) were similar between DM with metformin and DM with ALA group (11.83±0.07 vs. 12.37 ±1.82) and all of these two groups showed preserved IENFD significantly compared with DM group (8.46 ±1.98) (P<0.05). Sciatic nerve morphology of experimental animals showed similar trend to IENFD according to the groups in the respect of axonal diameter, myelin sheath thickness, and myelinated fiber diameter as figure 1.

Conclusions : Metformin gives beneficial effect with comparable effect to ALA in the preservation of peripheral nerves in mild diabetes. Therefore, further researches using different doses of metformin and severe diabetes model need to performed to clarify the association of metformin with diabetic peripheral neuropathy.
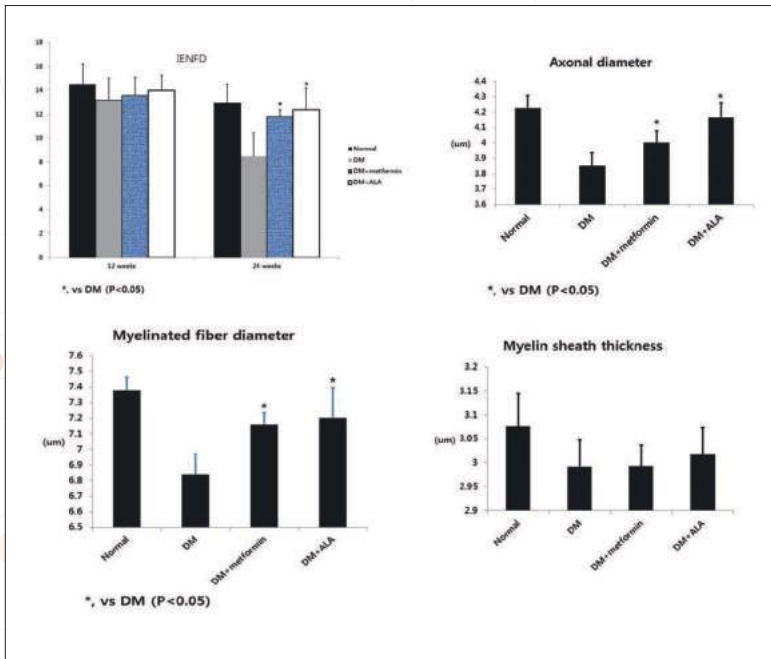
P40. PERIPHERAL NERVE PRESERVATION OF METFORMIN COMPARE TO ALPHA LIPOIC ACID (ALA) IN STZ/HFD INDUCED MILD DIABETIC RAT

P41. GAMMA-LINOLENIC ACID VERSUS α-LIPOIC ACID TO TREAT PAINFUL DIABETIC NEUROPATHY IN ADULTS: A 12-WEEK, RANDOMIZED, NON-INFERIORITY, DOUBLE PLACEBO TRIAL

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Objectives : Diabetic peripheral neuropathy (DPN) is the most common complication in patients with type 2 diabetes (T2DM) but remains therapeutic challenges for its painful symptoms. This multicentre, parallel group, double-blind, double-dummy, randomized noninferiority trial was conducted to evaluate the efficacy and safety of γ-linoleic acid (GLA) compared to α-lipoic acid (ALA) at 12 weeks in type 2 diabetic patients with painful DPN.

Methods : One hundred patients aged 20-75 years with painful DPN received either GLA (320 mg/d) and placebo or ALA (600 mg/d) with placebo during 12 weeks. Primary outcome was the mean change over 12 weeks of pain intensities measured by Visual Analogue Scales (VAS) and Total Symptom Scores (TSS). Secondary outcomes were changes of the Michigan Neuropathy Screening Instrument (MNSI) symptom questionnaires (MNSIQ) and physical examination (MNSIE) scores, current perception threshold, modified Brief Pain Inventory (mBPI)-DPN, and EuroQol-5 dimensions (EQ 5D). And Safety was assessed by recording treatment-emergent adverse drug reactions.

Results : Seventy-three patients had completed the study and were available for per protocol (PP). No statistical differences were observed for demographics and mean baseline VAS and TSS between the 2 groups at baseline. PP analysis showed that a significant reduction in the mean VAS and TSS scores in both groups compared to baseline but no difference between groups. The treatment difference for VAS (95% CI) between two groups was -0.65 (-1.526, 0.213) and the upper bound of the 95% CI did not exceed the predefined noninferiority margin ($\delta 1=0.51$). For TSS, treatment difference was -0.05 (-1.211, 1.101) but the upper bound of the 95% CI crossed the noninferiority margin ($\delta 2=0.054$). Measures of secondary outcomes were improved from baseline with no significant between-group difference. GLA and ALA were well tolerated without any serious adverse event associated with treatments.

Conclusions : GLA treatment in patients with painful DPN were noninferior to ALA in reducing the pain intensity measured by VAS over 12 weeks with tolerable safety profiles.

P42. EFFECT OF GOOD GLYCEMIC CONTROL ON THE DEVELOPMENT OF DIABETIC PERIPHERAL NEUROPATHY IN A RAT MODEL OF TYPE 2 DIABETES

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Introduction : There is no treatment for diabetic peripheral neuropathy (DPN). Current clinical guidelines emphasize good glycemic control, which has limited effect in type 2 diabetic patients. The aim of this study was to investigate if glycemic control also has limited effect on the development of DPN in a commonly used rat model of type 2 diabetes.

Methods : 12-week old male Sprague-Dawley rats were fed a normal chow diet (Control; n=16) or a 45% high-fat diet (DIO; n=74). After 8 weeks, the DIO animals received streptozotocin (STZ; 31 mg/kg) to induce diabetes. Four weeks after diabetes induction the STZ-DIO group was allocated into three treatment groups; STZ-DIO vehicle (n=19), STZ-DIO low-insulin (n=22) and STZ-DIO high-insulin (n=22). Blood glucose (BG) was monitored weekly. After 12 weeks of treatment thermal nociception using Hargreaves' Test and intraepidermal nerve fiber density (IENFD) were assessed to investigate small fiber damage while large fiber damage was assessed by motor nerve conduction velocity (MNCV).

Results : Mean BG during treatment period was higher in all three STZ-DIO groups compared to Control (P<0.001). Treatment with insulin (high and low dose) lowered BG in a dose-dependent manner. After 12 weeks of treatment, STZ-DIO vehicle and STZ-DIO low-insulin had increased thermal sensitivity compared to Control. IENFD was significantly lower in STZ-DIO vehicle and STZ-DIO low-insulin compared to both Control and STZ-DIO high-insulin. A tendency towards lower IENFD was observed in STZ-DIO high-insulin (P=0.09) compared to Control. No difference in MNCV was found between groups.

Conclusions : In summary our data suggest that good glycemic control is associated with less or delayed small fiber damage. However, 16 weeks of diabetes was not enough to cause large fiber damage in this study.

	Control (n=15)	STZ-DIO vehicle (n=14)	STZ-DIO low-insulin (n=21)	STZ-DIO high-insulin (n=20)	Overall P-value
Thermal nociception (sec)	10.7±3.2[A]	6.2±1.9[B]	7.3±3.5[B]	8.6±2.9[AB]	P<0.001
IENFD (profiles/mm)	9.0±2.5[A]	3.4±1.4[B]	4.3±2.1[B]	7.0±3.1[A]	P<0.001
MNCV (m/sec)	34.7±5.0	33.4±5.5	32.8±5.1	33.6±7.4	0.8

Table 1.
Data is presented as mean and standard deviation. Values sharing the same superscript letter are not statistically different. P <0.05 is considered significant

P43. HYPOGLYCEMIA AND HYPERGLYCEMIA ENHANCE OXIDATIVE STRESS THROUGH POLYOL PATHWAY IN SCHWANN CELLS: NOVEL ANTIOXIDATIVE MECHANISMS OF ALDOSE REDUCTASE INHIBITORS

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Objectives : Hypoglycemia due to diabetes treatment and postprandial hyperglycemia could be involved in the development of diabetic complications. However, the effects of hypoglycemia and glucose fluctuation on diabetic neuropathy remain unclear. We previously reported that recurrent short-term hypoglycemia and glucose fluctuation induced apoptosis and oxidative stress through endoplasmic reticulum (ER) stress in Schwann cells. In this study, we investigated the effects of aldose reductase inhibitor on hypoglycemia/hyperglycemia-induced apoptosis and oxidative stress in Schwann cells, and the induction of antioxidative enzymes by an aldose reductase inhibitor was also examined.

Methods : 1) Immortalized adult mouse Schwann (IMS32) cells were exposed to five different conditions such as normal glucose (NG) (5.5mM glucose), constant low glucose (LG) (2.5mM glucose), constant high glucose (HG) (25mM glucose), intermittent low glucose (ILG) (2.5mM glucose for 1 h, 3 times a day) and intermittent high glucose (IHG) for 3 days. 2) Cell viability was evaluated by MTT assay and oxidative stress was measured by TBARS assay. 3) Protein expressions of caspase-3, Cleaved caspase-3, Bcl-2, and aldose reductase were evaluated by Western blotting. 4) mRNA expressions of antioxidative enzymes were determined by quantitative RT-PCR. 5) Cells were treated with epalrestat, an aldose reductase inhibitor.

Results : 1) LG, HG, ILG and IHG decreased cell viabilities and increased TBARS levels. 2) High glucose (HG and IHG) and low glucose (LG and ILG) increased cleaved caspase-3, an apoptotic marker protein, and reduced Bcl-2, an antiapoptotic protein. 3) Epalrestat ameliorated cell death and oxidative stress which were induced by LG, HG, ILG and IHG. 4) Protein expression of aldose reductase was increased by LG, HG, ILG and IHG. 5) Epalrestat increased mRNA of antioxidative enzymes, HO-1 and catalase.

Conclusions : These findings indicate that recurrent short-term hypoglycemia and glucose fluctuation induced apoptosis and oxidative stress through polyol pathway in Schwann cells, and that aldose reductase inhibitor exerts its effects not only through the inhibition of polyol pathway, but also through the induction of antioxidative enzymes.

P44. EFFECT OF MITOQUINONE (MITO-Q) ON NEUROPATHIC ENDPOINTS IN AN OBESE AND TYPE 2 DIABETIC RAT MODEL

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Objective : This study sought to determine whether the addition of Mito-Q in the diet is an effective treatment for peripheral neuropathy (PN) in animal models of pre-diabetes and type 2 diabetes. Unlike other anti-oxidative stress compounds investigated as a treatment for PN, Mito-Q will specifically target the mitochondria. Even though Mito-Q has been shown to reduce oxidative stress generated by the mitochondria there have been no studies performed of the effect of Mito-Q on PN induced by diet-induced obesity or type 2 diabetes.

Methods : Diet-induced obese (12 weeks after high fat diet) or type 2 diabetic rats (12 weeks of high fat diet and 4 weeks after the onset of hyperglycemia) were treated via the diet with Mito-Q (0.93g/kg diet) for 12 weeks. Afterwards, glucose utilization, vascular reactivity of epineurial arterioles to acetylcholine and neuropathy related endpoints (see below) were examined.

Results : The addition of Mito-Q to the diets of obese and diabetic rats improved motor and/or sensory nerve conduction velocity, thermal nociception, intraepidermal nerve fiber density and cornea sensitivity. Surprisingly, treating obese and diabetic rats with Mito-Q did not improve glucose utilization or vascular reactivity to acetylcholine.

Conclusions : These studies imply that mitochondrial dysfunction contributes to peripheral neuropathy in animals modeling pre-diabetes and diabetes. However, improvement in PN following treatment with Mito-Q was not associated with improvement in glucose utilization or vascular reactivity of epineurial arterioles to acetylcholine.

Condition	MNCV (m/sec)	SNCV (m/sec)	Thermal nociception (sec)	IENF (profiles/mm)	Corneal sensitivity (cm)	Cornea nerve fiber length (mm/mm^2)
CONTROL	50.1 ± 1.6	37.2 ± 1.4	11.3 ± 0.5	21.8 ± 0.4	5.6 ± 0.1	8.1 ± 0.2
OBESE	52.7 ± 1.4	30.9 ± 1.1[a]	17.2 ± 0.7[a]	17.5 ± 0.4[a]	4.3 ± 0.1[a]	4.5 ± 0.4[a]
OBESE + MITO-Q	51.2 ± 1.7	34.6 ± 0.6	12.1 ± 0.4[b]	17.8 ± 0.2[a]	4.8 ± 0.2[a]	7.2 ± 0.4[b]
DIABETIC	40.9 ± 1.4[a,b]	30.1 ± 0.8[a]	20.1 ± 1.4[a]	14.0 ± 0.2[a,b]	4.3 ± 0.1[a]	4.2 ± 0.2[a]
DIABETIC + MITO-Q	48.9 ± 2.9[c]	33.8 ± 0.6	13.3 ± 0.8[c]	17.8 ± 0.4[a,c]	5.1 ± 0.2[c]	6.1 ± 0.4[a,c]

Data are presented as the mean ± S.E.M. a P < 0.05 compared to control rats; b P < 0.05 compared to obese rats; c P < 0.05 compared to diabetic rats. Parentheses indicate the number of experimental animals

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The Airport Josep Tarradellas Barcelona-El Prat is only 25km away from Melia Sitges Hotel. It is easy to get there by Taxi.
There are taxi ranks opposite the arrivals areas of terminal T1 and terminals T2 A, T2 B and T2 C. The approximate taxi ride fare until Sitges is 65€/70€.

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Attendees can collect the congress kit at the Registration Desk, placed at the ground floor next to the main entrance to Melia Sitges Hotel. All participants are requested to wear their congress badge during the whole conference. Accompanying persons, not registered as such, are not allowed to access to coffee break and lunches at the Conference nor to the social activities and gala dinner.

CONFERENCE HALL

The Symposiums, oral conferences and Young investigators oral presentations will take place at the Conference Center area, in Meeting room Tramuntana 1.

POSTERS

Tramuntana 2, Conference Center Area
Set Up Time: Presenters are requested to fix posters on September 13th, from 9h00 to 18h00.
Dismantling Time: presenters are requested to withdraw posters at the end of the meeting on September 16th from h. 12.15 to h. 13.30. The Organization will remove and eliminate all posters not withdrawn on time by presenters.

EXHIBITING AREA and COFFEE BREAKS

Tramuntana Hall, Conference Center

SLIDE CENTER

Speakers are requested to deliver presentations not later than two hours before the presentation time to our support team at the Neurodiab help desk located at the Tramuntana meeting rooms hall. Presentations must be in PowerPoint, 4:3. Slide. Help desk opens 30 minutes before the start of the sessions. Morning presentations can be delivered the day before.

REGISTRATIONS

ON LINE REGISTRATION possible until September 3rd
https://neurodiab2019.com/registration/
ON SITE REGISTRATION: Registration desk at the entrance of the Melia Sitges Hall. Payment can be made through credit card (Visa, Mastercard, Amex) or cash at the registration desk. Relevant invoice will be sent via e-mail in pdf.

WIFI

Free wifi is available in common areas, guest rooms and meeting rooms. Codes will be delivered at the hotel check-in desk.

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The Certificate of Attendance is available on request at the Neurodiab Registration Desk and will be sent by email after the congress.

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