28th ANNUAL MEETING
OF THE DIABETIC NEUROPATHY STUDY GROUP
OF THE EUROPEAN ASSOCIATION FOR THE STUDY OF DIABETES (EASD)

NEURODIAB

4 TO 7
SEPTEMBER
2018

SHERATON PARCO DE' MEDICI HOTEL

ROME
ITALY

www.neurodiab2018.com

FINAL PROGRAM

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www.neurodiab.eu

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Simona Frontoni

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University of Rome Tor Vergata
Rome, Italy
Endocrinology and
Diabetes - San Giovanni
Calibita Fatebenefratelli
Hospital, Rome, Italy

NEURODIAB 4 TO 7 SEPTEMBER 2018 SHERATON PARCO DE' MEDICI HOTEL ROME ITALY www.neurodiab2018.com

Dear Friends and Colleagues,

on behalf of the Local Organising Committee, it is a great pleasure for me to welcome you to Rome to participate in the **28th Annual Meeting of NEURODIAB**.

As in past editions, the meeting will include oral and poster sessions, but also keynote lectures and symposia, covering both experimental and clinical aspects in the field of diabetic neuropathy.

A special attention will be paid to young researchers, giving them the opportunity to present their research activities and bringing new scientific understandings and solutions for diabetic neuropathy.

All in the warm, friendly and unconventional atmosphere that has always characterized our Neurodiab meetings.

We really hope you'll enjoy the meeting!

Simona Frontoni
Chairman of Neurodiab

Fabiana Picconi
On behalf of the Local Organising Committee

NEURODIAB 2018 FACULTY

Praveen Anand, *London - United Kingdom*
Henning Andersen, *Aarhus - Denmark*
Angelo Antonini, *Padua - Italy*
Luciano Bernardi, *Helsinki - Finland*
Simona Frontoni, *Rome - Italy*
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Eirik Søfteland, *Bergen - Norway*
Vincenza Spallone, *Rome - Italy*
Abd Tahrani, *Birmingham - United Kingdom*
Solomon Tesfaye, *Sheffield - United Kingdom*
Andrea Truini, *Rome - Italy*
Tamás Várkonyi, *Szeged - Hungary*
Prash Vas, *London - United Kingdom*
Mark Yorek, *Iowa City - United States of America*
Dan Ziegler, *Düsseldorf - Germany*

PROGRAM OVERVIEW

NEURODIAB 4 TO 7 SEPTEMBER 2018 SHERATON PARCO DE' MEDICI HOTEL ROME ITALY www.neurodiab2018.com

Tuesday, 4 September 2018

13.00-14.00 Registration & Coffee

14.00-14.30 Welcome
Simona Frontoni

14.30-15.30 Welcome of the Authorities

15.30-17.30 **Oral Session**
Young investigators oral session
Chairs: **Henning Andersen and Simona Frontoni**

Wednesday, 5 September 2018

08.00-08.30 **Keynote Lecture**
Prediabetic neuropathy
Chair: **Peter Kempler**
Speaker: **Nicolaos Papanas**

08.30-10.00 **Oral Session**
Pathogenesis
Chairs: **Peter Kempler and Ariel Odriozola**

10.00-10.15 Coffee break

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Speaker: **Praveen Anand**

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Chairs: **Rodica Pop-Busui and Mark Yorek**

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Chairs: **Peter Kempler and Solomon Tesfaye**

Autonomic neuropathy: impact on carbohydrate metabolism and therapeutical challenges
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Speaker: **Andrea Truini**

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Appropriate approaches to the treatment of painful neuropathy: the role of oxycodone/naloxone
Speakers: **Angelo Antonini and Solomon Tesfaye**

11.15-13.15 **PARALLEL POSTER SESSIONS**

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Poster session
Treatment
Chair: **Prash Vas**

Poster session
Pathogenesis/Basic Science
Chair: **Louis Premkumar**

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DAILY PROGRAM

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Wednesday, 5 September 2018

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Prevalence of painful neuropathy in Italy
Chair: **Tamas Várkonyi**
Speaker: **Andrea Truini**

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Epidemiology and diagnosis
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Chair: **Abd Tharani**

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ORAL ABSTRACTS

O1 CLINICAL AND GENETIC FACTORS CONTRIBUTING TO PROTECTION FROM NEUROPATHY IN EXTREME DURATION PATIENTS WITH TYPE 1 DIABETES.

Azmi S.*[1], Ferdousi M.[1], Donn R.[1], O"Sullivan J.[1], Petropoulos I.[2], Ponirakis G.[2], Alam U.[3], Marshall A.[1], Sankar A.[1], Asghar O.[1], Boulton A.[1], Soran H.[1], Efron N.[4], Malik R.[1]

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OBJECTIVES:

Individuals with Type 1 Diabetes Mellitus (T1DM) for more than 50 years (medallists) represent a unique cohort of patients who may be protected from developing complications. We aim to assess neuropathy in these patients and identify factors that my offer protection from complications, .

METHODS:

Thirty-three medallists age (63.7±1.4 years), duration of diabetes (58.5±0.8 years) and HbA1c (65.9±2.1 mmol/mmol) underwent detailed assessment of neuropathy. 8/33 individuals with minimal evidence of neuropathy underwent exome sequencing.

RESULTS:

Medallists had a significantly lower cholesterol (P<0.001), HDL-C (P=0.03), triglycerides (P=0.001) and LDL-C (P<0.001) and higher HbA1c (P<0.001) with a significantly lower eGFR (P=0.005) and higher ACR (P=0.01). Medallists with minimal neuropathy had a shorter duration of diabetes (p=0.006), lower alcohol consumption (p=0.04), lower total cholesterol (p=0.04) and LDL (p=0.02), lower ACR (p<0.001) and higher eGFR (p=0.001) compared to medallists with neuropathy. They also had a lower neuropathy symptom profile (p=0.002), vibration perception threshold (p=0.02), warm threshold (p=0.05) and higher peroneal amplitude (p=0.005) and velocity (p=0.03), heart rate variability (p=0.001), corneal nerve fibre density (p=0.001), branch density (p<0.001) and length (p=0.001), compared to medallists with neuropathy. Targeted enrichment and sequencing was performed on 200 ng of DNA extracted from peripheral blood and sequence data was mapped with BWA software with the hg19 human genome as a reference. Variants were called using GATK v2.4.7 software and filtered out if they were non-functional in dbSNP138 (unless seen in HGMD) and in our in-house variant database. Exome sequencing, replicated by Sanger sequencing failed to identify any unique variant in medalist's without neuropathy.

CONCLUSIONS:

Medallists with minimal complications, particularly neuropathy, have a lower total cholesterol, LDL and alcohol consumption, but no evidence of any unique genetic variant contributing to this protection.

O2 STRENGTH AND BALANCE TRAINING IN PATIENTS WITH DIABETIC PERIPHERAL NEUROPATHY IMPROVES FUNCTIONAL STATUS BUT NOT QUALITY OF LIFE

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OBJECTIVES:

To test the effectiveness of a structured strength and balance training intervention in improving health related quality of life (HRQoL) and functional status in patients with diabetic peripheral neuropathy (DPN)

METHODS:

The study was a parallel group randomized controlled trial of 2 months of once weekly home-based strength and balance training with 143 DPN patients (70 intervention, 73 control). Participants aged 40-79 years, with physician diagnosed type 2 diabetes and peripheral neuropathy (neurothesiometer reading greater than 25 V and/or positive monofilament test in 2 or more sites in either foot) were recruited from outpatient clinics at 5 centres. Outcomes were assessed at baseline, 2 months and 6 months. Primary outcomes were change in physical component summary (PCS) score (SF 36 v2) and health utility score (EQ5D). Secondary outcomes were change in functional status. Functional status assessment included measurement of muscle strength at ankle, range of motion at knee, static balance, functional tasks (timed up and go, five times sit-to-stand, functional reach) and activities-specific balance confidence. Mean differences in scores between groups were compared using mixed models.

RESULTS:

Of the 143 participants enrolled and randomized, 14 (5 intervention, 9 control) were lost to follow up. The final intention-to-treat (ITT)analysis included 67 participants on each arm. There were no differences in baseline characteristics between the groups, except in terms of gender (Table 1). On ITT analysis, adjusted for gender, time and baseline covariate, there were no significant differences between groups on the primary outcomes (Table 2). There were significant improvements in muscle strength, range of motion, five times sit-to-stand and balance confidence.

CONCLUSIONS:

Short term structured strength and balance training produced sustained improvements in functional status at 6 months, but not HRQoL. We have previously reported that functional status, and specially balance confidence, are important correlates of HRQoL in patients with DPN. However, the magnitude of improvement in functional status in our study may not have been large enough to have an impact on HRQoL. Longer-term and more intensive interventions may be needed to influence HRQoL in these patients.

O2 STRENGTH AND BALANCE TRAINING IN PATIENTS WITH DIABETIC PERIPHERAL NEUROPATHY IMPROVES FUNCTIONAL STATUS BUT NOT QUALITY OF LIFE

Table 1: Baseline demographics and clinical characteristics by treatment

Characteristic	Intervention (n = 70)	Control (n = 73)	All patients (n = 143)
Mean Age (years), (range)	61.9 (47.6 – 78.4)	62.3 (43.2 – 78.4)	62.1 (43.2 – 78.4)
Male (%)	36 (51.4)	27 (37.0)	63 (44.1)
Indian (%)	56 (80.0)	54 (74.0)	110 (76.9)
Mean BMI (kg/m^2), (SD)	28.4 (5.6)	28.4 (5.9)	28.4 (5.7)
HbA1c (%), (SD)	8.3 (1.8)	8.6 (1.8)	8.5 (1.8)

* Three observations with missing monthly household income.

Table 2: Adjusted mean difference in repeated measure outcomes comparing intervention versus control

Characteristic	Mean difference	95% CI	p-value
Physical Component Summary (PCS)	0.92	-2.38 to 4.20	0.586
EQ-5D utility score	0.02	-0.02 to 0.05	0.290
Muscle strength – right ankle (lbs)	*0.85*	*0.03 to 1.68*	*0.043*
Range of motion – right knee (degrees)	*6.42*	*2.32 to 10.52*	*0.002*
Body sway velocity – eyes closed (mm/s)*	0.19	-0.01 to 0.39	0.065
Timed up and go (seconds)	-1.02	-2.07 to 0.02	0.054
Sit-to-stand (seconds)	*-1.21*	*-2.01 to -0.42*	*0.003*
Functional reach (cm)*	0.19	-1.59 to 1.97	0.836
Total ABC score	*5.50*	*1.31 to 9.68*	*0.010*

Note: random intercept mixed model, adjusted for time, respective baseline covariate and gender.
* Six observations with missing information.

O3 COMPOSITION AND SIZE OF STRIATED MUSCLES IN PATIENTS WITH TYPE-2 DIABETES WITH AND WITHOUT DIABETIC POLYNEUROPATHY - AN MRI STUDY

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OBJECTIVES:

The aim of the study was to assess the quality and quantity of striated muscles in the lower extremities in patients with type 2-diabetes (DM2), in relation to the presence of DPN using novel dedicated Magnetic Resonance Imaging (MRI).

METHODS:

Twenty DM2 patients with DPN, twenty DM2 patients without DPN, and twenty healthy subjects were enrolled in the study. The groups were matched on age, sex, and height. The groups were not matched on BMI (Healthy subjects (HC) 26.5, non-DPN 29.9, and DPN 34.9, p<0.01). Presence of neuropathy was determined based on standardized clinical examinations, and nerve conduction studies (NCS). Muscle strength of the extensors and flexors at the knee and ankle was determined by isokinetic dynamometry at the non-dominant leg. Skeletal muscles were visualized by a specialized MRI-protocol including Dixon, T2-mapping, and Diffusion Tensor Imaging (DTI).

RESULTS:

In patients with DPN maximal muscle strength was lower for all muscle groups, when compared to healthy subjects, adjusting for age, sex and BMI (dorsal-flexors (DF) (83%, p=0.02), plantar-flexors (PF) (74%, p<0.01), knee-extensors (KE) (80%, p<0.01), and knee-flexors (KF) (83%, p=0.01)). Patients without DPN had normal strength of all muscle groups. Intrinsic muscle strength was lower in PF of DPN patients compared with healthy subjects (24% reduction, p<0.01). When assessing the composition of muscles, a 42-93% increase in fat fraction was observed in all muscle groups of the DPN patients (p<0.01). Further, neuropathic patients had a considerably lower muscle mass, when normalizing the total contractile muscle volume of the non-dominant leg to body weight (HC 48.8 cm3/kg, non-DPN 43.6, and DPN 36.9, p<0.01). T2muscle was prolonged in PF of neuropathic patients (5%, p=0.01), and prolonged in KE and PF of DM2 patients without DPN (2%, p<0.05), compared with healthy subjects. In DPN patients a 9% increase in Fractional Anisotropy (FA), and an 8% increase in Mean Diffusivity (MD) were observed in KE (p=0.04) and DF (p<0.01), respectively.

CONCLUSIONS:

Type-2 diabetes patients with DPN had reduced muscle size and intrinsic muscle strength. Patients with and without DPN could be distinguished from healthy subjects by prolonged T2muscle. DPN patients had higher FF, FA and MD compared to patients without DPN and healthy subjects. In conclusion, this study suggests Dixon, DTI and T2muscle as noninvasive markers of disease activity and severity in striated muscles in patients with and without DPN.

O4 IMPACT OF GLYCEMIC VARIABILITY ON NEURORETINA IN PEDIATRIC PATIENTS WITH TYPE 1 DIABETES MELLITUS

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OBJECTIVES:

Very few data are available on the pediatric population with type 1 diabetes mellitus (T1DM), regarding the early structural or functional signs of retinal neurodegeneration (RN) and whether these changes may represent an early marker of neuropathic damage. Moreover, the role of glycemic control and daily glucose variability (GV) on early RN is still not clarified.

METHODS:

13 T1DM pediatric patients (ages 10-20 years), with no signs of DR and without peripheral neuropathy and 9 control subjects (C) comparable in gender and age were enrolled. All subjects underwent an Optical Coherence Tomography (OCT), with analysis of peripapillary retinal nerve fiber layer (RNFL) thickness and automatic segmentation of all neuroretinal layers measuring mean of subfoveal, inner and outer nasal (N)/temporal (T)/superior (S)/inferior (I) quadrants. The functional study was obtained by multifocal electroretinogram (mfERG) analysis, measuring the amplitude density (RAD) and implicit time (IT) from 4 concentric annular retinal regions (rings, R1-R4). Metabolic control was evaluated by HbA1c, and indexes of GV were calculated from continuous glucose monitoring.

RESULTS:

RNFL-S-inner thickness was significantly reduced in the T1DM group compared to C (mean difference=2,42 micron; p=0.043), as subfoveal inner nuclear layer (INL) (mean difference=2,91 micron; p=0.05) and N, T-outer plexiform layer (OPL) (mean difference=7,09 micron; p=0.025 and mean difference=2,04; p=0.002 respectively). No difference was observed for peripapillary RNFL thickness. IT in R2 and R4 was significantly increased in the T1DM group compared to C (mean difference=-2,58 ms; p=0.046 and mean difference=-3,23 ms; p=0.005; respectively). A negative correlation between OPL-T-outer and continuous overall net glycemic action indexes (CONGA-1 and 2) (r=-0.634, p=0.027; r=-0.603, p=0.05 respectively; Pearson correlation) were observed in T1DM patients. No significant correlation was found with HbA1c.

CONCLUSIONS:

Very precocious morphological and functional alterations of neuroretina are already present in T1DM pediatric patients without both vascular retinopathy and neuropathy, supporting the hypothesis that RN occurs early in the course of diabetes. Glycemic variability, but not overall glycemic load, seems to play a pathogenic role in the morphological abnormalities of neurosensory retina in T1DM pediatric population. A longitudinal evaluation is needed to identify if neuroretinal nerve damage is a predictor marker of diabetic neuropathy.

O5 SPINAL VEGFR2 SIGNALING LOSS AND RESULTANT HYPOXIA: A CAUSATIVE FACTOR IN THE DEVELOPMENT OF DIABETIC NEUROPATHIC PAIN

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OBJECTIVES:

The mechanisms of Diabetic neuropathy are not well understood, and hence treatment modalities are ineffective. We have previously seen a relation between vascular changes in the spinal cord and neuropathic pain development. This is driven by a loss of VEGF-A signaling in the spinal microvasculature. Here, we further investigate neuropathy as a consequence of hypoxia in a spinal endothelial cell specific inducible VEGF receptor 2 (VEGFR2) knockout mouse model.

METHODS:

Procedures were carried out in accordance with the UK Home Office Animals (Scientific Procedures) Act 1986. 30 transgenic mice (C57bl6 30g; both genders) were used. All mice used were VEGFR2fl/fl and either Tie2CreERT2 positive (n=18) or Tie2CreERT2 negative (n=12), dosed once intrathecally with 1μM hydroxytamoxifen. Hargreaves test was used to assess nociceptive behaviour. After 8 days, hypoxyprobe (60mg/kg) was injected i.p (intraperitoneal) 30 minutes before euthanasia. Animals were transcardially perfused with 4% PFA under terminal anaesthesia (sodium pentobarbital 60mg/kg i.p). In adjoining experiments, Acetazolamide (ACZ) (i.p 40m/kg) was injected 30 minutes prior to nociceptive behavioural testing. Spinal cord cryosections (40μM) were stained using Isolectin B4 (IB4), Anti-hypoxyprobe, and c-fos. Confocal imaging was performed followed by Imaris 8.1 3D rendering.

RESULTS:

VEGFR2 Knockout (KO) mice developed a pronounced heat hyperalgesia compared to controls (CTL) ($p<0.001$,n=6). The development of neuropathy was associated with a loss of IB4 stained vessels in the dorsal horn of the spinal cord, as detected by confocal microscopy. 3D rendering further revealed a significant reduction in vessel volume and diameter ($p<0.05$, n=6) in the KO as compared to CTL. A marked hypoxia was detected in the KO seen by an increase in the intensity of hypoxyprobe staining ($p<0.05$, n=6). Mapping of the dorsal horn of the spinal cord further revealed an increase in hypoxic neurons per lamina (lx) in the KO. This was concurrent with an increase in c-fos activated neurons per lamina. Injection of a carbonic anhydrase inhibitor (ACZ) reversed both pain ($p<0.001$,n=6) and neuronal activation ($p<0.001$,n=6).

CONCLUSIONS:

Thus our data suggests a loss of VEGFR2 signaling in the endothelium leads to spinal cord vascular degeneration and hypoxia, associated with the development of neuropathic pain. Administration of a Carbonic anhydrase inhibitor attenuated the hypoxia-driven activation of neurons, thus ameliorating neuropathic pain.

O6 A FOUR-YEAR LONGITUDINAL STUDY EXAMINING THE INFLUENCE OF AGE, ANTHROPOMETRIC AND OTHER METABOLIC VARIABLES ON METHODS OF SMALL AND LARGE FIBRE NEUROPATHY IN HEALTHY SUBJECTS

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OBJECTIVES:

The LDIFLARE (laser doppler imager) and CCM (corneal confocal microscopy) are both novel methods of assessing small fibre function (SFF) and structure (SFS) respectively and have been shown to be sensitive in detecting early diabetes neuropathy. While the LDIFLARE measures C-fibre mediated hyperaemic response in the foot, CCM measures nerve fibre indices in the corneal sub-basal layer. However, these outcomes can be affected by anthropometric and biochemical variables as we and others have demonstrated in previous cross-sectional studies. This four-year longitudinal study for the first time examines the influence of these variables including age on both methods in healthy individuals.

METHODS:

55 healthy volunteers (29 males) (age: 45.5±21.2 yrs.) underwent anthropometric, biochemical and neurological assessment for both small and large fibre neural assessments at yearly intervals. They were screened at baseline and annually for diabetes, hypothyroidism, vitamin B12/folate deficiencies and excluded if they had any such evidence along with cancer, alcoholism and peripheral arterial disease. SFF was assessed using the LDIFLARE while SFS was assessed with CCM with corneal indices measured as nerve fibre density (CNFD), branch density (CNBD) and fibre length (CNFL). Large fibre methods included vibration perception threshold (VPT) and sural nerve conduction velocity (SNCV) and amplitude (SNAP). Age trends were established using simple linear regression and independent effects measured with multivariate analysis.

RESULTS:

There was a significant age-related linear decline in LDIFLARE (-0.06cm2/yr; p = <0.001) and CCM parameters (CNFD: -0.15 fibres/mm2 /yr; p = 0.009, CNBD: -0.16 branches/mm2/yr; p = 0.01 and CNFL -0.10 mm/mm2/yr; p = 0.02). A significant inverse correlation was observed between fasting triglycerides (TG) and the LDIFLARE (p = 0.001) and all CCM indices (p = <0.05). Height, weight, BMI, blood pressure, HbA1c and cholesterol did not influence either method. At the end of the 4-year period, no relationship between age, anthropometric or biochemical outcomes was observed between VPT nor SNAP or SNCV (p = >0.05).

CONCLUSIONS:

This is the first longitudinal study examining the effect of age and other variables on both small and large fibre neural outcomes in healthy controls. It confirms the findings in our previous 2 cross-sectional studies (LDIFLARE decline of -0.06 to -0.07cm2/yr). By demonstrating the significant inverse correlations with age and triglycerides on both SFF and SFS, this study further reiterates their importance while devising robust normative reference values that can be reliably used in both clinical and research practice in the study of diabetes and other peripheral neuropathies using these methodologies.

O7 HOW DOES TYPE 2 DIABETES AFFECT THE CLINICAL PHENOTYPE OF VASCULAR COGNITIVE IMPAIRMENT?

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OBJECTIVES:

Type 2 diabetes mellitus (T2DM) is associated with an increased risk for vascular cognitive impairment (VCI). It is unknown, however, whether patients with VCI and T2DM have a distinctive clinical phenotype and prognosis compared to patients with VCI without T2DM. Our objective was to compare the clinical phenotype and the prognosis of patients with possible VCI with and without T2DM in an observational, prospective memory clinic cohort of well-defined patients with possible VCI (TRACE-VCI study).

METHODS:

We included 851 memory clinic patients (T2DM: n=147, no T2DM: n=704) with MRI evidence of vascular brain injury (i.e. possible VCI). At baseline, we assessed between-group differences in vascular risk factors, cognitive profile (assessing five domains), brain MRI abnormalities and cerebrospinal fluid (CSF) markers. After two years follow-up, we compared occurrence of cognitive decline, stroke, and death.

RESULTS:

Hypercholesterolemia, obesity, and history of a non-stroke vascular event were more common in possible VCI patients with T2DM compared to those without (all p<0.05; table 1). Possible VCI patients with T2DM performed worse on working memory (effect size: -0.17, p=0.03) compared to those without. The distribution of clinical diagnoses was similar between the groups. Patients with T2DM had more pronounced atrophy on brain MRI, and more lacunar infarcts, whereas microbleeds were less common (all p<0.05; table 2). The level of CSF markers for Alzheimer's disease did not differ between groups (table 2). At follow-up, there were no differences in cognitive decline and death. Stroke risk tended to be higher in patients with T2DM (odds ratio 2.75, 95% confidence interval 0.99-7.69; p=0.054).

CONCLUSIONS:

Features associated with T2DM in patients with possible VCI are more pronounced brain atrophy and a higher burden of lacunes. Presence of T2DM did not have a major impact on prognosis in these patients.

This abstract is presented on behalf of the TRACE VCI consortium: PMC5415656

O7 HOW DOES TYPE 2 DIABETES AFFECT THE CLINICAL PHENOTYPE OF VASCULAR COGNITIVE IMPAIRMENT?

Table 1. Patients characteristics

	Possible VCI without T2DM n = 704	Possible VCI with T2DM n = 147	*p*-value
Demographics			
Gender, % men	367 (52%)	92 (63%)	**0.02**
Age	67.6 ± 8.5	68.4 ± 7.9	0.28
Vascular risk factor profile			
Hypertension[a]	588 (84%)	132 (90%)	0.06
Hypercholesterolemia[b]	273 (39%)	106 (72%)	**< 0.001**
Obesity[c]	136 (20%)	40 (27%)	**0.04**
History of reported stroke	58 (8%)	17 (12%)	0.20
History of reported vascular event other than stroke[d]	58 (8%)	25 (17%)	**0.002**
Clinical diagnosis			
No objective cognitive impairment	172 (24%)	24 (16%)	0.31[e]
MCI	163 (23%)	44 (30%)	
Dementia	369 (52%)	79 (54%)	

VCI, vascular cognitive impairment; T2DM, type 2 diabetes mellitus

Data are presented as n (%), means ± SD, or median (range) [a] Based on a self-reported medical history, use of antihypertensive drugs, or a newly diagnosed hypertension defined as a systolic pressure ≥ 140 mm Hg or a diastolic pressure ≥ 90 mm Hg [b] Based on medical history or medication use. [c] Defined as a baseline body mass index ≥30, calculated as weight in kilograms divided by height in meters squared. [d] Defined as a history of myocardial infarction, surgery or endovascular treatment for coronary artery disease, any arterial occlusion or surgical intervention of a peripheral artery (such as an abdominal or leg artery) or carotid artery intervention (stenting or endarterectomy). [e] A Mann-Whitney U test for non-parametric data was performed.

O7 HOW DOES TYPE 2 DIABETES AFFECT THE CLINICAL PHENOTYPE OF VASCULAR COGNITIVE IMPAIRMENT?

Table 2. Brain MRI and cerebrospinal fluid features

	Possible VCI without T2DM n = 704	Possible VCI with T2DM n = 147	Mean difference in z-scores between patients with VCI with and without T2DM[a]
Total brain volume (% of ICV)	71.0 ± 4.1	70.0 ± 4.1	**-0.26 (-0.41 to -0.10)***
	VCI without T2DM n = 704	**VCI with T2DM n = 147**	**OR (95% CI)[a]**
Non-lacunar (sub)cortical infarcts	72 (10%)	20 (14%)	1.29 (0.75 to 2.21)
Lacunar infarcts	140 (20%)	42 (29%)	**1.52 (1.01 to 2.29)***
Microbleeds	320 (46%)	44 (31%)	**0.49 (0.33 to 0.73)***
Cerebrospinal fluid features			
	VCI without T2DM n = 454	**VCI with T2DM n = 79**	***p*-value**
Aβ42 (pg/mL)	614 (460-929)	697 (479-928)	0.25
Tau, (pg/mL)	361 (255-631)	396 (231-650)	0.74

VCI, vascular cognitive impairment; T2DM, type 2 diabetes mellitus; ICV, intracranial volume; OR, odds ratio; CI, confidence interval; Aβ, amyloid-beta

Data are presented as means ± SD, n (%), or median (range)

[a] Data adjusted for age and gender; *: p<0.05

O8 RESTING STATE FUNCTIONAL MRI STUDY OF PAIN NETWORK FUNCTIONAL CONNECTIVITY IN PAINFUL DIABETIC NEUROPATHY

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OBJECTIVES:

Painful neuropathy (Painful-DPN) affects up to a fifth of patients with diabetes and can lead to progressive disability and poor quality of life. There are no objective biomarkers and current treatments are less than optimal. We examined the resting functional connectivity of the cortical pain network in painful DPN as a possible objective biomarker for neuropathic pain.

METHODS:

54 patients with diabetes (No DPN, n=16; Painful DPN, n=23 Painless DPN, n=15) and 16 healthy volunteers underwent detailed clinical and neurophysiological assessments (NIS[LL]+7tests). Resting state fMRI data were acquired at 3T (Achieva, Philips Healthcare) and data analysis was performed using the Conn Functional Connectivity Toolbox in SPM. Seed region of interest analysis was performed in the somatosensory cortex and insula cortex to represent the sensory discriminatory and affective components of pain processing respectively

RESULTS:

There was increased functional connectivity in the somatosensory cortex (-42,-22,56; TFCE, corrected $p<0.05$) and reduced functional connectivity in the insular cortex (34,62,60; TFCE, corrected $p<0.05$) in patients with painful DPN compared to other study cohorts. Somatosensory functional connectivity significantly correlated overall neuropathy severity score ($r=0.57$; $p=0.03$). There were no significant correlations between quantitative pain assessments with somatosensory functional connectivity (HADS-A $r=-0.35$, $p=0.20$), Short Form 36, $r=-0.43$; $p=0.11$ and Chronic Pain Acceptance Questionnaire $r=-0.16$, $p=0.57$). Conversely, insula cortex functional connectivity was significantly correlated with affective measures of the chronic pain condition (HADS-A $r=-0.48$, $p=0.02$; SF-36 $r=-0.51$, $p=0.01$; CPAQ $r=-0.65$, $p=0.001$) but not with neuropathy composite score ($r=-0.09$, $p=0.70$).

CONCLUSIONS:

We have demonstrated that abnormal pain network functional connectivity reflects closely the roles of each brain region. Alterations in functional connectivity of the insula cortex, which is involved with interoceptive awareness and the emotional experience, correlated with subjective measures of pain and behaviour unique to the chronic pain condition. Whereas, the somatosensory cortex which is involved with nociceptive/sensory discrimination was more closely related to objective measures of neuropathy severity based on neurophysiological assessments. This novel, quick (five minute) MRI scan captures the multi-dimensional aspects of chronic pain and has a great potential to be an objective assessment tool in both clinical trials and practice.

O9 THE ASSOCIATION BETWEEN COGNITIVE FUNCTIONING AND CEREBRAL PERFUSION IN PATIENTS WITH TYPE 2 DIABETES MELLITUS

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OBJECTIVES:

Type 2 diabetes mellitus (T2DM) is associated with cognitive impairment, an increased risk of dementia and occurrence of cerebral small vessel disease. Impaired cerebral perfusion is one of the features of cerebral small vessel disease. We therefore investigated the association between cognitive functioning and cerebral perfusion in patients with T2DM.

METHODS:

We examined 95 patients with T2DM (32 males, mean age 62.2±5.5 years, diabetes duration 9.7±6.6 years). Cognitive functioning was assessed using a standard neuropsychological test battery covering the domains memory, executive functioning, and processing speed. Cerebral perfusion was assessed using SPECT scans and quantified by comparison to a database of healthy individuals (expressed as a standard deviation). Linear regression analyses adjusted for age and gender were performed to study the association of cognitive functioning and global and regional (frontal, occipital, parietal, temporal, cerebellum, caudate nucleus, putamen, and thalamus; both left and right) cerebral perfusion.

RESULTS:

There were no statistically significant associations between cognitive functioning and global cerebral perfusion (memory B (95%-CI): -0.106 (-0.349↔0.136), $p=0.386$; executive functioning: 0.001 (-0.216↔0.218), $p=0.996$; processing speed: -0.189 (-0.405↔-0.028), $p=0.087$). A worse memory domain score was associated with reduced perfusion in the thalamus (left: -0.278 (-0.242↔-0.053), $p=0.003$; right: -0.283 (-0.237↔-0.054), $p=0.002$). A worse processing speed domain score was associated with reduced perfusion in the left frontal lobe (-0.289 (-0.388↔-0.088), $p=0.002$).

CONCLUSIONS:

We found a strong association between reduced perfusion in the thalamus and memory impairment in patients with T2DM. This reduced perfusion might be one of the underlying functional correlates of cognitive impairment in patients with T2DM.

O10 COGNITIVE FUNCTION AND CEREBRAL BLOOD FLOW ON MRI IN TYPE-2 DIABETES

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OBJECTIVES:

There is approximately a 2-fold increase in the risk of developing mild cognitive impairment (MCI) in patients who have Type 2 diabetes mellitus (T2DM). In addition to cognitive assessment, brain perfusion Single Photon Emission Computed Tomography is often used in the clinical work-up of patients with suspected cognitive decline. However, in the context of T2DM, Cerebral Blood Flow (CBF) status in relation to MCI has not been fully investigated. This study sought to assess regional CBF in matched T2DM patients with and without MCI using a non-invasive, quantitative, Magnetic Resonance Imaging (MRI) technique.

METHODS:

Seventy-four age and gender matched subjects [28, T2DM+normal cognition (T2DM); 17, T2DM+MCI (T2DM/MCI) and 29, healthy volunteers (HV)] were recruited. All subjects underwent clinical evaluation including the Addenbrooke's Cognitive Assessment [ACE-R]. Pseudo-Continuous Arterial Spin Labelling (ASL) Magnetic Resonance Imaging (MRI) was also performed to assess cerebral perfusion. Imaging was performed at 3T. The ASL data was modelled to yield quantitative arterial CBF maps in neuroanatomical regions involved with various cognitive and memory functions.

RESULTS:

As expected, mean T2DM/MCI ACE-R score (mean+/-SD; 83+/-4) was significantly lower in the MCI group when compared to other groups (HV=96+/-2, T2DM=94+/-3; ANOVA $p<0.001$). There was a significantly lower mean CBF in T2DM/MCI compared to T2DM and HV in the medial temporal lobes (CBF 76.8 ml/100g/min, ANOVA $p<0.05$), insula (CBF 67.5 ml/100g/min ANOVA $p<0.005$), and frontal lobes (CBF 71.8 ml/100g/min, ANOVA $p<0.005$). Significant correlations were observed between ACE-R score and regional CBF measurements in the medial temporal lobes, ($p<0.05$, $r=0.25$) thalamus ($p<0.05$, $r=0.23$) and the insula ($p<0.05$, $r=0.29$).

CONCLUSIONS:

This study demonstrates significantly lower CBF in T2DM MCI subjects in neuroanatomical regions associated with various cognitive and memory functions. This may be essential in helping our understanding of the pathological mechanisms that occur behind the increased risk of developing cognitive impairment associated with T2DM.

O11 INCREASED PROINFLAMMATORY MACROPHAGES IN SURAL NERVE CORRELATE WITH REDUCED INTRAEPIDERMAL NERVE FIBER DENSITY IN HUMAN TYPE 2 DIABETIC SUBJECTS

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OBJECTIVES:

Type 2 diabetes (T2DM) is characterized to associate with systemic inflammatory reaction. Pro-inflammatory M1 macrophages (M1) is prevalent relative to more potent than anti-inflammatory M2 macrophages (M2) in fatty tissue, liver and pancreatic islets in subjects with of T2DM, which result in tissue damage and dysfunction responsible for the onset and progression of the disease. The skewing of such macrophage infiltration is recently proposed to play a role in the development of diabetic complications such as nephropathy and neuropathy (DPN). There are few reports, however, concerning macrophage infiltration in human DPN. The aim of this study is to clarify the significance of macrophage infiltration in peripheral nerves in patients with T2DM.

METHODS:

Sural nerve and calf skin were obtained from autopsy cases in Hirosaki University Hospital. Eleven cases (Male 6, Female 5) of Non-T2DM (nDM) and 11 cases (Male 3, Female 8) of T2DM (T2D) were subjected to the evaluation. Punched out skin tissues served for estimation of intraepidermal nerve fiber density (IENFD). Excised sural nerve was embedded in paraffin and cross-sections underwent double immunohistochemistry for CD68 (Pan-macrophage) and CD206 (M2). M1 (proinflammatory) was defined as CD68+ and CD206- and M2 (anti-inflammatory) was as CD206+, respectively. IENFD was assessed by double immunofluorescence for PGP9.5 (nerve fibers) and Type IV collagen (basement membranes).

RESULTS:

Average age (mean±SE) (nDM 67.2±4.2 yrs and T2DM 69.0±3.0 yrs) and BMI (nDM 23.1±1.4, T2D 21.1±1.2) were comparable between 2 groups. HbA1c was significantly greater in T2DM (7.2±0.5%) than nDM (5.5±0.2%)($p<0.05$). Pathological evaluation showed 2.4 times M1 in T2D more than that in nDM ($p<0.05$) in the sural nerve. On the other hand, M2 was comparable between 2 groups. Correlation analysis between macrophage infiltration and clinical parameters disclosed that the M1 population proportionally correlated with the value of HbA1c ($p<0.05$), whereas there was no correlation between M2 population and HbA1c. IENFD inversely correlated with M1 population ($p<0.05$).

CONCLUSIONS:

M1-predominant proinflammatory condition is associated with skin fiber loss, implicating the pathogenic role of M1 macrophage in DPN.

O12 HUMAN ADIPOSE STEM CELLS AND THEIR SECRETOME REVERT PAINFUL NEUROPATHY AND NEUROINFLAMMATION IN STREPTOZOTOCIN-DIABETIC-MICE

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OBJECTIVES:

Up to now the pharmacological treatments for painful diabetic neuropathy are not fully satisfactory, and it is necessary to explore new approaches. A new possibility might be the use of mesenchymal stem cells considering that they possess immunomodulatory properties, low immunogenicity and regenerative potential. Interestingly, it has been suggested that the effect of stem cells depends on secretion of a broad range of biologically active factors.
In this study, we evaluated the effects of Mesenchymal Stem Cells isolated from human adipose tissue (hASC) and of their conditioned medium/secretome (CM-hASC) on the neuropathic symptomatology, in a mouse model of diabetic neuropathy induced by streptozotocin.

METHODS:

Diabetes was induced in male mice with low STZ doses.Mechanical and thermal allodynia after STZ was monitored by using respectively Von Frey test and Acetone test. When neuropathic pain was established (2 weeks after STZ), mice were treated by i.v. injection with either 106 hASC or CM-hASC obtained from 2x106 serum-free cultured cells. As control, we evaluated the effect of the CM obtained from 2x106 human fibroblasts (CM-hF). We also tested the intraplantar route of administration. Tissue levels of pro-inflammatory and anti-inflammatory cytokines were measured in the main stations of pain transmission (sciatic nerve, dorsal root ganglia and spinal cord) and we also evaluated loss of nerve fibers and skin thickness.

RESULTS:

Both hASC and their secretome were able to reverse painful symptoms.The effects were very rapid, 3 hours after treatments, and long lasting, in fact they were maintained 14 weeks after hASC or CM administration; on the contrary CM-hF was unable to evoke any mechanical-antiallodynic effect in diabetic neuropathic mice. The effect was present after i.v. as well as intraplantar treatment. In all tissues obtained from neuropathic mice, we observed a pro-inflammatory profile, characterized by high pro-inflammatory and low anti-inflammatory cytokine levels. hASC and CM treatments were able to restore a correct pro-/anti-inflammatory cytokine balance both 1 week and 12 weeks after treatments and to restore skin innervation.

CONCLUSIONS:

The data obtained suggest that i.v. or local hASC treatment may be a favorable approach for diabetic complications such as neuropathic pain, indicate that cells effect is likely to be mediated by their secreted products and suggest that cells may eventually be substituted with their CM.

O13 MAGNESIUM PREVENTS METHYLGLYOXAL-MEDIATED NEUROTOXICITY AND IS ASSOCIATED WITH DIABETIC POLYNEUROPATHY

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OBJECTIVES:

Both magnesium (Mg2+) depletion and carbonyl stress have been implicated in the development of type 2 diabetes (T2D) and neuropathic pain. We aimed to assess whether 1.) Mg2+ and methylglyoxal (MG) levels are associated with diabetic sensorimotor polyneuropathy (DSPN) and 2.) Mg2+ supplementation can prevent methylglyoxal (MG)-mediated neurotoxicity under experimental conditions.

METHODS:

We measured serum Mg2+ levels in patients with recent-onset T2D with DSPN (rdDSPN; n=51) and without DSPN (noDSPN; n=184) from the German Diabetes Study as well as longer-term T2D patients with DSPN (ltDSPN; n=191) from the PROPANE study. Demographic and clinical data (noDSPN/rdDSPN/ltDSPN): age: 52.1±11.1/53.3±10.3/68.3±10.3 [mean±SD] years; male: 64/77/79%; BMI: 31.5±5.7/32.2±6.3/30.5±5.4 kg/m²; diabetes duration: 0.5±0.3/0.4±0.2/13.1±9.3 years; HbA1c: 6.4±0.9/6.8±1.2/7.2±1.2%. Plasma MG concentration was determined in recent-onset T2D patients using HPLC. Human neuroblastoma cells (SH-SY5Y), immunofluorescence staining, high-content image analysis (HCA), and quantitative Western blot analyses were used to characterize the neurotoxic MG and neurotrophic Mg2+ effects.

RESULTS:

Mg2+ concentrations were lower in both DSPN groups compared to noDSPN (0.86±0.07mM; $P<0.05$) and also lower in ltDSPN than rdDSPN (0.77±0.08 vs 0.83±0.08 mM; $P<0.01$). MG concentration did not differ between the noDSPN and rdDSPN groups (276±8 vs 304±18nM), but a strong inverse association of MG with Mg2+ (β=-0.395; $P=0.005$) was found in the rdDSPN group. To determine the neurotoxic effect of MG and a possible neurotrophic effect of Mg2+, SH-SY5Y cells were exposed to 0, 400, and 800µM MG alone or in presence of 30mM MgCl2 for 24h. The treatment with 400 and 800µM MG resulted in a 28% and 70% reduction of cell viability, respectively, while MgCl2 supplementation attenuated the neurotoxic effect of 400 and 800µM MG by ~8%. In addition, HCA showed that Mg2+ supplementation resulted in higher neurite count and neurite lengths ($P<0.0001$). The analyses of cell lysates for MG 5-hydro-5-methylimidazolones (MG-H1) revealed that Mg2+ supplementation resulted in a reduction of MG-H1 protein modifications ($P<0.05$).

CONCLUSIONS:

Under experimental conditions, Mg2+ supplementation prevents MG-mediated neuronal injuries by reducing MG-H1 protein modifications. Since hypomagnesemia is associated with both DSPN and increased MG levels, Mg2+ supplementation could be a promising treatment to protect from carbonyl stress induced nerve damage in DSPN.

O14 EXENDIN-4 STIMULATES MYELINATION IN A CO-CULTURE OF ADULT RAT DORSAL ROOT GANGLION NEURONS AND IMMORTALIZED ADULT RAT SCHWANN CELLS

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OBJECTIVES:

In addition to its insulinotropic actions on pancreatic beta-cells, glucagon-like peptide (GLP)-1 can also prevent the deterioration of neurons and glial cells following axonal injury and in neurodegenerative disorders. Although the neurotrophic actions of exendin (Ex)-4, a GLP-1 receptor agonist, on adult rat dorsal root ganglion (DRG) neurons have been reported, its underlying beneficial effects on myelination and remyelination remain unknown and therefore define the aim of this study.

METHODS:

DRG neurons were seeded onto type I collagen-coated Aclar coverslips and 2-well chamber slides and maintained in a serum-free culture medium for 7 days. Neurite outgrowth was observed under a phase-contrast microscope, following which DRG neurons were co-cultured with immortalized adult rat Schwann cells (IFRS1); the cell density ratio of neurons to IFRS1 cells was adjusted to approximately 1:10. The co-cultured cells were maintained in a serum-free culture medium supplemented with 50 μg/mL ascorbic acid and different concentrations (0, 10, or 100 nM) of Ex-4 for up to 21 days. Myelin formation in the co-culture was evaluated by immunocytochemistry and Western blotting using antibodies against myelin proteins, including myelin protein zero (MPZ) and peripheral myelin protein 22 (PMP22).

RESULTS:

Ex-4 dose-dependently accelerated the movement of IFRS1 cells toward the neurites emerging from DRG neurons at 14 days of co-culture when analyzed under a phase-contrast microscope. At 21 days of co-culture, Ex-4 increased the number of MPZ-immunoreactive IFRS1 cells surrounding beta-III tubulin-immunoreactive neurites and upregulated the protein expression of PMP22.

CONCLUSIONS:

Ex-4 dose-dependently stimulates the myelination process in the DRG neuron–IFRS1 co-culture. These findings imply the efficacy of Ex-4 in accelerating axonal regeneration and remyelination following peripheral nerve injury. This DRG neuron–IFRS1 co-culture system can be used to investigate myelination and demyelination mechanisms and to develop novel strategies for preventing and restoring diabetic and other sensory neuropathies.

O15 IMPROVEMENT IN PAINFUL DIABETIC NEUROPATHY AFTER 3 MONTHS FROM ADMINISTRATION OF A SUPPLEMENT CONTAINING SOD, ALA, B12 AND CARNITINE.

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OBJECTIVES:

The aim of the study is to investigate the effect of a new combination of four elements [Superoxide Dismutase (SOD), Alpha Lipoic Acid (ALA), Acetyl L-Carnitine (AC), Vit. B12] contained in one pill in Painful Diabetic Neuropathy (PDN). It is a combination of two antioxidants plus Vit B12 and Carnitine.

METHODS:

In current prospective, double-blind, placebo controlled, age matched study, 65 patients with Diabetes Mellitus Type 2 (DMT2), 31 women, with mean age 63±11 years, mean duration of DM 15 years, randomized in 2 groups: group A: n= 32 received placebo and group B: n=33 received the pill with the combination of the four elements (SOD, ALA, B12, ACL). All patients were on treatment either with a combination of antidiabetic drugs or with a combination with insulin and drugs. Treatment of diabetes did not change during the three 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 Reflex Tests (CRT): R-R variation during deep breathing [assessed by mean circular resultant (MCR)], Valsalva maneuver (Vals), 30:15 ratio and blood pressure response to standing (OH). We used a pain (PS) and a quality of life (QL) questionnaire, also.

RESULTS:

All indices of measurements between the 2 groups including HbA1c (group A 6.8±1.2 vs group B 7.2±1.2 p=0.660) did not differ at baseline. The following indices increased significantly in group B(baseline vs final): BIO 35±13 vs 28±15 ($p<0.001$), MNSIQ 4.3±3.0 vs 4.2±2.99 (p=0.009), QL 39.0±11.4 vs 37.2±10.9 ($p<0.001$) and PAIN 20.5±7.1 vs 18.6±6.7 ($p<0.001$). Indices of CARTS and MNSIE did not differ significantly in group B (baseline vs final). We did not observe a significant change in all indices: in group A (placebo group).

CONCLUSIONS:

In current study after 3 months from the administration of the combination with four elements in one pill, we observed an improvement in vibration perception threshold as measured by biothesiometer, in Pain, in Quality of Life and in MNSI Questionnaire. The pill contains two anti-oxidants (SOD, ALA), Vit B12 and Acetyl L-Carnitine and those could be helpful in the management of painful symptoms in patients with PDN or could be a good starting point for a valid adjuvant for the treatment of pain symptoms.

O16 EFFECT OF ALPHA-LIPOIC ACID SUPPLEMENTATION ON OXIDATIVE STRESS IN PATIENTS WITH DIABETIC NEUROPATHY

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OBJECTIVES:

Diabetic neuropathy (DN) develops on a background of hyperglycemia and is associated with increased oxidative stress and altered nitric oxide (NO) production. Previous studies have shown that the enhanced oxidative stress in diabetes correlates with decreased paraoxonase-1 (PON1) enzyme activity. Elevated ADMA levels are linked to oxidative stress reducing the synthesis of NO and inducing superoxide production by uncoupling NO synthase. Oxidative stress induces changes in nerve conduction velocity in diabetic patients. There is strong evidence that alpha-lipoic acid (ALA) as an antioxidant may improve nerve conduction and relieve neuropathic pain. We aimed to determine the PON1 paraoxonase and arylesterase activities, ADMA and NO levels in DN and to clarify the relationship between these parameters and nerve conduction velocity after treatment with ALA.

METHODS:

Forty-two patients with DN were involved in the study. The nerve conduction velocity was tested by Neurometer® CPT/C. We measured the PON-1 paraoxonase and arylesterase activities spectrophotometrically. ADMA levels were determined with ELISA. NO concentrations were measured by the Griess reaction.

RESULTS:

The NO concentrations were significantly higher ($p<0.01$) and ADMA levels were significantly lower ($p<0.001$) in DN after the use of ALA. Increased paraoxonase ($p<0.05$) and arylesterase ($p<0.05$) activities were found in diabetic patients treated with ALA. Significantly higher paraoxonase activities were associated with increased nerve conduction velocity after the ALA treatment (<0.05). Significantly lower ADMA levels were found in diabetic patients with improved nerve conduction ($p<0.05$).

CONCLUSIONS:

Our results suggest a beneficial effect of ALA supplementation on protection against oxidative damage in DN.

O17 THERAPEUTIC EFFECTS OF TOPILOXOSTAT ON MURINE DIABETIC POLYNEUROPATHY MAY OPERATE DIFFERENTLY DURING DISEASE PROGRESSION.

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OBJECTIVES:

The cause of diabetic polyneuropathy (DPN) is multifactorial. Xanthine oxidase (XO), a potent inducer of reactive oxygen species (ROS), catalyzes the final step of purine metabolism. We previously showed beneficial effects of XO inhibitor on DPN in obese type 2 diabetic model, db/db mice. While suppression of ROS is presumed to be the main efficacy of XO inhibitor in DPN, the precise mechanism still remains unclear. We explored the mechanism how XO-inhibitor, topiloxostat (To) ameliorates DPN in db/db mice.

METHODS:

C57BL6 mice (C57) and db/db mice (db/db) (5 wks of age) were daily treated with 1mg/kg (dbT1) and 2mg/kg (dbT2) To (per os) for 4 or 8 wks. During experimental period, nerve conduction velocity (NCVs) and tail flick response were monitored. At end, dissected sciatic nerves served for evaluation of histology, gene expression and ROS.

RESULTS:

Compared to C57, there was a significant delay of NCVs in db/db at 4 wk, whereas elevated threshold of tail flick test was first evident in db/db at 8 wk. To-treatment improved these measures in a dose dependent manner ($p<0.05$ dbT2 vs C57 for NCVs, $p<0.05$ db/db vs dbT1, $p<0.01$ db/db vs dbT2 for tail flick). Histological assessment of sciatic nerves elucidated a significant increase in macrophages labeled by anti-Ibal antibody in db/db compared to C57 ($p<0.01$) at 4 wk. There were also increased mRNA expressions of TNFα, iNOS, MCP2 and IL-1β at 4 wk ($p<0.01$ vs C57). To-treatment significantly suppressed macrophage infiltration and mRNA expression of the proinflammatory genes ($p<0.05$ db/db vs dbT2). In contrast, there was neither any significant change in macrophage infiltration in the sciatic nerve of db/db at 8 wk, nor proinflammatory gene expressions except for TNFα ($p<0.05$ db/db vs C57). TBARS measurement disclosed elevated ROS levels at both 4 and 8 wk To-treatment in db/db compared to C57 ($p<0.01$ db/db vs C57). Although To-treatment successfully suppressed ROS at both time points, the effect was more robust at 4 wk ($p<0.01$ db/db vs dbT2 at 4 wks, $p<0.05$ vs db/db vs dbT2 at 8 wk).

CONCLUSIONS:

Beneficial effects of To on neuropathy in db/db mice were associated with suppression of proinflammatory changes only in the early phase, but not at the later phase. It was therefore suggested different mechanism may operate in the later stage for the efficacy of To on DPN.

O18 AUTONOMIC FUNCTION IS ASSOCIATED WITH FUTURE CHANGES IN GLUCOSE METABOLISM IN NON-DIABETIC INDIVIDUALS: THE WHITEHALL II STUDY

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OBJECTIVES:

Deterioration in autonomic nervous system function is associated with adverse changes in glucose metabolism in patients with prediabetes and diabetes. The temporal nature of this association is not investigated in non-diabetic individuals. We investigated autonomic function (AF) and 5-year changes in glucose metabolism in individuals without diabetes.

METHODS:

The analysis is based on up to 7,421 person-examinations for 3,104 study participants of the Whitehall II cohort. Measures of AF included 2-minute resting heart rate (rHR) and six heart rate variability (HRV) indices. Associations between baseline AF measures and subsequent 5-year changes in fasting and 2-hour glucose and insulin concentrations, insulin sensitivity (HOMA-IS and ISI0-120) and beta-cell function (HOMA-β) were estimated using mixed-effects models adjusting for baseline measures of the metabolic outcome, age, sex, ethnicity (Model 1) and subsequently also for body mass index (BMI), metabolic covariates and medication (Model 2).

RESULTS:

In the fully adjusted models a doubling in the HRV index RMSSD was associated with a 5-year decrease in HOMA-β of -2.2% (95%CI -4.2;0.0, p=0.046), and a doubling of the LF/HF ratio was associated with an increase in HOMA-β of 2.3% (95%CI 0.6-4.1, p=0.009). A doubling of LF power and LF/HF ratio was associated with 5 year change in fasting serum insulin of -1.1%(95%CI -2.2;0.1, p=0.039) and 1.9%(95%CI 0.2;3.6, p=0.029), respectively. A doubling of the HRV index SDNN was associated with a decrease in 2-hour insulin concentration of -4.2% (95%CI -8.1;-0.1, p=0.045). rHR remained significantly associated with all measures of insulin resistance, beta-cell function and insulin in the fully adjusted model

CONCLUSIONS:

More beneficial levels of AF measures were associated with improved insulin sensitivity and recuded beta-cell function and lower serum insulin concentrations in non-diabetic individuals. Autonomic dysfunction may be a novel risk marker for diabetes and could be a future target for intervention.

O19 RISK FACTORS FOR THE PRESENCE AND THE PROGRESSION OF CARDIOVASCULAR AUTONOMIC NEUROPATHY IN TYPE 2 DIABETES: ADDITION-DENMARK

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OBJECTIVES:

To study the course of cardiovascular autonomic neuropathy (CAN) and examine the effects of cardiometabolic risk factors on the presence and the progression of CAN in type 2 diabetes.

METHODS:

Measures of CAN and cardiometabolic risk factors were obtained in 777 and 452 unselected participants from the ADDITION-Denmark study at the 6- and 13-year follow-up examination, respectively. Of these participants, 306 had the CAN measures acquired at both time-points. CAN status was assessed by cardiovascular autonomic reflex tests (CARTs) (R-R responses to lying-to-standing, deep breathing and the Valsalva maneuver) with the Vagus® device and defined as: no CAN (normal CARTs), early and reversible CAN (one abnormal CART) and manifest CAN (two or three abnormal CARTs). We evaluated changes in CAN status (progression or improvement) of participants between year 6 and year 13. Risk factors associated with the presence of manifest CAN at year 6 and year 13, respectively were examined comparing groups by Kruskal-Wallis and chi-squared tests as appropriate. Factors associated with the risk of prevalent manifest CAN (at year 6 and year 13) and incident manifest CAN (between year 6 and year 13) were estimated by logistic regression models adjusting for sex, age, diabetes duration and trial-randomization group.

O19 RISK FACTORS FOR THE PRESENCE AND THE PROGRESSION OF CARDIOVASCULAR AUTONOMIC NEUROPATHY IN TYPE 2 DIABETES: ADDITION-DENMARK

RESULTS:

In this cohort we observed a diverse but overall progressive change irrespective of randomization group in participant's CAN status between year 6 and year 13 (see figure). Of the 221 participants free of CAN at year 6 and reassessed for CAN at year 13, 11% developed manifest CAN. Participants with prevalent manifest CAN at both year 6 and year 13 were heavier, and had higher HbA1c and triglyceride levels compared to the participants without manifest CAN. In addition, a higher risk of prevalent CAN at year 6 was also associated with lower levels of LDL cholesterol and the presence of albuminuria. We found no statistically significant associations between the evaluated risk factors and the risk of incident manifest CAN; however, similar directions for risk factor associations were seen as for risk factors associated with prevalent CAN.

CONCLUSIONS:

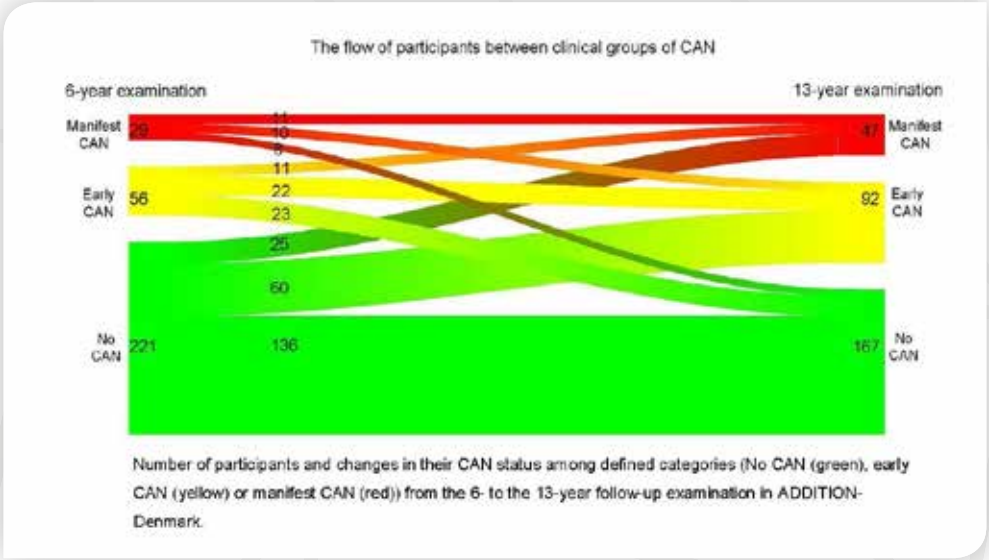
In this cohort of people with screen-detected type 2 diabetes receiving a multifactorial treatment for diabetes, the over-all prevalence of manifest and early CAN increased over a period of 7 years. Hyperglycemia, obesity and hypertriglyceridemia were associated with prevalent CAN, and a non-statistically significant suggestion for a role of these risk factors in the development of CAN was seen. Yet, a diverse phenotype was observed in the change of CAN status, potentially reflecting both an impact of the multifactorial intervention provided and the intrapatient variability of CAN assessment.

Risk of prevalent and incident manifest CAN for risk factors in multivariate logistic regression analyses: ADDITION-Denmark

Characteristics year 6	Risk of manifest CAN Year 6 (n=777) OR (95% CI)	Characteristics year 13	Risk of manifest CAN Year 13 (n=452) OR (95% CI)	Characteristics year 6	Risk of incident manifest CAN (n=221) OR (95% CI)
HbA1c (%)	1.55 (1.23;1.94) *	HbA1c (%)	1.54 (1.19;1.99) *	HbA1c (%)	1.01 (0.68;1.49)
BMI (kg/m²)	1.08 (1.01;1.11) *	BMI (kg/m²)	1.05 (1.00;1.09) *	BMI (kg/m²)	1.04 (0.95;1.13)
Pulse pressure (mmHg)	1.00 (0.98;1.03)	Pulse pressure (mmHg)	1.01 (0.99;1.04)	Pulse pressure (mmHg)	0.97 (0.93;1.02)
Total cholesterol (mmol/L)	0.77 (0.58;1.03)	Total cholesterol (mmol/L)	0.83 (0.66;1.04)	Total cholesterol (mmol/L)	0.75 (0.45;1.24)
HDL cholesterol (mmol/L)	0.64 (0.30;1.37)	HDL cholesterol (mmol/L)	0.42 (0.16;1.05)	HDL cholesterol (mmol/L)	0.29 (0.07;1.14)
LDL cholesterol (mmol/L)	0.63 (0.44;0.88) *	LDL cholesterol (mmol/L)	0.73 (0.53;1.01)	LDL cholesterol (mmol/L)	0.82 (0.51;1.31)
Triglycerides (mmol/L)	1.30 (1.06;1.59) *	Triglycerides (mmol/L)	1.44 (1.14;1.83) *	Triglycerides (mmol/L)	1.12 (0.72;1.73)
Any albuminuria †	1.82 (1.15;2.89) *	Any albuminuria †	1.56 (0.88;2.76)	Any albuminuria †	0.76 (0.24;2.42)
Current smoker	1.22 (0.79;1.89)	Current smoker	1.02 (0.45;2.32)	Current smoker	0.54 (0.14;2.09)

The risk of manifest CAN at year 6 and year 13 and of incident manifest CAN between year 6 and year 13 of risk factors expressed by ORs (95%CI) from multivariate logistic regression models adjusted for sex, age, diabetes duration and trial randomization-group. * p-value < 0.05; † Any albuminuria: Albumin/creatinine ratio ≥ 3.5 mg/mmol for women and albumin/creatinine ratio ≥ 2.5 for men.

O19 RISK FACTORS FOR THE PRESENCE AND THE PROGRESSION OF CARDIOVASCULAR AUTONOMIC NEUROPATHY IN TYPE 2 DIABETES: ADDITION-DENMARK



Number of participants and changes in their CAN status among defined categories (No CAN (green), early CAN (yellow) or manifest CAN (red)) from the 6- to the 13-year follow-up examination in ADDITION-Denmark.

O20 IN OBESE PATIENTS THE PROFILE COMBINING CARDIAC AUTONOMIC DYSFUNCTION WITH A HIGH FINDRISK SCORE IS ASSOCIATED WITH A HIGH RISK OF NEW DYSGLYCEMIA OR PROGRESSION TO DIABETES UNAFFECTED BY BARIATRIC SURGERY

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OBJECTIVES:

The Finnish risk score (Findrisk) has been developed to evaluate the risk of incident type 2 diabetes within 10 years. We have previously shown that in overweight or obese patients a higher Findrisk score is associated with current glycemic and metabolic disorders and with cardiac autonomic dysfunction (CAD). The aim was to examine the combined predictive value of CAD with a high Findrisk score for the onset or aggravation of glycemic abnormalities.

METHODS:

We included 168 patients who were initially assessed by an oral glucose tolerance test and for CAD. The presence of CAD was defined by at least one abnormal out of three tests (taking age into account) which evaluate mostly cardiac vagal activity (deep breathing, lying-to-standing, Valsalva). They were 38±13 years with BMI 38±7 kg/m². They were divided into 4 groups according to a low Findrisk (≤12) without or with CAD (Groups 1 and 2: 42 and 29 patients) or high (>12) without or with CAD (groups 3 and 4: 54 and 43 patients). Glycemic status was reassessed in means 12.5 years later. Fifty-two patients underwent bariatric surgery, mostly restrictive, between the two assessments.

RESULTS:

Dysglycemia (diabetes or prediabetes) was present at the initial assessment, respectively in 11/4/16/13 patients in groups 1 to 4 (NS). Bariatric surgery was performed respectively in 16/5/18/13 patients (NS). At the new assessment, the number of dysglycemic patients had increased in group 4: 12/2/18/26, with a significantly higher rate of dysglycemia in group 4 compared with the other groups ($p<0.0001$), even after adjustment for age ($p=0.003$). The onset of new dysglycemia or progression to diabetes was observed in 26 of the 43 patients of group 4 and in 32 of the 124 patients of combined groups 1, 2, 3 ($p<0.0001$), in 58.4% of operated patients and 41.6% of non operated patients; in group 4, in 53.8% of operated patients and 62.5% of non operated patients and in groups 1 to 3, in 17.9% of operated and 31% of non operated patients.

CONCLUSIONS:

These data suggest that in obese or overweight patients the profile combining CAD with a high Findrisk score is associated with a higher risk of new dysglycemia or progression to diabetes than each factor taken alone, and this risk is not attenuated by bariatric surgery.

O21 EFFECTS OF SLOW BREATHING AND APNEAS ON ARTERIAL STIFFNESS IN TYPE 2 DIABETIC AND OBESE PATIENTS

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OBJECTIVES:

Several studies have shown that slow breathing (SLB) improves oxygen saturation and the baro-chemoreflex interaction through the stimulation of parasympathetic nervous system. We recently reported that a short period of SLB can trigger the onset of apneas in OSAS patients. The activation of sympathetic nervous system is a physiological response to apnea. We aimed to evaluate the effects of SLB and apnoeas on arterial stiffness.

METHODS:

66 patients (42 type 2 diabetic and 24obese) underwent the following protocol: spontaneous breathing (5 min), slow breathing at 6 cycles/min (5 min) and finally 10 minutes of spontaneous breathing (POST-SLB). Among them, 40 patients (26 diabetics, 53±12 years, BMI 36.6±6.2 kg/m2, HbA1c 6.9±1.7%) developed apnoeas during the POST-SLB; 26patients (16diabetic, 53±14years, BMI 33.8±8.3kg/m2, HbA1c 7.3±1.8%) did not develop respiratory abnormalities after SLB. We recorded heart rate and blood pressure (by Finapres®) continuously during the protocol. We calculated arterial stiffness (augmentation index, AIx and pulse wave velocity, PWV) with a software that reproduces the central aortic pressure waveform from the periphery by a transfer function (validated from Sphygmocor®).

RESULTS:

At baseline arterial stiffness was similar in both groups of patients: with apnoeas(APN+) and without apnoeas(APN-) (AIx% 16.9±9.2 vs15.9±7.4, NS; PWV m/s 8.3±1.7vs 7.9±1.0, NS) as well as systolic (SBP mmHg 131 vs 124, NS) and diastolic blood pressure (DBP mmHg 72 vs 73, NS). During SLB, all patients improved AIx (average -2.3% in APN+ and -2.0% in APN-, $p<0.001$ vs baseline), PWV did not change (p NS), SBP decreased (-8.8mmHg in APN+ and -6.8mmHg in APN-,$p<0.001$) as well as DBP (-4.1mmHg in APN+ and -3.2mmHg in APN-,$p<0.001$). During POST-SLB, AIx increased in APN+ and became even higher than at baseline (+1.1%,$p<0.05$) while in APN- AIx returned to baseline, PWV did not change in the two groups, SBP returned to baseline values in APN+ while it remained low in APN- (-6.7mmHg,$p<0.01$), DBP showed the same trend.

CONCLUSIONS:

Slow breathing can reduce BP through the stimulation of parasympathetic nervous system and influence arterial stiffness favorably (AIx proner to acute changes than PWV). Conversely apnoeas induce sympathetic activation that increases BP and worsens arterial stiffness. These important changes highlight the role of the autonomic nervous system in the cardiovascular risk related to OSAS and suggest an acute benefit of slow breathing. The long-term outcomes of repeated sessions of SLB remain to be explored.

O22 DIABETES GASTRIC AUTONOMIC NEUROPATHY: A COMMON AND NEGLECTED ISSUE IN DIABETES PATIENTS

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OBJECTIVES:

Diabetes neuropathy is one of the most common complication and many a times presenting symptom of diabetes. It consist of motor, sensory as well as autonomic neuropathic symptoms. Gastric symptoms such as abdominal discomfort, episodic constipation or diarrhea are more common in diabetes populations, which may be due to diabetes Gastro autonomic neuropathy. But usually these symptoms are under reported or under investigated. We tried to analysed the prevalence symptoms of diabetes gastric automic neuropathy in a diabetes patient presenting to physician OPD.

METHODS:

We surveyed for the presence of symptoms of diabetes gastric autonomic neuropathy since 3 months or more in patient with diabetes presenting to physician in multiple OPD Centers in Ahmedabad through clinical questionnaires from 1st July 2017 to 31st dec 2017.

Inclusion criteria:
1. Age 18 to 60 years
2. Type 2 diabetes since one year or more, on stable drug regimen since three months or more and HbA1c less than or equal to 8.
3. No past history of any gastrointestinal surgery
4. No past history or any gastrointestinal diseases.
5. Thyroid disease on stable regimen since 6 month or more with normal thyroid function test
6. Normal renal function (MDRD eGFR more than 45)
7. Normal liver enzyme (less than three times upper normal level)
8. Normal ultrasound abdomen and pelvis (except fatty liver)
9. Fatty liver with normal NAFLD fibrosis score
10. Normal pancreatic enzyme level (less than three times upper normal level)

Exclusion criteria:
1. Patient not meeting inclusion criteria
2. Pregnancy
3. Lactating mother
4. History of smoking or alcohol consumption
5. Fatty liver with intermediate or severe NAFLD fibrosis score.

RESULTS:

During the period of six months total 5332 patients were screened for the presence of one or more symptoms of Diabetes autonomic neuropathy since three months or more through clinical questionnaire. Out of 5332 patients screened only 1008 patients met the inclusion criteria. We found that of 1008 patients who met inclusion criteria 449 patient (44.54%) were having one or more symptoms of diabetes autonomic neuropathy since three months or more.

CONCLUSIONS:

Diabetes gastric autonomic neuropathy is a more common and undereported issue. This patients may have underlying cardiac autonomic neruropathy, which remains undisguised if these patients are not further investigated. Further investigation and research is also warranted in this area.

O23 CARDIOVASCULAR AUTONOMIC NEUROPATHY AND SERUM URIC ACID: PREVENTING EARLY RENAL LOSS IN TYPE 1 DIABETES (PERL) TRIAL

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OBJECTIVES:

Elevated serum uric acid (SUA), an established risk factor for diabetic nephropathy (DN) may also be a risk factor for cardiovascular autonomic neuropathy (CAN). We evaluated the cross-sectional association between CAN and SUA levels in subjects with type 1 diabetes (T1D), mild to moderate chronic kidney disease (CKD) and a SUA ≥4.5 mg/dl enrolled in the ongoing PERL trial that is evaluating the effect of allopurinol on kidney function decline, specifically iohexol plasma disappearance glomerular filtration rate (iGFR).

METHODS:

497 subjects with T1D enrolled in PERL trial were evaluated for measures of renal function such as iGFR, estimated GFR (eGFR), and albumin excretion rates (AER). Standard 12 lead ECG was digitized and used to derive the RR interval by the ECGSCAN software (AMPS inc , NY). Measures of CAN included resting heart rate, standard deviation of normal RR interval (SDNN), and QTi (Bazzett formula).

RESULTS:

The mean age and duration of diabetes was 51 ± 11 years and 35 ± 12 years. The glycemic control was suboptimal with mean HbA1c of 8±1%. Subjects in the highest tertile of serum UA levels had worse measures of renal function (iGFR 60 ± 16 vs 74 ± 60 ml/min/1.73 m2 , eGFR 65.7 ± 18.1 vs. 82.7 ± 17.2 ml/min/1.73 m2 , AER 370 ± 783 vs. 1181 ± 475 mcg/mg creatinine) compared to those in the lowest tertile. SDNN correlated negatively with SUA levels ($r = -0.11$, $P = 0.0093$). In a multiple linear regression model, lower SDNN was associated with higher SUA levels independent of age, gender, BMI, blood pressure, and HbA1c ($\beta = -0.061$, SE= 0.021, $P = 0.0049$), but this association was no longer significant when adjusted for iGFR($\beta = -0.0184$, SE= 0.024, $P = 0.46$).

CONCLUSIONS:

In summary, elevated SUA was significantly associated with CAN in subjects with T1D independent of some traditional cardiovascular risk factors. This relationship operated, at least in part, through the inverse association of SUA levels with renal function which suggests that CAN and CKD share common pathological pathways which could be targeted by lowering SUA

O24 EARLY PARALLEL IMPAIRMENT OF SMALL AND LARGE FIBERS IN RECENT-ONSET TYPE 1 DIABETES PATIENTS

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OBJECTIVES:

We previously demonstrated an early parallel involvement of small and large fibers in recent-onset type 2 diabetes. Here we hypothesized that this pattern may also be pertinent to recent-onset type 1 diabetes (T1D).

METHODS:

We assessed nerve conduction velocity (NCV), quantitative sensory testing, and heart rate variability in 339 patients recently diagnosed with T1D and 108 control subjects with normal glucose tolerance (C). Demographic and clinical data (C/T1D): age: 34.9±10.1/34.7±11.1 (mean±SD) years; male: 69/59%; BMI: 26.1±5.3/24.6±3.9 kg/m²; diabetes duration: -/0.45±0.52 years; HbA1c: 5.1±0.3/6.7±1.3%. Intraepidermal nerve fiber density (IENFD) and dermal mitochondrial superoxide dismutase 2 (SOD2) expression were determined in subsets of 88/76 C/T1D subjects, respectively.

RESULTS:

After adjustment for sex, age, BMI, and smoking, motor NCV was slowed in T1D patients compared to C individuals in the peroneal (45.8±4.1 vs 47.8±3.8 m/s; P<0.0001), median, 55.0±3.8 vs 56.6±3.6 m/s; P<0.0001), and ulnar (56.7±4.9 vs 58.2±3.6 m/s; P=0.001) nerves, as was sural sensory NCV (45.4±5.2 vs 46.8±4.6 m/s; P<0.007). Likewise, warm temperature detection threshold was elevated (38.2±3.4 vs 37.4±2.9°C; P=0.007) and standard deviation (SD) of N-N intervals was diminished in T1D patients compared to C subjects (86±27 vs 99±33 ms; P=0.001). Moreover, both IENFD (9.9±4.2 vs 11.1±3.3 fibers/mm; P=0.01) and dermal SOD2 area were reduced in T1D patients compared to C persons (0.15±0.11 vs 0.24±0.16%; P=0.0001).

CONCLUSIONS:

These findings point to an early parallel impairment of both small and large nerve fibers accompanied by a diminished antioxidant defense in well-controlled recent-onset type 1 diabetes patients.

O25 RETINAL NEURAL LOSS IN SWEPT-SOURCE OPTICAL COHERENCE TOMOGRAPHY IS RELATED TO THE ACCUMULATION OF ADVANCED GLYCATION END PRODUCTS AND SMALL FIBER NEUROPATHY IN TYPE 1 DIABETIC PATIENTS PARTICIPATING IN POZNAN PROSPECTIVE STUDY (POPROSTU)

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OBJECTIVES:

Retinopathy is regarded as a neurodegenerative diabetic complication. The impaired sudomotor function is a sensitive marker of small fiber neuropathy (SFN). The aim of our study was to assess the relationship between retinal neural loss and SFN in patients with type 1 diabetes (T1D) participating in Poznan Prospective Study (PoProStu).

METHODS:

The study included 74 T1D subjects (46 men), aged 43 (IQR: 39-48)years, treated from the onset of the disease with intensive functional insulin therapy and observed prospectively with a median follow-up of 20 (19-21) years. Sudomotor function was assessed on the basis of electrochemical skin conductance (ESC) with SUDOSCAN device. The accumulation of advanced glycation end products in the skin was assessed with skin autofluorescence (AF) with AGE Reader. Retinal layers thickness were measured with swept-source optical coherence tomography (SS-OCT, Topcon). We assessed retinal nerve fiber layer (RNFL) and ganglion cell layer (GCL) thickness, central and average retinal thickness (RT). The results are presented for all eyes examined.

RESULTS:

At follow-up T1D patients' median A1c was 7.8 (7.2-8.5)%, skin AF 2.4 (2.1-2.7)AU, Feet ESC 80 (75-82.75) μS. We found diabetic retinopathy (DR) in 30 patients (40%), diabetic peripheral neuropathy (DPN) in 16 (22%), diabetic kidney disease (DKD) in 22 (29%). Patients with proliferative diabetic retinopathy (PDR) as compared to patients with NPDR and without DR had thinner average RT, total, superior and inferior RNFL thickness. We found negative correlations between skin AF and average RT (Rs=-0.19, p=0.02), superior GCL (Rs=-0.21, p=0.01), inferior GCL (Rs=-0.21, p=0.01), total GCL (Rs=-0.22, p=0.008), total RNFL (Rs=-0.20, p=0.017), inferior RNFL (Rs=-0.29, p<0.001) thickness. We found also positive correlations between FeetESC and average RT (Rs=0.34, p<0.001), superior GCL (Rs=0.31, p<0.001), inferior GCL (Rs=0.37, p<0.001), total GCL (Rs=0.35, p<0.001), total RNFL (Rs=0.18, p=0.029), inferior RNFL (Rs=0.22, p=0.008) thickness. In multiple linear regression models average RT, total GCL thickness and total RNFL thickness were related to Feet ESC independently from Hand ESC, skin AF and diabetes duration (β=0.39, p<0.001; β=0.49, p<0.001; β=0.17, p=0.005), R2=0.16, p<0.001, R2=0.21, p<0.001, R2=0.14, p<0.001 respectively.

CONCLUSIONS:

Small fiber neuropathy is closely and independently related to the neurodegeneration of the retina in type 1 diabetic subjects. Accumulation of advanced glycation end products has significant impact on the retinal neural loss in adults with long lasting T1D.

O26 CORNEAL NERVE FRACTAL DIMENSION ANALYSIS DETECTS A DISTINCT PATTERN OF LOSS BETWEEN PERIPHERAL NEUROPATHIES OF DIFFERENT AETIOLOGY.

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OBJECTIVES:

Corneal nerve fractal dimension analysis (CNFrD) is a novel metric to study the geometrical complexity of corneal nerves in corneal confocal microscopy (CCM) images. We have applied CNFrD in patients with clinically diagnosed peripheral neuropathies of different aetiologies to assess if there is a distinct pattern of corneal nerve loss amongst these conditions.

METHODS:

Patients with diabetes and peripheral neuropathy (DPN+) (n=29), without DPN (DPN-) (n=68), HIV associated sensory neuropathy (HIV-SN) (n=20), chemotherapy induced peripheral neuropathy (CIPN) (n=13), chronic inflammatory demyelinating polyneuropathy (CIDP) (n =34) and healthy controls (n=70) underwent CCM in their respective centres under the same imaging protocol and their images were analysed for corneal nerve fiber length (CNFL), CNFrD and the ratio of CNFrD/CNFL to adjust fractal dimension analysis for nerve length.

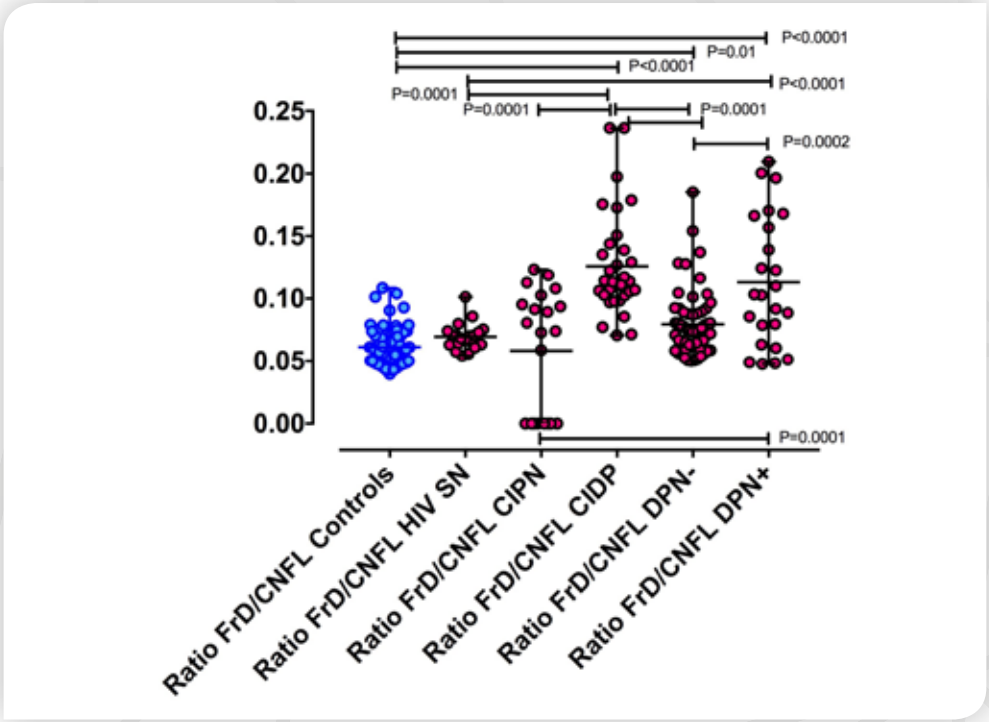
RESULTS:

DPN+ and CIPN patients were significantly older compared to DPN-, CIDP, HIV-SN and Controls (P<0.0001). CNFL was significantly reduced compared in DPN+, DPN-, CIDP and CIPN patients compared to controls (14.6±8.2 v 20.1±5.3 v 12.2±3.9 v 18.1±3.6 v 25.6±5.3mm/mm2, P<0.0001). CNFL was significantly lower in DPN+ compared to DPN- (P<0.0001) and HIV-SN (P<0.0001) and in CIDP compared to CIPN (P<0.0001) and HIV-SN (P<0.0001). CNFrD was significantly reduced in DPN+, DPN- and CIDP patients compared to controls (1.4±0.08 v 1.46±0.04 v 1.44±0.09 v 1.5±0.02, P<0.0001). CNFrD was significantly lower in DPN+ and in CIDP compared to DPN- (P<0.0001), CIPN (P<0.0001) and HIV-SN (P<0.0001). The ratio of CFNrD/CNFL was significantly increased in DPN+, DPN- and CIDP compared to controls (0.11±0.05 v 0.07±0.02 v 0.12±0.04 v 0.06±0.01, P<0.0001-0.01). The ratio of CNFrD/CNFL was significantly increased in DPN+ compared to HIV-SN (P<0.0001), DPN- (P=0.0002) and CIPN (P<0.0001) and in CIDP compared to HIV-SN (P<0.0001), CIPN (P<0.0001) and DPN- (P<0.0001).

CONCLUSIONS:

CCM can detect distinct patterns of corneal nerve loss in aetiologically different peripheral neuropathies in addition to varying neuropathic severity. These findings suggest a role for CCM in phenotyping neuropathy.

O26 CORNEAL NERVE FRACTAL DIMENSION ANALYSIS DETECTS A DISTINCT PATTERN OF LOSS BETWEEN PERIPHERAL NEUROPATHIES OF DIFFERENT AETIOLOGY.



O27 PREVALENCE OF NEUROPATHY IN PREDIABETES ESTIMATED BY QUANTITATIVE ASSESSMENT OF SUDOMOTOR FUNCTION

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OBJECTIVES:

Evidence has increasingly shown that patients with prediabetes have microvascular dysfunction representing end-organ damage typical of diabetes.
Sweat glands are innervated by small C fibers and sudomotor function assessment can be used to evaluate the peripheral autonomic nervous system. Measurement of Electrochemical Skin Conductance (ESC) is a simple, non-invasive, quick and quantitative method allowing assessment of sweat gland function. Previous studies have reported that ESC measurement correlates well with other validated standard neuropathy tests, especially in diabetes.
This study aimed to estimate the prevalence of neuropathy and nephropathy, another microvascular complication, in a large population of patients with prediabetes.

METHODS:

Study population. 825 prediabetic individuals (58% females), 58.6 ± 7.6 years old, with Impaired Fasting Glucose (IFG) and/or Impaired Glucose Tolerance (IGT) were recruited in the ongoing multicentre European Randomized Clinical Trial (ePREDICE) that aims to prevent the development of major microvascular complications through early intensive intervention in people with prediabetes.
Measurements: ESC was measured using the Sudoscan device (Impeto Medical, Paris, France). Subjects placed both palms and soles on stainless-steel electrodes during the 3-min scan. ESC expressed in microSiemens (µS), calculated for each foot and hand were recorded. Neuropathy was defined according to ESC results: a) No neuropathy: hands ESC ≥ 60 µS and feet ESC ≥ 70 µS; b) Neuropathy: hands ESC between 40 – 60 µS or feet ESC between 50-70 µS; and c) Severe neuropathy: hand ESC < 40 µS or feet ESC < 50 µS. Kidney function was also evaluated using Kidney Disease Improving Global Outcomes (KDIGO) Clinical Practice guidelines calculating the estimated glomerular filtration rate (eGFR) using the CKD-EPI and MDRD-4 formulae.

RESULTS:

The percentages of neuropathy and nephropathy in this population are displayed in the Table. In this population of people with prediabetes the prevalence of some degree of neuropathy and nephropathy appeared comparable (32% and 31%, respectively). The percentage of neuropathy increased with the decrease in eGFR (Figure).

CONCLUSIONS:

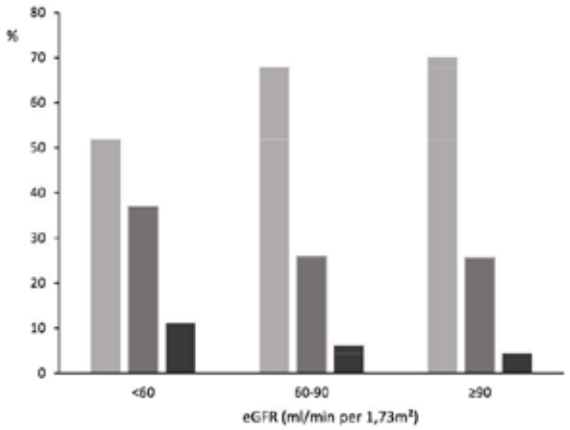
Evaluation of the 2 complications seems complementary. Such high prevalence justifies early intensive intervention whose efficacy can be evaluated using ESC assessment, a non-invasive and quantitative test.

O27 PREVALENCE OF NEUROPATHY IN PREDIABETES ESTIMATED BY QUANTITATIVE ASSESSMENT OF SUDOMOTOR FUNCTION

Table 1. The prevalence of neuropathy and nephropathy in 825 people with prediabetes. Results are expressed as percentages.

Neuropathy	
No neuropathy (hands ESC ≥ 60 and feet ESC ≥ 70 µS)	68
Neuropathy hands ESC < 60 or feet ESC < 70 µS)	26
Severe neuropathy (hands ESC < 40 or feet ESC < 50 µS)	6
Nephropathy	
Normal eGFR (CKD-EPI ≥ 90 ml/min per 1.73m²)	69
Decreased eGFR (90 > CKD-EPI ≥ 60 ml/min per 1.73m²)	28
Severe decrease in eGFR (MDRD < 60 ml/min per 1.73m²)	3

Figure. Percentage of neuropathy by estimated glomerular filtration rate (eGFR) (light grey: no neuropathy; dark grey: neuropathy; black: severe neuropathy)



O28 CORNEAL NERVE FIBRE LOSS IS ASSOCIATED WITH WHITE MATTER HYPERINTENSITIES IN PATIENTS WITH ACUTE ISCHEMIC STROKE

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OBJECTIVES:

To determine whether corneal nerve pathology can act as a surrogate biomarker for the presence of White Matter Hyperintensities (WMH) in people with acute stroke.

METHODS:

236 patients admitted with acute ischemic stroke underwent corneal confocal microscopy to quantify corneal nerve fibre density (CNFD), corneal nerve branch density (CNBD) and corneal nerve fibre length (CNFL) and MRI to quantify deep white matter (DWMH) and periventricul (PWMH) WMH's according to the Fazekas scale. Statistical analysis was performed using ANOVA and multiple regression.

RESULTS:

DWMH and PWMH were absent (49%,41%) or present with mild (33%,32%), moderate (13%,18%) and severe (5%,9%) severity in patients with acute ischemic stroke. 58% of of all the stroke patients had type 2 diabetes and 51% of the stroke patients with type 2 diabetes had WMH's.
CNFD (P=0.009) and CNFL (P=0.015) were significantly lower in patients with severe DWMH compared to no DWMH. CNFD was significantly lower in patients with mild PWMH compared to no PMWH (P=0.049). CNFL (P=0.015) and CNBD (P=0.012) were significantly lower in patients with severe PWMH compared to no PWMH.
Multiple regression analysis showed a correlation between CNFD and DWMH severity (β= -2.040, P=0.007) and HbA1c (β= -0.686, P=0.028). Also, CNFD showed correlation with PWMH severity (β= -1.606, P=0.017) and HbA1c (β= -0.615, P=0.049). There was no correlation of DWMH and PWMH with age, cholestrol, triglycerides and blood pressure.

CONCLUSIONS:

Corneal confocal microscopy allows rapid non-invasive imaging of corneal nerve pathology in patients with mild and severe PWMH and severe DWMH and furthermore corneal nerve fibre density correlates with the severity of WMH and HbA1c.

O29 ASSOCIATION OF CORNEAL ENDOTHELIAL CELLS WITH CEREBRAL SMALL VESSEL DISEASE IN PATIENTS WITH ACUTE ISCHEMIC STROKE

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OBJECTIVES:

To determine whether corneal endothelial cells pathology can act as a surrogate biomarker for the presence of White Matter Hyperintensities (WMH).

METHODS:

180 patients admitted with acute ischemic stroke underwent corneal confocal microscopy to quantify endothelial cells density (ECD), cells area (ECA), cells perimeter (ECP), polymegathism and pleomorphism and MRI to quantify deep white matter (DWMH) and periventricul (PWMH) WMH's according to the Fazekas scale. Patients were further classified into no vessel disease (NVD), small vessel disease (SVD) and large vessel disease (LVD). Statistical analysis was performed using ANOVA and multiple regression.

RESULTS:

DWMH and PWMH were absent (53%,45%) or present with mild (34%,32%), moderate (11%,17%) and severe (2%,6%) severity in patients with acute ischemic stroke.
53% of the stroke patients had type 2 diabetes and 50% of the stroke patients with type 2 diabetes had WMH's.
There was no significant difference in ECD (P=1.000), ECA (P=1.000), ECP (P=1.000), polymegathism (P=1.000) and pleomorphism (P=1.000) in patients without DWMH compared to to any grade of DWMH severity. Similarly, there was no significant difference in ECD (P=0.666), ECA (P=0.630), ECP (P=0.528), polymegathism (P=1.000) and pleomorphism (P=1.000) in patients without PWMH compared to with PWMH.
Furthermore, ECD, ECA, ECP, Polymegathism and pleomorphism were not significantly different in NVD compared to SVD (P=1.000) and LVD (P=1.000). Multiple regression analysis, except age (P=0.034), showed no correlation of ECD with DWMH (P=0.364), systolic blood pressure (P=0.744), diastolic blood pressure (P=0.298), HbA1c (P=0.849), cholesterol (P=0.813) and triglycerides (P=0.364). Also, except age (P=0.047), there was no correlation of ECD with PWMH (P=0.995), systolic blood pressure (P=0.901), diastolic blood pressure (P=0.312), HbA1c (P=0.912), cholesterol (P=0.843) and triglycerides (P=0.544).

CONCLUSIONS:

Corneal confocal microscopy allows rapid non-invasive imaging of corneal endothelial cells in patients with acute stroke. Endothelial cells showed no correlation with WMH. Furthermore, corneal endothelial cells fibre density was only correlated with age.

O30 POLYMER COATED PROPRIETARY CREAM FORMULATION OF RESINIFERATOXIN NANOPARTICLES FOR THE TREATMENT OF PAIN ASSOCIATED WITH DIABETIC PERIPHERAL NEUROPATHY

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OBJECTIVES:

Diabetes is a major problem in developed and developing countries. One of the major complications of diabetes is diabetic peripheral neuropathy (DPN) resulting in pain from the extremities referred to as painful DPN (PDPN). We have been working on Transient Receptor Potential Vanilloid 1 (TRPV1) receptor, an ion channel expressed in the peripheral terminals of sensory neurons that is activated by capsaicin. TRPV1 agonists such as resiniferatoxin (RTX) can be useful to treat painful conditions by virtue of their ability to cause calcium influx leading to peripheral nerve terminal desensitization/depletion.

METHODS:

Preparation of polymer coated proprietary cream formulation of RTX and testing it in animal models of diabetic peripheral neuropathy.

RESULTS:

We have been working on an ultrapotent TRPV1 agonist, resiniferatoxin (RTX), obtained from the spurge Euphorbia resinifera, which has a high affinity for the receptor and able to fully activate the receptor in femtomolar concentration ranges. Therefore, lower concentrations can activate the channel slowly in a ramp-like fashion avoiding rapid depolarization and preventing generation of action potentials, as a result RTX cream does not induce pain during application. We have prepared a polymer coated proprietary cream formulation of RTX nanoparticles trade marked as (NanoResinizinTM) and determined the permeability of RTX across artificial skin membranes. We have determined the lowest effective concentration range of RTX in animal models (rats) of diabetes that alleviates pain associated with DPN. We have used radiant heat and a state of the art Diode laser fiber type selective stimulation (DLss) approach for Aδ or C fibers. This method can be applied effectively in humans during the phase II of the translational phase.

CONCLUSIONS:

Recently, an eight percent capsaicin containing patch (Qutenza) has been approved for the treatment of PDPN in Europe. Since activation of TRPV1 depolarizes the nerve terminal and generates action potentials leading to pain, lidocaine, a local anesthetic is applied to numb the area prior to application of capsaicin patch. We propose that NanoResinizinTM cream will be cost effective and can replace the use of capsaicin (8%) plus lidocaine to treat painful conditions, use of which is both cumbersome and associated with significant side effects.

O31 AUTONOMIC NEUROPATHY AND CARDIOVASCULAR MORTALITY IN TYPE 2 DIABETES (T2D) WITH LOWER LIMB NEUROPATHIC AND NEUROISCHEMIC LESIONS. ITALIAN LEUKEMIA ASSOCIATION TREVISO PROJECT.

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OBJECTIVES:

Diabetic foot is an advanced complication leading on non traumatic limb amputations and cardiac mortality; the pathogenesis and cardiovascular implication is a debating issue. Epidemiological studies confirm that prevalence of cardiovascular mortality in diabetic foot is similar to lung cancer mortality and its reduction a public health burden. One possible link between diabetic foot peripheral neuropathy and cardiovascular death could be autonomic neuropathy, peripheral precursor bone marrow derived cell homing and cardiac neuroischemia.

METHODS:

Subjects: We studied 200 T2D patients with neuropathic foot lesions with (87) or without (117) critical limb ischemia (pO2 <30 mm Hg) at time of treatment and after prospective 5 years for survival. We observed 42 cardiac deaths (DD) all in neuroischemic patients and 158 alive patients (AD). DD were older (69±1 vs 64±1 yrs), without differences in diabetes age, BMI, lipidic parameters and HbA1c (8.3±0.3 vs 8.9±0.4) oximetry and TUC lesion grade. At basal time, all neuropathic patients had autonomic failure but only DD patients were orthostatically hypotensive (Δ mm Hg22±3 vs 35±2 $p<0.04$) At time 0 in peripheral blood samples we evaluated: white and red blood cell count in whole blood; haematopoietic cluster differentiaton (CD34+) on progenitor (ProC) and VEGF receptor (KDR+) on CD34 endothelial precursor cells (PreC) by flow cytometry. Available retrospective biochemical data (2-12 years) were considered for mathematical indexes relative to HbA1c and glycemic variability [Stability (SI) and Lability (LI) indexes, Standard Deviation (SD), Coefficient of Variation (CV), CONGA(CO)],

O31 AUTONOMIC NEUROPATHY AND CARDIOVASCULAR MORTALITY IN TYPE 2 DIABETES (T2D) WITH LOWER LIMB NEUROPATHIC AND NEUROISCHEMIC LESIONS. ITALIAN LEUKEMIA ASSOCIATION TREVISO PROJECT.

RESULTS:

Results: At basal time serum haemoglobin and absolute lymphocyte count (L) were significantly reduced in DD versus AD (11±.3 vs 13±.1 gr/dl; 1634±98 vs2157±80/mm3 p< 0.0004). In DD group we observed significant reduced circulating preC (4.7±0.8 vs 6.6±0.4 % of 106 events p= 0.047), and increased circulating proC (.12 ±0.2, vs 0.09±0.004 % 106 of events p=0.03), with a significant different ratio of nCD34+/CD34+KDR+(148±26 vs 89±10 106 events p=0.01). As for L cells distribution, also nCD34+/CD34+KDR+ seem to correlate with orthostatic Δ PAO but not with glycemic variability indexes

CONCLUSIONS:

Conclusions: By prospective data we demonstrated how autonomic failure impacts on cardiac mortality in type 2 diabetic patients with prevalent neuroischemic foot. Glycemic variability and tissue glycosylation do not explain in our population immunological assessment, stemness behaviour and cardiac death. We hypothyze that peripheral homing of endothelial progenitor and immune cells could be irreversibly lost by blood flow redistribution inducing oxidative stress, apoptosis and regenerative incapacity.

O32 SARCOPENIA AND PERIPHERAL NEUROPATHY IN PATIENTS WITH DIABETES MELLITUS TYPE 2

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OBJECTIVES:

Purpose of this pilot crossectional study is to evaluate clinical and instrumental features of peripheral neuropathy and sarcopenia in patients with type 2 diabetes mellitus (DM) in hospital settings.

METHODS:

144 patients over 60 years old were examined: 81 DM patients and 63 sex and age-matched patients without DM. Antropometric and clinical characteristics were evaluated. Peripheral neuropathy was studied with calculation of TSS, NDS and NIS-LL scales. Muscle strength was measured with carpal dynamometry, muscle function was evaluated with short physical performance battery (SPPB) tests. Skeletal muscle mass index (SMMI) was evaluated with bioimpedance testing using ABC-01 MEDASS analyser (Russia). Patients with decrease of skeletal muscle mass index and/or muscle strength and/or muscle function were diagnosed as sarcopenic (S)

RESULTS:

Sarcopenia revealed in 32 (40%) patients with DM (S+DM), aged 74,5 [68;79] years and 10 [4,25;16] years diabetes duration with HbA1c 9,8 [7,1;10,9] % and in 27 (43%) patients without DM (S-DM) aged 76 [67,5;79] years. . S+DM patients demonstrated more often chronic kidney disease (59%) than S-DM (26%, p=0,009). S+DM patients noted more often frequency of falls (72%) in comparison with S-DM group (48%, p=0,050). S+DM group demonstrated more often frequency of fractures (69%) than S-DM group (37%), p=0,014. Antropometric and bioimpedance characteristics did not differ between groups. Both groups demonstrated low SMMI: 6,3 [5,62;6,5] in S+DM and 6,25 [5,63;6,48] kg/m2 in S-DM groups (p=0,962). Dynapenia was more pronounce in S+DM (15 [10;19,75]) vs S-DM group (20 [15,75;23,00] kg, p=0,09). Muscle function did't differ between groups.
Diabetic neuropathy was diagnosed in 31 (97%) patients in S+DM. Peripheral neuropathy was moderate severity (NDSm: 4,75[3;6], NISLL: 12[6,5;1] points) with mild pain intensity (TSS 3,16 [0;5,99] points). S+DM patients had decreased VPT (4 [3;5] c.u. using 128 Hz tuning fork and 21 [14;28] volts with biothesiometer. Decreased pressure perception to monofilament SW5.07 revealed in 88% of S+DM patients. Pain, temperature, sense of position, Achilles reflexes, muscle weakness of toe extensors and flexors were disturbed in patients with S+DM. S-DM group doesn't demonstrate such extent of neuropathy severity in lower extremities.

CONCLUSIONS:

Sarcopenia revealed in 40% of patients with DM2 and in 43% of patients without DM2. Bioimpedance characteristics such as fat mass, muscle mass, mineral mass of bones were similar in both sarcopenia groups. DM patients with sarcopenia characterised by moderate severity of diabetic neuropathy with large and small fiber function loss. Combination of large fiber neuropathies with decreased muscle mass in T2DM patients with sarcopenia increases the risk of falls and fractures more intensively than in patients with sarcopenia without diabetes mostly due to peripheral neuropathy

O33 THE PREVALENCE AND CHARACTERISTICS OF DIABETIC SYMMETRIC SENSORIMOTOR POLYNEUROPATHY IN JAPANESE TYPE 2 DIABETIC PATIENTS

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OBJECTIVES:

This study aims to investigate the prevalence and characteristics of diabetic symmetric sensorimotor polyneuropathy (DSPN) in type 2 diabetic patients registered in the Japan Diabetes Complication and its Prevention Prospective (JDCP) study.

METHODS:

In the JDCP study, 6,338 diabetic patients who had been treated by diabetes specialists were registered in 2007 - 2009. Of these, type 2 diabetic patients who could be evaluated for DSPN were analyzed by using t-test, chi-square test and logistic regression analysis. The diagnosis of DSPN was performed by using simple diagnostic criterion for diabetic polyneuropathy proposed by Diabetic Neuropathy Study Group in Japan. This criterion should meet two or more of the following three items: 1) sensory symptoms (SS) considered to be due to DSPN, 2) bilaterally decreased or absent Achilles tendon reflex (ATR) and 3) decreased vibratory perception threshold (VPT) in bilateral medical malleoli.

RESULTS:

Of the total of 6,338 participants, 5,451 patients (mean age 61.4 yrs-old, duration of diabetes 10. 8 yrs, BMI 24.5 and HbA1c 7.42%) were analyzed. The prevalence of positive SS, bilaterally decreased/absent ATR and symmetric decrease in VPT were 25.8%, 40.9% and 48.1%, respectively. Based on simple diagnostic criterion, DSPN was observed in 35.8% of the total. Among them, 15.3% of the total (42.6% of diagnosed as DSPN patients) were asymptomatic DSPN defined by both bilaterally decreased/absent ATR and decreased VPT in bilateral medical malleoli without any sensory symptoms. The decrease/absence of bilateral ATR showed high sensitivity (87.2%) and specificity (84.8%) in the diagnosis of DSPN. In the group with DSPN, we investigated the odds ratio (OR) of covariates for neuropathy and found that the age (OR 1.57, $p<0.001$), the duration of diabetes (OR 1.32, $p<0.001$), BMI (OR 1.19, $p<0.001$), T-cho (OR 0.98, $p<0.05$), insulin therapy (OR 1.59, $p<0.001$), systolic blood pressure (OR 1.06, $p<0.01$), HbA1c (OR 1.15, $p<0.001$), oral administration of biguanide (OR 1.22, $p<0.01$) and exercise therapy (OR 0.85, $p<0.05$) showed significance.

CONCLUSIONS:

Baseline survey of the JDCP study showed the prevalence of DSPN defined by simple diagnostic criterion for diabetic polyneuropathy in type 2 diabetic patients was similar to that reported previously in JAPAN and suggested that the evaluation of bilateral ATR would be useful for the diagnosis of DSPN.

O34 CONTEMPORARY PREVALENCE OF DIABETIC NEUROPATHY IN TYPE 1 DIABETES (T1D): FINDINGS FROM THE T1D EXCHANGE

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OBJECTIVES:

Diabetic peripheral neuropathy (DPN) is a major cause of disability, mortality and poor quality of life in patients with T1D, with prior reported prevalence rates of up to 35%. The contemporary prevalence of DPN in T1D patients was evaluated in T1D Exchange Registry centers throughout the United States.

METHODS:

The Michigan Neuropathy Screening Instrument (MNSI), a validated 15-item self-administered questionnaire, was used to assess DPN in adults ≥18 years with ≥ 5 years of T1D duration. A score of ≥4 was used to define DPN. Diabetes-related characteristics and laboratory data were obtained through the most recent clinic update. Chi-square and t-tests were used to compare demographic and diabetes-related characteristics between those with and without DPN. Linear regression was used to determine the effect of DPN on HbA1c, adjusted for possible confounders.

RESULTS:

In preliminary analyses of 5,058 participants across 62 sites (mean age 39±18 years, T1D duration 22±14 years, 56% female, 88% non-Hispanic White, mean HbA1c 8.1±1.6%), the prevalence of DPN was 10%. Those with DPN were older (52±17 vs 37±18 years), more likely to be female (61% vs 55%), had longer T1D duration (32±16 vs 21±13 years), lower annual household income (37% vs. 59% earning ≥$75K), and lower education level (55% vs. 69% with college degree) than those without DPN (all $p<0.001$). They also had higher systolic blood pressure (126±17 vs 123±14 mmHg), triglycerides (117±89 vs 95±62 mg/dL), tobacco use (9% vs 4%) and prevalence of established CVD (26% vs 6%), despite higher use of CVD-modifying agents such as statins (64% vs 31%) and ACE-inhibitors/ARBs (45% vs 23%) (all $p<0.001$). Participants with DPN had higher HbA1c (8.4±1.7% vs 8.1±1.6%), even after adjusting for multiple confounders ($p<0.01$).

CONCLUSIONS:

The prevalence of DPN in this national T1D cohort is lower than prior published reports, reflecting current clinical care practices, and highlighting other non-glycemic risk factors for DPN including CVD risk factors and socioeconomic status.

O35 VALIDITY OF A POINT-OF-CARE NERVE CONDUCTION DEVICE FOR POLYNEUROPATHY: RESULTS FROM THE CANADIAN STUDY OF LONGEVITY IN TYPE 1 DIABETES

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OBJECTIVES:

Point-of-care nerve conduction devices (POCD) have been studied in younger patients and may facilitate screening for polyneuropathy in non-specialized clinical settings. However, performance may be impaired with advanced age owing to age-related changes in nerve conduction. We aimed to evaluate the validity of a POCD as a proxy for standard nerve conduction studies (NCS) in older adults with type 1 diabetes (T1D).

METHODS:

Sural nerve amplitude potential (AMP) and sural nerve conduction velocity (CV) was measured in 68 participants with ≥ 50 years T1D duration and 71 controls (from age/sex-matched subgroups) using POCD and NCS protocols. Agreement was determined by the Bland-Altman method, and validity was determined by receiver operating characteristic curves.

RESULTS:

T1D were 53% female, aged 66±8yr and had diabetes duration 54yr[52,58]. Controls were 56%(p=0.69) female and aged 65±8yr(p=0.36). Mean AMPPOCD and CVPOCD for the 139 participants was 7.4±5.8μV and 45.7±11.2m/s and mean AMPNCS and CVNCS was 7.2±6.1μV and 43.3±8.3m/s. Mean difference of AMPPOCD−AMPNCS was 0.3±3.8μV and was 2.3±8.5m/s for CVPOCD−CVNCS. A AMPPOCD of ≤6μV had 80% sensitivity and 80% specificity for identifying abnormal AMPNCS, while a CVPOCD of ≤44m/s had 81% sensitivity and 82% specificity to identify abnormal CVNCS. Abnormality in AMPPOCD or CVPOCD was associated with 87% sensitivity, while abnormality in both measures was associated with 97% specificity for polyneuropathy identification.

CONCLUSIONS:

The POCD has strong agreement and diagnostic accuracy for identification of polyneuropathy in a high-risk subgroup and thus may represent a sufficiently accurate and rapid test for routinely detecting those with electrophysiological dysfunction.

O36 THE PREVALENCE OF PERIPHERAL NEUROPATHY IN PREDIABETES: A SYSTEMATIC REVIEW AND META-ANALYSIS

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OBJECTIVES:

There is an excess of peripheral neuropathy in prediabetes and its inferred causality remains controversial. We performed a systematic review and meta-analysis to determine the prevalence of peripheral neuropathy in prediabetes from published research.

METHODS:

Five electronic databases namely, MEDLINE, EMBASE, PubMed, Web of Science and Cochrane Central Register of Controlled Trials were searched from inception to October 2017. Original, observational studies were included providing prevalence data for a population with prediabetes, aged ≥18 years. Additional studies were identified from reference lists and two reviewers independently identified eligible studies, extracted data and undertook risk assessment scores. A pooled prevalence estimate, with 95% CI, was calculated using the random-effects method (REVMAN 5.3). Subsequent subgroup analysis based on the method of neuropathy assessment used was undertaken.

RESULTS:

In total, 1503 studies were identified. After the removal of duplicates and the subsequent exclusion of 1255 studies, 59 studies remained. The full-text of the remaining studies were assessed for eligibility and 21 studies (participants=6494) met a priori inclusion criteria for the meta-analysis. The pooled prevalence estimate of neuropathy in prediabetes was 18% (95% CI: 14-22%) with a marked level of heterogeneity (I2 = 96%) which was partly explained by the method of neuropathy assessment. Subgroup analyses showed the prevalence was dependent on the method of assessment, namely questionnaires with physical examination 16% (95% CI: 11 - 21%, I2 = 95%) (n=9), quantitative testing 19% (95% CI: 11 - 27%, I2 = 96%) (n=8), physical examination 14% (95% CI: 10-19%, I2 = 9%) (n=2), or a combination of methods 11% (95% CI: 5 - 18%) (n=1). One study did not disclose the method of neuropathy assessment and was therefore excluded from the subsequent sub-analyses. The pooled prevalence of neuropathy in diabetes was 34% (95% CI: 33 - 35%, I2 = 99%) (n=17). The overall risk of bias of all studies was low at 2.1 (95% CI: 1.6-2.5) (out of 10).

CONCLUSIONS:

The prevalence of peripheral neuropathy is higher than expected suggesting screening for neuropathy should occur much earlier and in prediabetes. Future large, population based studies using accurate and quantitative means of quantifying small nerve fibres are required to determine the precise prevalence of neuropathy.

POSTER ABSTRACTS

P1 CLINICAL FACTORS ASSOCIATED WITH REGRESSION OF CARDIOVASCULAR AUTONOMIC NEUROPATHY IN ADULTS WITH TYPE 2 DIABETES

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OBJECTIVES:

Cardiovascular autonomic neuropathy (CAN) is a significant cause of morbidity and mortality in subjects with diabetes. Although risk factors for CAN progression have been established in a number of researches, it is still not identified whether CAN could be regressed and which clinical factors are associated with this regression. This study aimed to determine the clinical variables for CAN regression.

METHODS:

Subjects with type 2 diabetes and CAN but free of cardiovascular disease at baseline were enrolled in this retrospective longitudinal study and these subjects were followed up over 2-3 years. CAN was classified as early (1 abnormal parasympathetic test), definite (2 or 3 abnormal parasympathetic tests), severe (definite plus orthostatic hypotension), atypical (any other combination of abnormalities), according to heart rate variability measured by DICAN system. CAN regression was defined as follows: 1) from early to normal, 2) from definite to early or normal, 3) from severe to definite, early or normal, 4) from atypical to the disappearance of one abnormal parasympathetic results or orthostatic hypotension.

RESULTS:

Among a total of 759 subjects with type 2 diabetes and CAN, 227 (29.9%) subjects had regressed, 489 (64.4%) subjects remained unchanged, and 43 (5.7%) subjects had progressed during follow-up period. CAN regression was associated with younger age, male gender, body weight loss, shorter duration of diabetes, higher triglycerides, higher estimated GFR, normoalbuminuria, none use of statin, none use of anti-hypertensive drug, and none use of anti-platelet agents in univariate analysis, whereas glycemic parameters including mean HbA1c during follow-up was not associated with this regression. In multivariate analysis, age (odds ratio [OR] 0.64, 95% confidence interval [CI] 0.57-0.72, p <0.001), and weight gain (OR 0.95, 95% CI 0.92-0.99, p = 0.019) were significantly associated with the CAN regression. Age-stratified incidence of CAN regression was 88.5% in <40 years, 63.6% in 40-49 years, 30.7% in 50-59 years, 18.6% in 60-69 years, and 15.5% in ≥70 years. Change in body weight-stratified incidence of CAN regression was 34.9% in < -2.0% (first tertile), 28.7% in
-2.0 to 1.1% (second tertile), and 26.1% in >1.1% (third tertile) of body weight change. In subjects aged ≤58 years (N = 343), who experienced relatively high rates of CAN regression than in other age group, current smoking (OR 0.40, 95% CI 0.21-0.78, p = 0.007) was an additional predictor for CAN regression along with weight gain (OR 0.91, 95% CI 0.86-0.96, p <0.001) and duration of diabetes (OR per 5 years 0.71, 95% CI 0.56-0.91, p = 0.007).

CONCLUSIONS:

CAN regression occurred more frequently in younger subjects with type 2 diabetes. Smoking cessation and body weight reduction were the modifiable factors for CAN regression in younger subjects with type 2 diabetes.

P2 PROGRESSION OF CARDIOVASCULAR AUTONOMIC NEUROPATHY AND CARDIOVASCULAR DISEASE IN TYPE 2 DIABETES

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OBJECTIVES:

To examine whether the progression rate of cardiovascular autonomic neuropathy (CAN) stage is an independent predictive factor for cardiovascular disease (CVD) in type 2 diabetes.

METHODS:

Standardized cardiovascular autonomic reflex tests (CARTs) using traditional Ewing's methods were performed at baseline and follow-up CARTs were performed within 3 years after the baseline test. We estimated the primary CVD endpoint, which was defined as coronary artery disease and ischemic stroke. The association between the progression rate of CAN stage and CVD was examined using time-dependent Cox proportional hazard models.

RESULTS:

At baseline, 578 patients completed follow-up CARTs; the cohort comprised 329 women (56.9%) with a mean age of 58.3 ± 10.3 years and a mean diabetes duration of 10.1 ± 6.2 years. One hundred and seventy-six patients (30.4%) developed CAN progression between baseline and follow-up CARTs. The median time of follow-up was 7.3 years. During the study period, the CVD event occurred in 55 patients (9.3%). The overall incidence rate of CVD event was 1.27 per 100 patient-years. In multivariable Cox proportional hazards regression analysis, patients with progression of CAN stage showed a 3.32 times higher risk (95% confidence interval, CI 1.81–6.14, P <0.001) of CVD than those without progression. Patients who experienced CAN progression from the normal to definite stage had the greatest risk of CVD compared with other patients (hazard ratio 4.91, 95% CI 2.05–11.77, P for trend = 0.001). The association between the progression of CAN and CVD increased in participants aged under 60 years, with a diabetes duration below 10 years, a BMI below 25 kg/m2, and a mean HbA1c >9% (P for interaction <0.001).

CONCLUSIONS:

CAN stage progression was associated with an increased risk of CVD in this type 2 diabetes cohort. Rapid progression of CAN showed the greatest risk of CVD among CAN progression groups. Thus, regular screening and risk management for CAN progression is necessary to prevent CVD in type 2 diabetes.

P3 EXOGENOUS PYRUVATE AS A CRITICAL MOLECULE FOR MAINTENANCE OF GLYCOLYSIS-TRICARBOXYLIC ACID CYCLE IN SCHWANN CELLS UNDER HIGH GLUCOSE CONDITIONS

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OBJECTIVES:

Endogenous pyruvate produced from glucose via glycolysis is a key molecule in energy production under aerobic and anaerobic conditions, whereas exogenous pyruvate is incorporated into cells via monocarboxylate transporters and principally works as an antioxidant. It has been reported that the treatment of diabetic animals with pyruvate alleviates oxidative stress and restores retinopathy and nephropathy. This study aimed to explore the beneficial effects of pyruvate on diabetic neuropathy and the role of exogenous pyruvate in the functional maintenance of Schwann cells under high glucose conditions.

METHODS:

Immortalized adult mouse Schwann cells (IMS32) were exposed to normal (5 mM) and high glucose (>15 mM) conditions in the presence or absence of sodium pyruvate (1 mM) for up to 24 h. Cell viability and glucose uptake and metabolism under each culture condition were evaluated using MTS cell proliferation assay, trypan blue staining, liquid chromatography coupled with tandem mass spectrometry, metabolome and the Extracellular Flux Analyzer.

RESULTS:

Rapid IMS32 cell death under high glucose conditions in the absence of exogenous pyruvate was surprisingly observed. The subsequent analyses resulted in the following findings: 1) Pyruvate starvation had no influence on glucose uptake into IMS32 cells but had an inhibitory effect on glycolytic flux, mitochondrial respiration, and ATP synthesis under high glucose conditions.
2) Exposure of IMS32 cells to high glucose and pyruvate-deficient conditions induced substantial increases in the intracellular contents of the polyol pathway products, such as sorbitol and fructose, and glycolysis intermediates, such as fructose 1, 6-bisphosphate and glycelaldehyde 3-phosphate. Substantial decreases were observed in tricarboxylic acid (TCA) cycle intermediates.
3) Supplementation with TCA cycle intermediates (e.g., 2-oxoglutarate) as well as pyruvate completely prevented IMS32 cell death and ATP depletion.
4) Treatment with benfotiamine, a transketolase activator that reduces flux in the collateral glycolysis pathways, completely prevented IMS32 cell death.

CONCLUSIONS:

Pyruvate starvation enhances glucose flux in the polyol and other collateral glycolysis pathways and reduces flux in the glycolysis-TCA cycle in IMS32 cells under high glucose conditions. These metabolic alterations can decrease ATP production in mitochondria, thereby causing rapid Schwann cell death.

P4 SYMPTOMS OF DIABETIC POLYNEUROPATHY ARE RELATED TO FALLS AND FRACTURES IN PATIENTS WITH TYPE 2 DIABETES

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OBJECTIVES:

Distal sensorimotor polyneuropathy may cause impaired balance and unstable gait, which combined with decreased joint mobility and incoordination leads to an increased risk of falls and bone fractures. Falls may have serious consequences including decreased mobility, physical inactivity and higher morbidity and mortality.

METHODS:

We performed a cross-sectional analysis of survey data on patients with type 2 diabetes included in the cohort established by the Danish Center for Strategic Research in Type 2 Diabetes (DD2) in 2011. Questionnaires were sent to 7,011 and 77% of patients returned the questionnaire with complete data on falls and neuropathic symptoms. Based on patients past medical history we obtained information concerning the frequency of fall-related bone fractures.

RESULTS:

We analyzed data from 5,315 patients with type 2 diabetes that had answered questions concerning MNSI and fall frequency. Falls were reported in 17% (896) of patients during the past year, and 9% (505) had experienced 2 or more falls.

CONCLUSIONS:

Cross-sectional data from this large national database show that patients with type 2 diabetes with 4 or more neuropathic symptoms have a 3-4 fold higher odds ratio of falls unrelated to alcohol consumption, smoking, physical activity, BMI, gender and age. At the meeting, we will present results concerning frequency of fall-related fractures.

P5 CORNEAL CONFOCAL MICROSCOPY SHOWS NERVE REGENERATION AFTER TREATMENT WITH EXENATIDE/ PIOGLITAZONE OR BASAL/BOLUS INSULIN IN PATIENTS WITH POORLY CONTROLLED T2DM

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OBJECTIVES:

There are no approved therapies for diabetic peripheral neuropathy (DPN), a major risk factor for diabetic foot ulceration and amputation. The LEADER trial has recently shown a reduction in the incidence of foot ulceration and amputation in T2DM patients treated with Liraglutide. The aim of the study is to compare the effects of combination therapy with Exenatide once weekly/Pioglitazone vs basal plus prandial insulin on structural and functional measures of DPN in patients with poorly controlled T2DM.

METHODS:

In a sub-group of the Qatar Study (n=46; age=50±1, female=47%, BMI=30.9±1.1, diabetes duration=11.1±1.0 years), patients with T2DM and poor glycemic control (HbA1c=10.5±0.3) despite treatment with maximal dose of sulfonylurea and metformin were randomly assigned to receive pioglitazone (30mg) plus weekly Exenatide (2mg) (combination) or basal plus prandial insulin (insulin), and underwent corneal confocal microscopy, assessment of painful neuropathy using DN4, vibration perception threshold using a Neurothesiometer and sudomotor function using Sudoscan.

RESULTS:

Participants were examined at baseline and at 12 months follow up. HbA1c was markedly reduced in the combination (10.6±1.8% to 7.1±1.4%, P<0.0001) and insulin (10.4±1.3% to 7.2±0.9%, P<0.0001) therapy groups and combination therapy also reduced triglycerides (P=0.01). Subjects on insulin showed a significant increase in corneal nerve branch density (CNBD) (P<0.001) and fibre length (CNFL) (P<0.001) but not fibre density (CNFD), whereas subjects on combination therapy showed an increase in CNBD (P=0.04) and DN4 (P=0.06). Both therapies showed no improvement in vibration perception (P=0.5-0.7) or sudomotor function (P=0.2-0.8). There was no relationship between the degree of HbA1c reduction and improvement in corneal nerve parameters.

CONCLUSIONS:

Exenatide/pioglitazone combination therapy and insulin therapy equally effectively reduce HbA1c in poorly controlled T2DM patients and induce corneal nerve fibre regeneration and a reduction in painful neuropathic symptoms, without an improvement in vibration perception or sudomotor function.

P6 RISK OF DEATH IN PATIENTS WITH TYPE 2 DIABETES AFFECTED BY MODERATE AND SEVERE DIABETIC NEUROPATHY: A 10 YEARS FOLLOW UP STUDY.

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OBJECTIVES:

Diabetic Neuropathy is a well known risk factor for increased mortality and morbility in Diabetic patients. We analysed the ten years survival data (from 2008 to 2018) of a population of 468 Type 2 Diabetic patients diagnosed with moderate and severe DN followed in our outpatient clinic. The study aimed to seek whether the severity of DN affects the mortality rate in order to identify a potential subgroup of neuropathic patients which needs a closer outpatient follow-up.

METHODS:

A total of 468 Type 2 Diabetic patients diagnosed with moderate or severe DN (defined by electrophysiological study findings and DMNS) was followed up for ten years in our outpatient clinic. Age at baseline was 61,5±11,8 years (Mean± SD), Male/Female ratio 324/144, disease duration 18±9 years, patients with moderate DN were 174, patients with severe DN were 294. Number of patients deceased and mortality rates were calculated.

RESULTS:

The mortality rate among patients with moderate DN (n=294) was 14,6% in the first 5 years (43 patients died out of 294) and 18,7% in the following 5 years (47 patients died out of 251), with an overall mortality rate in 10 years of 30,6%. Mortality rate in patients with severe DN (n=174) was 11,4% in the first 5 years (20 patients died out of 174) and 23,2% in the following 5 years (36 patients died out of 154), with an overall mortality rate in 10 years of 32,2%.

CONCLUSIONS:

The diabetic patients we studied who were affected by severe DN showed an higher mortality incidence (three times more) in comparison with patients affected by moderate DM.

P7 TIME- AND FREQUENCY-DOMAIN MEASURES OF HEART RATE VARIABILITY PREDICT CARDIOVASCULAR OUTCOME IN PATIENTS WITH TYPE 2 DIABETES

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OBJECTIVES:

To evaluate the association between impaired heart rate variability (HRV) and cardiovascular disease (CVD) in patients with type 2 diabetes (T2DM).

METHODS:

A total of 655 patients with T2DM who underwent cardiovascular autonomic function testing were consecutively recruited and followed up prospectively. Time- and frequency-domain HRV were assessed for 5 minutes by beat-to-beat heart rate recording. We estimated the development of CVD events during a follow-up period.

RESULTS:

During a median follow-up of 7.8 years, 9.6% (n=49) of patients developed CVD (10.6 per 1,000 patient-years). The mean age and diabetes duration were 54.9 ± 8.6 years and 9.4 ± 7.3 years, respectively. Patients who had cardiovascular autonomic neuropathy (CAN) had decreased HRV compared with those with normal autonomic function. Multivariable Cox hazard regression analysis revealed the lowest 10th percentile of the SD of the normal-to-normal interval (HR 2.62; 95% CI 1.30–5.31), total power (HR 2.81; 95% CI 1.37–5.79), low-frequency power (HR 2.68; 95% CI 1.28–5.59), and high-frequency power (HR 2.24; 95% CI 1.09–4.59) were significant predictors for developing CVD in patients with T2DM.

CONCLUSIONS:

Time- and frequency-domain measures of HRV independently predicted cardiovascular outcome in patients with T2DM.

P8 IN THE OBESE PATIENTS WITH IMPAIRED GLUCOSE TOLERANCE OR TYPE 2 DIABETES HIGHER GLUCOSE VARIABILITY MAY CONTRIBUTE TO REDUCE PERIPHERAL MICROCIRCULATORY BLOOD FLOW AND INCREASE CARDIAC WORK INDEPENDENTLY FROM SYMPATHETIC ACTIVITY

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OBJECTIVES:

In diabetic patients, alterations of cardiac autonomic reflex tests were associated with changes in cardiac contractility. Excess in sympathetic activity might be involved in the increase in cardiac output often present in obese patients. We previously reported the role of glucose variability in the alteration of microcirculation. The aim was to compare cardiac contractility in obese or overweight patients with normal(NGT), impaired glucose tolerance(IGT) or type 2 diabetes(T2D), and to examine the role of sympathetic activity, glucose variability and changes in microcirculatory blood flow in cardiac contractility

METHODS:

We included 95 patients(38 NGTs, 30 IGTs and 27 well-controlled T2Ds), 30 of them with well-controlled hypertension and all free of cardiovascular history. Cardiac vagal activity HF-HR, sympathetic activity LF-HR and sympatho-vagal balance LF/HF-HR were evaluated by spectral analysis of heart rate variations(Task Force Monitor®) and stroke volume(SV), cardiac output, cardiac index(CI), index of contractility(IC) and thoracic fluid content(TFC, indicative of central blood volume) by thoracic impedance. Radial and central blood pressure and carotid-to-femoral pulse wave velocity(PWV) were measured by Sphygmocor® and cutaneous blood flow(CBF) by laser doppler Periflux®. Glycemic variability was evaluated in IGTs and T2Ds by calculating standard deviation(SD-glucose), CONGA and J-index from 24-hours CGMS

RESULTS:

T2Ds had similar blood pressure and PWV, were older and had higher SV, CI, IC and TFC than IGTs and NGTs($p<0.04$ to 0.001), and lower meanCBF than IGTs($p<0.02$), with no differences for sympatho-vagal activity. In all patients SV and IC correlated positively with LF-HR($p<0.006$ for both). In IGTs and T2Ds, SV and IC also correlated positively with LF-HR($p<0.002$ for both). Compared with IGTs, T2Ds had higher mean glucose, CONGA and J-index($p<0.001$ for all). In IGTs and T2Ds taken together meanCBF correlated negatively with SD-glucose and J-index($p<0.01$ and 0.05 even after age and BMI adjustment). MeanCBF also correlated negatively with HbA1c($p<0.01$). In multivariate analysis meanCBF remained correlated with SD-glucose and J-index independently of HbA1c. CI and IC correlated with TFC independently of age and LF-HR($p<0.008$ and 0.001)

CONCLUSIONS:

The present data suggest that higher glucose variability may reduce peripheral microcirculation and thus increase central blood volume, and subsequently increase cardiac work(Starling law), independently from sympathetic activity

P9 THE UTILITY OF SUDOSCAN IN A REAL-LIFE DIABETIC NEUROPATHY CLINIC IN THE UK

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OBJECTIVES:

SUDOSCAN is a validated tool for the diagnosis of diabetic peripheral (DPN), autonomic (DAN) and small fibre neuropathy. SUDOSCAN assesses sudomotor function based on Electrochemical Skin Conductance (ESC) and has been validated against multiple diagnostic tools. The utility of using of SUDOSCAN in real life setting has not been examined before. Hence, in this study we aimed to assess the utility of SUDOSCAN in real-life clinical practice.

METHODS:

We conducted a cross-sectional study in a single specialist diabetic neuropathy clinic in the UK. Patients were referred to the clinic when a diagnosis of diabetic neuropathy was suspected. SUDOSCAN and its ethnicity-specific normative values were used as per the manufacturer information. DPN and/or DAN definitions were based on the clinician. A sample of 81 consecutive patients was examined in this study.

RESULTS:

Out of 81 patients 15 had a diagnosis other than DAN or painful DPN and were excluded. Out of the remaining 66 patients 19.7% had DAN, 89.4% had painful DPN. [74.2% - Type 2 diabetes (median duration 16 years, range 1-64), 68.2% - men, 69.7% - White Europeans, 68.2% - insulin-treated. Based on the ESC values 16.7%, 30.3%, and 53% had normal, moderate and severe sudomotor dysfunction respectively in the feet and 37.9%, 22.7% and 39.4% had normal, moderate and severe sudomotor dysfunction respectively in the hands.

Feet (r=0.36, p=0.003) and hands (r=0.33, p=0.007) ESCs correlated positively (r=0.34, p=0.01 for both) and cardiac autonomic score correlated negatively (r=-0.28, p=0.02) with MDRD- estimated glomerular filtration rate (eGFR).

Out of 22, 17 and 16 patients with normal foot inspection, 10g monofilament and vibration sensation tests, 68.2%, 76.5%, and 75.0% had abnormal SUDOSCAN results based on feet ESCs. In patients with normal lower limb nerve conduction studies (NCS) (7 out of 28), 5 (71.4%) had abnormal Feet ESCs. In patients with abnormal lower limb NCS (21/28) 14.3% (n=3) had normal feet SUDOSCAN test.

There was no significant difference in ESCs or the proportion of abnormal SUDOSCAN results between patients with and without clinically-evident painful DPN. However, the prevalence of abnormal hands SUDOSCAN results was greater amongst patients with clinically evident DAN vs no DAN (54.7% vs. 92.3%, p=0.01). Hands ESCs were lower in the group with DAN vs. no DAN (50.8 ±23.2 µS vs. 34.2µS±17.9, p=0.02). Hands ESCs had an AUC of 0.71 (using ROC) a mean hands ESC of 69, 50, and 42 µS had sensitivity of 26.4%, 60.4%, 64.2% and specificity of 100%, 84.6%, 69.2%, to detect clinical DAN.

CONCLUSIONS:

Using the SUDOSCAN in the clinic identified a high proportion of patients with DPN that would have been missed using routinely used methods. The hands SUDOSCAN results can identify patients with higher risk of DAN. Further studies in specialist diabetes clinics and longitudinal studies assessing the utility of SUDOSCAN are needed.

P10 PERICYTE MEDIATED REDUCTION IN SPINAL CORD BLOOD FLOW IN DIABETIC NEUROPATHIC PAIN

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OBJECTIVES:

The role that the neurovascular network within the spinal cord plays in regulating nociception has not been investigated; especially in diabetic neuropathic pain. We have recently identified that blood vessels in the spinal cord of diabetic animals are narrower than in non-diabetic animals, with such a pathology implicated in the development of pain and drug efficacy. We hypothesise that this reduction in vessel diameter could be as a result of vasoconstriction, related to changes in the cells surrounding these vessels (pericytes) due to alterations in the hormone angiotensin II, and activation of its receptors.

METHODS:

All Experiments were designed in accordance with UK Home Office legislation, Animals (Scientific Procedures) Act 1986 and ARRIVE guidelines. A rodent model of type 1 diabetes was induced in Female Sprague dawley rats (~200g) (n=6/group). Streptozotocin (intraperitoneal 50mg/kg) was administered and animals were insulin supplemented. All studies were carried out with age matched controls. Animals body weight was monitored and levels of blood glucose determined (hyperglycaemia>15mmol/l). 8 weeks following streptozotocin administration, animals were administered with hypoxyprobe (60mg/kg) intraperitoneal 30 minutes prior to being terminally anaesthetised (intraperitoneal 60mg/kg Sodium Pentobarbital) and cardiac perfused with 4% paraformaldehyde. Lumbar spinal cords were extracted and processed (40µM thick sections) for confocal microscopy to identify the endothelium (CD31), pericytes (NG2, PDGFRβ) and AT1R.

RESULTS:

In diabetic animals that displayed neuropathic pain there was a significant reduction in vessel diameter in the spinal cord versus age matched controls ($p<0.0001$). This was associated with increased levels of hypoxia indicated through increased hypoxyprobe staining in the dorsal horn of the spinal cord of diabetic animals ($p<0.05$, $p<0.0001$). Furthermore, this vasoconstriction in diabetic animals was significantly prevalent when in close proximity to pericytes (AT1R positive, $p<0.05$).

CONCLUSIONS:

This demonstrates that pericyte function has a role in modulating the neurovascular network and pain. This highlights a novel mechanism by which diabetic neuropathic pain may manifest.

P11 IS SEXUAL FUNCTION IMPAIRED IN MEN AND WOMEN WITH RECENT-ONSET DIABETES?

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OBJECTIVES:

It is unclear whether sexual function is altered in men and women with recent-onset type 1 (T1D) or type 2 diabetes (T2D). We hypothesized that sexual dysfunction is present as early as in recent-onset diabetes, albeit to a different extent depending on sex and diabetes type.

METHODS:

We assessed sexual function in 156 male individuals with T1D and 299 with T2D (mT1D/mT2D [mean±SEM]: age: 37±1/52±1 years, BMI: 25.0±0.3/31.0±0.3 kg/m²; diabetes duration: 177±8/179±6 months, HbA1c: 6.8±0.1/6.4±0.1%) from the baseline cohort of the German Diabetes Study with a diabetes duration ≤12 months and corresponding age-matched controls with normal glucose tolerance (NGT) (mCON1/mCON2: n=45/55, age: 36±1/53±1 years, BMI: 28.0±0.9/29.5±0.8 kg/m²), and in 188 female participants with diabetes (T1D/T2D: n=92/96) and 20 age-matched controls with NGT (fDM/fCON: age: 43±1/41±3 years, BMI: 28.8±0.5/25.1±1.0 kg/m²; diabetes duration: 179±7/- months, HbA1c: 6.6±0.1/5.3±0.1%). Prospective assessment over 5 years was performed in subgroups of 54 male participants with T1D and 92 with T2D. Male sexual function was evaluated using the International Index of Erectile Function (IIEF) score including 5 domains, and female sexual function with the 'Short questions for sexual problems' score (KFSP-F, 4 subscores).

RESULTS:

At baseline, no differences in IIEF scores were found between mT1D patients and mCON1 (e.g. total score (TS) [points]: 64±1 vs 62±2; erectile function domain (EF): 28±0.4 vs 27±1) or mT2D and mCON2 (e.g. TS: 56±1 vs 59±2; EF: 23±0.5 vs 25±1). In fDM participants only 1 out of 4 KFSP-F subscores was reduced compared to fCON (arousal/lubrication score: 5.2±0.1 vs 5.8±0.2; $p<0.05$). At baseline, associations with IIEF scores were found for higher age and BMI, but not HbA1c (e.g. TS in mT2D: age: $r=-0.273$, $p<0.0001$; BMI: $r=-0.187$; $p=0.001$; HbA1c: $r=-0.075$, $p=0.196$). IIEF scores did not change from baseline after 5 years in men with T1D (TS: 64±2 vs 65±2, EF: 28±1 vs 28±1), whereas sexual function declined in men with T2D (e.g. TS: 52±2 vs 57±2, EF: 22±1 vs 24±1; $p<0.05$), but statistical significance was lost after adjustment for age.

CONCLUSIONS:

Sexual function appears to be largely preserved in both men and women with well controlled recent-onset diabetes. The subsequent decline in erectile function after 5 years in men with T2D appears to be associated with aging rather than diabetes progression.

P12 THE REFERENCE DISTRIBUTION OF ANNUAL CHANGE IN CORNEAL NERVE FIBRE LENGTH IN DIABETES

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OBJECTIVES:

The measurement of corneal nerve fibre length (CNFL) by in vivo corneal confocal microscopy is a biomarker for the presence of diabetic sensorimotor polyneuropathy (DSP). Currently, there are no reference values for the change in CNFL in clinical DSP prediction. We aimed to determine the reference distribution of annual CNFL change, the threshold of abnormality, its prevalence in T1D and T2D, and its clinical predictors.

METHODS:

We examined longitudinal data from 156 non-diabetic controls and 297 diabetes participants (224 T1D and 73 T2D) from an ongoing multi-centre NIH-funded study of IVCCM in diabetes. Participants were included if they had at least 1-year of follow-up data and were classified as progressors with "rapid corneal nerve fibre loss" (RCNFL) if the loss of CNFL was beyond the 5th percentile of the non-diabetic controls.

P12 THE REFERENCE DISTRIBUTION OF ANNUAL CHANGE IN CORNEAL NERVE FIBRE LENGTH IN DIABETES

RESULTS:

Non-diabetic controls were 46.1±15.8 y, had a median of 3 follow-up visits over a median of 2.3 y, baseline CNFL of 16.4±4.3 mm/mm2, and the median annual change in CNFL was 2.0%[90% CI, -14.3 to 26.0%]. The threshold value of -14.3% thus became the definition for progressors or abnormal loss of CNFL, termed RCNFL. Diabetes participants were 49.6±15.5 y, had a median of 3 visits over a median of 2 y, baseline CNFL of 14.3±4.4 mm/mm2 and the median annual change in CNFL was 1.8%[90% CI, -26.1 to 25.0%]. There were 33(11.1%) cases of RCNFL in the diabetes sub-cohort, which was comparable between T1D (26(11.6%)) and T2D (7(9.6%)). Progressors did not differ from non-progressors for baseline levels of age, sex, BMI, HbA1c or CNFL levels. However, progressors were more likely to have baseline DSP (16(50%) vs. 83(32%), p=0.048), lower cooling detection threshold (21.3°C±8.5 vs. 25.3°C±7.2, p=0.048) and lower heart rate variability (26.3±13.1 vs. 38.2±25.4, p=0.036).

CONCLUSIONS:

A rapid loss of CNFL (RCNFL) exceeding 14%/y occurs in ~11% of diabetes patients. This rate of corneal nerve loss is considered abnormal compared to healthy controls and may identify patients at the highest risk for the development or progression of DSP.

P13 SIMULTANEOUS PANCREAS AND KIDNEY TRANSPLANTATION RESULTS IN CORNEAL NERVE REGENERATION AND INCREASED KERATOCYTE DENSITY IN PATIENTS WITH T1DM

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OBJECTIVES:

We have quantified corneal nerve morphology and keratocyte density in patients before and 12 months after simultaneous pancreas-kidney (SPK) transplantation.

METHODS:

14 participants who had undergone SPK and 11 healthy age-matched controls were studied. All participants underwent assessment of the neuropathy disability score, quantitative sensory testing (QST), corneal confocal microscopy (CCM) and nerve conduction studies (NCS). Corneal nerve fiber density (CNFD), branch density (CNBD), length (CNFL) and keratocyte density (KD) were quantified at baseline and after 12 months.

RESULTS:

KD (342.55± 8.08 vs. 376.03 ± 6.56, P=0.004), CNFD (8.47 ± 1.62, vs. 27.96 ± 2.17, P<0.0001), CNBD (8.99 ± 2.02 vs. 37.51 ± 5.85, P=0.001) and CNFL (6.26 ± 0.82 vs. 15.82 ± 1.12, P<0.0001) were significantly reduced in In T1DM patients prior to SPK compared to controls. At baseline there was a significant correlation between KD, CNFD (r=0.474, P=0.01) and CNFL (r=0.434, P=0.03). 12 months after SPK there was significant increase in KD (342.55 ± 8.08 vs. 371.57 ± 4.63, P=0.003), CNFD (8.47 ± 1.62 vs. 11.62 ± 2.43, P=0.04) and CNFL (6.26 ± 0.82 vs. 7.6 ± 0.17, P=0.05) with no change in QST and NCS. There were no changes in corneal nerves or KD over 12 months in controls. KD correlated significantly with HbA1c (r=-0.703, P=0.005) in the SPK group at 12 months. There was no correlation between change in KD or HbA1c and corneal nerve parameters.

CONCLUSIONS:

Keratocyte density and corneal nerve parameters increase after SPK and the former is associated with HbA1c.

P14 DOES AUTONOMIC FUNCTION DETERIORATE OVER TIME IN TYPE 1 DIABETES? RESULTS OF A 12-YEAR FOLLOW-UP.

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OBJECTIVES:

Previous studies have shown that the autonomic function deteriorates over time in individuals with diabetes. However, the relationship between autonomic worsening and physiological ageing have not been fully elucidated. Reports from prospective trials (Steno and DCCT) showed that optimal medical treatment reduces or stabilizes the decay regarding the autonomic function/diabetic complications. So far only heart rate variability (HRV) or autonomic score has been evaluated. Therefore, in a 12-year follow up we tested the relative contribution of diabetes and ageing on the autonomic score and the baroreflex sensitivity (BRS) (a more comprehensive test of autonomic function) in individuals with type 1 diabetes.

METHODS:

Seventy-five individuals with type 1 diabetes (age at 1st visit 26.3±5.3, mean±SD, diabetes duration 7.9±1.9, 33 females, HbA1c 7.5±1.2) completed 3 visits (5.0±0.2 and 12.0±0.5years apart, respectively) over a 12-year follow-up. Ninety-five healthy controls (aged 39.0±12.5, 44 females, age range 18-69) provided reference values and physiological autonomic function decay with ageing.
During each visit standard autonomic function test, BRS and the standard deviation of heart period intervals (SDNN) were evaluated. From the data of healthy controls, we obtained for each variable the physiological ageing decay curve. We then compared the physiological ageing decay expected at each visit with the observed data in the diabetic patients to compare the influence of diabetes per se with that of physiological ageing.

RESULTS:

At the second visit the glycemic control showed a minor but significant deterioration vs baseline (HbA1c 8.1±1.0 vs 8.0±1.0, p:<0.001) and then remained stable. A clear decay in all indices of autonomic function was found from the 1st to the 3rd visit for all variables. However, when the pure effect of diabetes was compared with the physiological ageing, the effect of diabetes on the BRS and the blood pressure drop on standing was no longer significant and only 50% of the decay was explained by diabetes in HRV-based autonomic indices (see table).

CONCLUSIONS:

In optimally treated individuals with type 1 diabetes the apparent worsening in autonomic function observed over a 12-year follow-up is mainly explained by physiological ageing. The diabetes-dependent reduction in HRV seems to have only a minor impact, since the BRS and the drop in blood pressure on standing are not significantly influenced by diabetes.

P14 DOES AUTONOMIC FUNCTION DETERIORATE OVER TIME IN TYPE 1 DIABETES? RESULTS OF A 12-YEAR FOLLOW-UP.

	Visit 1	Visit 2			Visit 3		
	t0	Physiologic ageing alone †	Ageing + diabetes	*p*	Physiologic ageing alone ‡	Ageing + diabetes	*p*
BRS (avg)	17.1 (7.7)	15.2 (7.7) ***	14.1 (10.3) **	***ns***	12.5 (7.7) ***	14.3 (11.0) *	***ns***
SDNN	40.2 (19.7)	36.2 (19.7) ***	28.6 (17.2) ***	***<0.001***	30.6 (19.8) ***	22.4 (14.4) ***	***<0.001***
E:I	1.39 (0.16)	1.35 (0.16) ***	1.28 (0.13) ***	***<0.001***	1.30 (0.16) ***	1.21 (0.11) ***	***<0.001***
30:15	1.64 (0.26)	1.61 (0.26) ***	1.52 (0.23) **	***0.02***	1.56 (0.26) ***	1.38 (0.20) ***	***<0.001***
Valsalva	2.01 (0.44)	1.95 (0.44) ***	1.78 (0.29) ***	***<0.001***	1.86 (0.44) ***	1.69 (0.38) ***	***0.002***
SBP fall on standing	0.68 (10.0)	-1.46 (10.0) ***	3.58 (12.68) **ns**	***0.01***	-4.48 (10.0) ***	-1.75 (8.56) **ns**	***ns***

Data are means (SD).
SDNN = mean of the Standard Deviation of all Normal to Normal R-R interval, BRS = Baroreflex Sensitivity, E:I = ratio of the longest electrocardiographic R–R interval during expiration to the shortest during inspiration, 30:15 = heart rate response to standing, Valsalva = heart rate response to the Valsalva manoeuvre, SBP = Systolic Blood Pressure.

† values that individuals with type 1 diabetes would have had just because of the physiologic ageing process at the second visit, as compared to the first visit.
‡ values that individuals with type 1 diabetes would have had just because of the physiologic ageing process at the third visit, as compared to the first visit.

* p<0.05 vs visit 1
** p<0.01 vs visit 1
*** p<0.001 vs visit 1

P15 PAINFUL DIABETIC NEUROPATHY IN THE REAL WORLD SETTING: EPIDEMIOLOGY, TREATMENT AND FOLLOW-UP

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OBJECTIVES:

Painful diabetic neuropathy (PDN) affects 13-21% of diabetic patients and causes a considerable deterioration in quality of life. We considered the population of patients with PDN treated for neuropathic pain, analyzing differences among risk factors and diabetic complications, in relation to pharmacological treatment for PDN (single vs multiple drugs) and gender. Moreover the tolerability of treatment was evaluated.

METHODS:

In 111 diabetic patients with at least probable PDN treated with one or more drugs (pregabalin, duloxetine, tapentadol), the following data have been collected: age, gender, type of diabetes, duration of disease, presence of micro and macrovascular complications and risk factors (HbA1c and its standard deviation, BMI, waist circumference, total cholesterol, triglycerides, AST, ALT, smoking and alcohol habits), HbA1c reductions> 0.66% / month. Data were compared with 412 patients without PDN. Adherence to therapy was assessed by telephone interview.

RESULTS:

Patients with PDN in pharmacological treatment were mostly males (72.9%), while those treated with multiple drugs had a lower standard deviation of HbA1c, compared to patients on monotherapy. Male patients had significantly higher prevalence of autonomic neuropathy, diabetic retinopathy, peripheral artery disease, smoking habits and alcohol intake, compared to women. Patients with PDN showed significantly higher prevalence of autonomic neuropathy, diabetic retinopathy, diabetic foot, peripheral artery disease and cerebral vasculopathy, compared to patients without PDN. 34.23% of patients with PDN experienced an increase in HbA1c > 0.66%/ month. Only one patient stopped treatment due to side effects.

CONCLUSIONS:

In patients with PDN, multiple drug treatment for pain is associated with a lower standard deviation of HbA1c, probably for the longer duration of therapy and the closer clinical follow-up. Patients with PDN, especially males, showed higher prevalence of diabetic complications (except for coronary artery disease and nephropathy) with respect to patients without PDN. Pharmacological treatment is generally well tolerated.

P16 A COMPOSITE OF QUESTIONS DERIVED FROM THE NORFOLK QOL-DN QUESTIONNAIRE IS A PREDICTIVE TOOL FOR MORTALITY IN PATIENTS WITH DIABETES

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OBJECTIVES:

The objective of this study was to evaluate if linguistically-translated Norfolk Quality of Life for Diabetic Neuropathy questionnaire (QoL-DN) can predict mortality in patients with diabetes mellitus.

METHODS:

A subset of 481 patients with type 2 diabetes from Cluj-Napoca Diabetes Center and Outpatient Clinic included in a 2012 epidemiological study in 21,756 adult patients from 51 Romanian Diabetes Centers were followed for 4 years.

RESULTS:

In 4 years, 31 (6.6%) subjects died, 17 (54.8%) were male; with a mean ±SE age of 67.26±1.80 yrs. and a mean duration of diabetes of 10.29±0.82 yrs. The QoL-DN Total score in 2012 was statistically significantly higher (worse) in patients who subsequently died than in individuals who were alive 4 years later (42.81 ± 5.24 vs. 27.18 ± 1.06, OR=1.02, 95%CI 1.00-1.03, p=0.008) adjusted for age and diabetes duration. High scores for questions (24 to 63) had the power of discrimination between subjects who died and those who survived (p<0.05) as did "yes" to the question about ulceration. We therefore propose a Norfolk QOL mortality risk score viz: the sum of the significant statistically questions (for mortality) in the item Symptoms with response Yes = 1 / No = 0 and the significant statistically questions of the Physical Functioning/Large Fiber, Activities of daily living, Small Fiber, Autonomic items with Likert scale response from 0 = Not at all / 1 = A little / 2 = Somewhat / 3 = Moderately to 4 = Severely and the question on ulceration with (Yes = 1 / No = 0). The mortality risk score ranged from -4 to 72 was significantly greater in those who died compared with survivors (25.84±3.02 vs. 14.99± 0.62, p<0.001). The cut-off for the mortality risk score was obtained using ROC (receiver operating characteristics) as the maximum of the Youden index: 11.5 (Sensitivity=83.9, Specificity=46.7, area under the curve (AUC)=0.699, p<0.001). From the individuals with mortality risk score≥11.5 (optimal cut-off) in 2012 9.8% died in the next 4 years compared with 2.3% of the individuals with a mortality risk score <11.5, p=0.001.

CONCLUSIONS:

We propose here a composite of items derived from the Norfolk QoL-DN questionnaire as a novel "Mortality Risk Score" that can prospectively identify patients with a high mortality risk over a period of 4 years.

P17 DETECTION OF DIABETIC NEUROPATHY IN A SUBURBAN POPULATION IN MEXICO

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OBJECTIVES:

To detect the prevalence of symmetric distal diabetic neuropathy affecting extremities and relate it to the years of evolution of the disease.

METHODS:

Various methods to evaluate the presence of diabetic neuropathy (DN) or sensory alteration were used, along with the DN4 Questionnaire, and the physical examination using tools such as the reflex hammer, Semmes-Weinstein monofilament of 10 grams of pressure, and a tuning fork of 128 Hz or cycles. HbA1c was also taken into account.
Patients were divided into IV groups according to years of evolution of DM2; Group I consisted of those with 0 to 5 years of evolution and was formed by 34 patients, Group II of patients with 6 to 10 years of evolution and consisted of 25 patients, Group III of patients with 11 to 15 years of evolution and was formed by 19 patients, and Group IV of those with 16 years or more of evolution and was formed by 23 patients.

RESULTS:

We examined 101 patients with DM2. Within the studied sample 32 people were males (31.68%) and 69 were females (68.31%), with an average age of 55.75 years ± 11.80. Average evolution of DM2 was 10.60 years ± 8.67 with an average of 10 years for both sexes. The general prevalence of DN was 58.41%: Group I presented a prevalence of DN of 32.35% (n=11), Group II of 48% (n=17), Group III with a prevalence of 89.47% (n=17), and Group IV with a prevalence of DN of 82.60% (n=19). The general average of HbA1c level was of 7.83 ± 1.79 for the 101 patients. During interrogation only 24 of the 59 patients (40.67%) referred symptoms of DN. During the physical examination 77.96% (n=46) of the 59 patients presented some alteration during exploration with a 128-cycle tuning fork and 49.15% (n=29) presented an alteration during exploracion with monofilament.

CONCLUSIONS:

Diabetic neuropathy is the first complication found in patients with DM2. It is only diagnosed in roughly 40% of patients with DM2 The main risk factor for DN is time of evolution and lack of metabolic control, reflected by high HbA1c levels. The use of a 128-cycle tuning fork is the most important tool one can use to detect the presence of DN (77.96% of cases). The monofilament detects nearly half of cases with alterations in the sensibility, increasing the risk of suffering an ulcer or diabetic foot. In Latin America the education of the medical personnel in the use of the tuning fork and monofilament in the physical examination of the patient with DM is indispensable in order to diagnose DN.

P18 HIGH PREVALENCE OF DIABETIC PERIPHERAL NEUROPATHY(DPN) IN VEGETARIANS

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OBJECTIVES:

Background: Peripheral Neuropathy is one of the most common complications of Diabetes and it is more symptomatic in comparison with other complications of DM like nephropathy, retinopathy. Western part of Indian states like Gujarat and Rajasthan have more vegetarian population, and the diabetic patients come often with the similar complaints of burning sensation in feet, numbness, shooting pain , insensate foot. Vitamin B12 deficiency is more prevalent in vegetarians and Metformin is also associated with vitamin B12 deficiency.
Aim: To see the prevalence of Peripheral Neuropathy and it's correlation to Vitamin B12 deficiency in diabetic vegetarian patients.

METHODS:

Materials and Methods: From August 2017 to March 2018 prospective observational study was conducted in clinical setup for total number of 164 vegetarian Type-1(>5 yrs of T1DM) and Type-2 Diabetes patients , in which they were asked for several questions for symptomatic confirmation of peripheral neuropathy, monofilament and vibration perception(VPT) threshold test by Bio-esthesiometer were performed and Vitamin B12 level was done.

RESULTS:

Result: 43% (n=70)of the patients found to have DPN of those Vegetarian Diabetic patients,76% (n=124) of those patients had low Vitamin B12 level. Breakup Study of positive DPN :According to symptoms and VPT 22 patients(31%) had severe DPN and 31 patients(44%) had very low level of vitamin B12(<100 pg/mL).

CONCLUSIONS:

Conclusion: Diabetic Peripheral Neuropathy is more prevalent in vegetarians(43% in our study) as Diabetic Peripheral Neuropathy varies from 10%-26% in all studies, it has definite correlation with vitamin B12 deficiency, which further needed to be established.

P19 SEX DIFFERENCES IN NEUROPATHY AND NEUROPATHIC PAIN: RESULTS FROM THE CANADIAN STUDY OF LONGEVITY IN TYPE 1 DIABETES

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OBJECTIVES:

Neuropathy and neuropathic pain are common complications in type 1 diabetes (T1D). We aimed to determine if sex-specific differences in the prevalence of neuropathic pain and neuropathy exist in patients with longstanding T1D.

METHODS:

In Phase 1 of the study, 361 Canadians with ≥50 years of T1D completed questionnaires which included subjective assessment for neuropathy defined by Michigan Neuropathy Screening Instrument Questionnaire score ≥3, termed NEUROPATHY¬MNSI-Q. In Phase 2 of the study, we studied a sub-cohort of 75 diabetes participants and 75 age- and sex-matched non-diabetic controls who completed objective neurological examinations which included assessment of abnormal nerve conduction studies (NCS) for neuropathy, termed NEUROPATHY¬NCS.

RESULTS:

In the Phase 1 cohort, more females than males reported neuropathic pain [87(42%) vs 41(27%); p=0.003)], but the presence of neuropathy (NEUROPATHY¬MNSI-Q) did not differ by sex [87(42%) females vs. 66(43%) males, p=0.82], and thus neuropathic pain was independent of the presence of neuropathy [adjusted OR for neuropathic pain in females compared to males, 2.7 (1.4-5.0; p=0.002)]. In the Phase 2 participants, neuropathic pain was similar between the sexes (29% females vs 21% males, p=0.43) while NEUROPATHY¬NCS was less prevalent among females (83% females vs 97% males, p=0.05). Though not statistically significant, in a combined analysis of Phase 2 participants adjusted for NEUROPATHY¬NCS, females had a tendency to a higher adjusted OR for neuropathic pain compared to males [OR 2.0 (95% CI 0.8-4.7), p=0.11].

CONCLUSIONS:

In conclusion, in patients with longstanding TID, neuropathic pain appears to be greater among females compared to males independent of the presence of neuropathy. Further research using larger datasets with objective neuropathy measures are required to further confirm and address these sex-specific differences.

P20 DEPRESSION DOES NOT PREDICT THE FIRST OR THE RECURRENT DIABETIC FOOT ULCERS

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OBJECTIVES:

The objective of this study was to assess if there is any association between depression and first or recurrent foot ulcer in patients with diabetes mellitus (DM).

METHODS:

The current study included 49 patients with DM complicated by diabetic polineuropathy and different forms of depression admitted in our center during June 2009 - June 2010 and followed for 36 months. General characteristics of the study group are shown in the table below. The presence of depression was assessed by Beck Depression Inventory II (BDI – II) and the cut-off point ≥ 10 permitted identification of both clinical forms and subclinical depression symptoms. The exclusion criteria were: the presence of peripheral artery disease, history of lower limb amputations, Charcot deformity and other severe chronic medical diseases or complications of diabetes precluding participation. Logistic regression was used to establish the correlation between depression and first or recurrent foot ulcer.

RESULTS:

The majority of patients with depression and ulcer come from urban areas (83.33%), aged 50-59 years old (66.67%), age of DM between 20-29 years (41.67%), stage II obesity (58.33%), mild non-proliferative diabetic retinopathy (50%) and KDOQI stage III chronic kidney disease (33.33%). Only 20.4% received pathogenic therapy with Benfothiamine and/or Alpha lipoic acid before admission and only 4.08% symptomatic therapy. The great toe was the most affected area (41.66%). All the recurrent ulcers had the same localization. The mean BDI – II score was higher in subjects who developed an ulcer vs. subjects without ulcer (17.83 vs. 13). There was no significant relationship between depression and first (p=0.214) or recurrent foot ulcers (p=0.97) in our study population.

CONCLUSIONS:

Depression wasn't a predictor of first or recurrent foot ulcer in our study population and in the followed-up period.

Parameter	Interval		Mean value		Standard deviation	
	Ulcer	Without ulcer	Ulcer	Without ulcer	Ulcer	Without ulcer
Age (years)	38 - 77	38 - 79	57.46	54.86	±9.31	±10.73
A1c (%)	8.1 - 14	6.8 – 12.3	10.37	9.42	±2.03	±1.4
BMI (kg/m²)	30.8-43.48	18.67 -38.2	37	28.96	±3.68	±5.91
Age of DM	7 - 32	5 - 38	18.25	15.13	±8.49	±8.37

P21 THE DIFFERENCES REGARDING FOLLOW-UP RECOMMENDATIONS AFTER APPLYING 2 DIFFERENT SCREENING INSTRUMENTS FOR DIABETIC FOOT

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OBJECTIVES:

The aim of this study was to compare the recommendations for diabetic foot screening after applying two different instruments: "The Inlow's 60-second diabetic foot screening" and "The 3-minute diabetic foot exam".

METHODS:

The current study included 50 adults with type 2 and type 1 diabetes (with diabetes duration > 5 years) admitted in the Cluj-Napoca Diabetes Clinic during April-May 2017. The two tests were performed on each patient in two separate days by a medical doctor with 5 year experience in the field of diabetic foot. The patients previously seen by the foot surgeon, unable to speak or understand Romanian language and those with cognitive or hearing impairment were excluded. For the 60-second test, the highest score from left or right foot was used to recommend the screening interval.

RESULTS:

The majority of subjects comes from urban areas (64%), had type 2 diabetes (84%), age - 60.9±13.06 years, with diabetes duration of 16.71±10.34 years, body mass index of 30.89±8.05kg/m² and A1c 9.73±2.39%. 74% of the subjects had diabetic neuropathy, 40% chronic kidney disease and 38% diabetic retinopathy. The duration and score for each screening instrument are shown in the table number 1. Based on the two instruments, the screening recommendations corresponded in only 52% of the subjects. The differences in number and percentages of subjects according to the considered screening periods are shown in the table number 2. Only 6 (12%) patients reported podiatric special care and only 10% had an appropriate footwear.

CONCLUSIONS:

Our study shows that, based on "The Inlow's 60-second diabetic foot screening", the patients may benefit from a shorter period between the initial examination and the next recommended follow-up compared to "The 3-minute diabetic foot exam".

P21 THE DIFFERENCES REGARDING FOLLOW-UP RECOMMENDATIONS AFTER APPLYING 2 DIFFERENT SCREENING INSTRUMENTS FOR DIABETIC FOOT

	60-second diabetic foot screening		3-minute diabetic foot exam
	Duration (min:sec)	Score	Duration (min:sec)
Interval	1:25 – 3:12	2 - 16	2:51 - 4:38
Mean value	2:04	7.84	3:31
STDEV		±3.22	

Tabel no. 1: Duration and score for the 2 screening instruments

Recommended screening	60-second diabetic foot screening		3-minute diabetic foot exam	
	No. subjects	Percentage (%)	No. subjects	Percentage (%)
≤ 3 months	6	12	5	10
3 – 6 months	26	52	15	30
yearly	18	36	30	60

Tabel no. 2: The number and percentages of subjects according to the recommended screening

P22 THE RELATIONSHIP BETWEEN ELECTROCHEMICAL SKIN CONDUCTANCE AND QUALITY OF LIFE IN PATIENTS WITH DIABETIC PERIPHERAL NEUROPATHY WITH AND WITHOUT ULCER

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OBJECTIVES:

To explore the relationship between electrochemical skin conductance (ESC) and the quality of life in patients with generalized diabetic peripheral neuropathy (GDPN) and to assess the value of feet ESC to discriminate between patients with GDPN as related to the absence or presence of a history foot ulcer (HFU).

METHODS:

Between January and April 2017, 50 male & female Saudi patients with diabetes mellitus were evaluated for inclusion criteria in the study. Patients with secondary causes of peripheral neuropathy, peripheral vascular disease, critically ill were excluded. Informed consent obtained. The study protocol was approved by the Hospital's local Ethics committee. Confirmed diabetic peripheral neuropathy (DPN) was assessed clinically through neuropathy symptom score (NSS), neuropathy disability score (NDS). Objectively Large-fiber DPN (L-F DPN) was confirmed through nerve conduction studies for the right and left Sural, Peronial and Tibial nerves. Confirmed Large fiber was defined according to the Toronto Diabetic Neuropathy Expert Group. Small-fiber DPN was confirmed objectively using feet ESC assessed by Sudoscan. GDPN was present if the patient had L-F&S-F DPN. Through individual interviews all participants responded to the Arabic version of NeuroQol instrument that included 6 domains: pain (P), loss/reduction in sensitivity (LS), diffuse sensory-motor symptoms (DSMS), limitations in daily activities (LDA), interpersonal problems (IP) and emotional distress(ED).Scores ranged (1-15). Data are presented as mean_SD or percentage. Pearson's correlation coefficient was used to assess the relationship between variables. Independent T test was used to evaluate the variances between variables in participants with and without HFU. SPSS 20 was used for statistical analysis.

RESULTS:

Mean age 54.1± 8.9. All patients had generalized DPN, 56% had a HFU. Mean NeuroQol instrument score was 6.11±2.7. Mean ESC feet 34.02±24.83 µs .There was a negative correlation between NeuroQol instrument score and ESC feet -0.541** p<0.0001. There was a significant negative correlation between Feet ESC and all domains of the Arabic version of the NeuroQol instrument: P (-0.476** p<0.0001), LS (-0.507** p<0.0001), DSMS (-0.537** p<0.0001), LDA (-0.492** p<0.0001), IP (-0.520** p<0.0001), ED (-0.363** p<0.01). Discriminate analysis for feet-ESC and NeuroQol score was performed between group A: patients with GDPN without HFU & group B:patients with GDPN with HFU, showed significant differences for feet ESC: 51.77±22.08 µs, 20.07±16.79 µs respectively p<0.0001, and for NeuroQol scores 4.87±2.29, 7.08 ±2.64 p<0.03 respectively, although both groups A&B had GDPN.

CONCLUSIONS:

Our study demonstrated that decreased feet ESC level predicts poor quality of life in patients with GDPN. Sever sudomotor dysfunction is associated with the occurrence of FU. Further studies are warranted.

P23 THE RELATIONS OF VARIABLES OF NERVE CONDUCTION STUDIES TO CLINICAL SYMPTOMS SCORES IN PATIENTS WITH TYPE 2 DIABETES

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OBJECTIVES:

Diabetic peripheral neuropathy (DPN) presents a various degree of symptoms from wide spectrum of nerve damages. Nerve conduction studies (NCSs) are considered to be the gold standard for nerve damage, but they are often dissociated with subjective symptoms in patients with DPN. The aim of this study was to investigate the NCS manifestations according to symptoms quantified by the Michigan Neuropathy Screening Instrument (MNSI) symptom scores.

METHODS:

We retrospectively enrolled patients with type 2 diabetes mellitus with or without symptoms of neuropathy in this study. Demographic and clinical laboratory data, and results of MNSI and NCS were collected. DPN was diagnosed by both MNSI score ≥ 3.0 and abnormal NCS results.

RESULTS:

One hundred ninety eight patients (115 men, 83 women) with mean age of 62.6 ± 12.3 and mean duration of diabetes 12.7 ± 8.5 were included in final analysis. The mean MNSI score was 2.8 (range, 0.0 to 9.0), and 69 patients (34.8%) were diagnosed as DPN. MNSI scores were positively correlated with median motor nerve latency, and negatively with median motor, ulnar sensory, peroneal, tibial and sural nerve conduction velocities (NCVs) with statistical significances. When patients were divided into quartile groups according to MNSI symptom scores, peroneal NCV were significantly decreased along increases of the quartiles. Multivariate analysis revealed that peroneal NCV was independently associated with MNSI scores after adjustment of age, sex, and HbA1c.

CONCLUSIONS:

Peroneal NCVs were found to be decreased along the increases of MNSI scores in patients with type 2 diabetes, and to be representative NCS variable as a clinical parameters known to be associated with DPN.

P24 THE RELATIONSHIP BETWEEN PERIPHERAL NEUROPATHY, THE RISK OF FALLS AND DEPRESSION IN ELDERLY PEOPLE WITH DIABETES

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OBJECTIVES:

The prevalence of diabetes in elderly people is increasing worldwide. Depression and falls are two common problems that threaten the health of older people. Some studies have reported that diabetic neuropathy was associated with depression and decreased muscle strength. We performed this study to investigate the relationship between peripheral neuropathy, the risk of falls and depression in older people with diabetes.

METHODS:

One hundred and thirty diabetic people 65 years old or older were enrolled. Medical history and laboratory results were obtained through interviews and electronic medical records. The Michigan Neuropathy Screening Instrument questionnaire (MNSIQ) and the Geriatric Depression Scale were used to assess diabetic peripheral neuropathy (DPN) and depression, respectively. The risk of falls was evaluated using assessment of balance (unipedal stance test) and a questionnaire sheet composed of fall risk indices.

RESULTS:

The age of the subjects was 71.8±4.2 years old, the ratio of men to women was 6:4, those HbA1c level was 7.6±1.2%, and the duration of diabetes was 15.7±10.9 years. Forty-one (31.5%) of the subjects had DPN, 62 (47.7%) subjects had depression, 106 (81.5%) subjects had impaired balance, and 37(28.5%) subjects had the risk of falls. The subjects who had depression presented a higher MNSIQ (3.2±2.4 vs 2.2±2.2; $p<0.05$) than those who had not. The patients who had impaired balance presented a higher prevalence of DPN (35.8 vs 12.5%; $p<0.05$). The subjects who had the risk of falls presented a higher MNSIQ (3.8±2.4 vs 2.2±2.2; $p<0.01$) and a higher prevalence of DPN (51.4 vs 23.7%; $p<0.01$) than those who had not. In multiple logistic analyses, depression (OR 1.2; 95% CI: 1.0-1.4), and the risk of falls (OR 2.7; 95% CI: 1.0-6.9) were found to be independent determinants of DPN after adjusting for other covariates.

CONCLUSIONS:

In conclusion, DPN is associated with depression and the risk of falls in elderly people with diabetes. It suggests that the prevention of DPN may improve the health of older people with diabetes.

P25 PREDICTIVE VALUE OF MORTALITY RISK SCORE IN PATIENTS WITH DIABETES, A COMPOSITE OF ITEMS DERIVED FROM THE NORFOLK QUALITY OF LIFE FOR DIABETIC NEUROPATHY QUESTIONNAIRE

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OBJECTIVES:

The objective of this study was to evaluate the "Norfolk Mortality Risk Score" a composite of items derived from the linguistically-translated Norfolk Quality of Life for Diabetic Neuropathy questionnaire (QoL-DN) in 1602 patients followed for 4 years.

METHODS:

A subset of 1602 patients from the original 21,756 patients with diabetes mellitus was followed for 4 years. A part of the patients (where doctors agreed to participate) where selected from the 51 sites included in a 2012 epidemiological study which screened 21,756 adults patients, excluding those from the Cluj-Napoca Diabetes Center and Outpatient Clinic (from where this score was composed).

RESULTS:

In 208 patients who died in 4 years, the QoL-DN Total score in 2012 was statistically significantly higher (worse) than in 1394 individuals who were alive after 4 years (45.78 ± 1.91 vs. 26.98 ± 0.67, OR=1.02, 95%CI 1.02 – 1.03, $p<0.001$ - logistic regression - adjusted for age, gender, diabetes type and diabetes duration. The new Norfolk Mortality Risk Score: high scores for the (24 to 63) questions that had the power of discrimination among the deceased and the survivors as shown in a previous study and "yes" to the question about ulceration was computed. Mortality Risk Score with range between -4 to 72 was significantly different between deceased and survivors (26.34±1.06 vs. 15.12± 0.39, OR=1.04, 95%CI 1.03 – 1.06, $p<0.001$). The cut-off 11.5 for the Mortality Risk Score obtained previously with ROC (receiver operating characteristics) was analyzed for this sample. Sensitivity was 80.8, 95%CI 74.8-85.9; specificity was 50.9, 95%CI 48.3 – 53.6, $p<0.001$. The mean Mortality Risk Score of deceased individuals in this sample did not differ significantly from the mean mortality risk score of deceased individuals previously reported (26.34±1.06 vs. 25.84±3.02, $p=0.637$). Also the mean Mortality Risk Score of individuals who survived at 4 years in this sample did not differ significantly from the mean Mortality Risk Score of individuals who were alive after 4 years in the sample previously reported (15.12± 0.39 vs. 14.99± 0.62, $p=0.354$).

CONCLUSIONS:

The results previously reported were confirmed by this study: the new Norfolk Mortality Risk Score based on a composite of items derived from Norfolk QoL-DN questionnaire can identify patients with a high 4 year mortality risk.

P26 DETERMINANTS AND ACCURACY OF PROSCICARD TESTS IN THE DETECTION OF CARDIAC AUTONOMIC NEUROPATHY IN ADULT PATIENTS WITH TYPE 1 DIABETES

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OBJECTIVES:

Previous studies showed that impaired sudomotor function might be regarded as a sensitive marker of autonomic neuropathy. However, the gold standard in diagnosis of cardiac autonomic neuropathy (CAN) is Ewing battery, which consists of four tests; evaluation of heart rate (HR) at rest, HR during deep breathing, Valsalva manoeuvre and orthostatic test. The aim of our study is to assess the accuracy of tests in detecting CAN and its determinants in adult patients with type 1 diabetes (T1D).

METHODS:

The study included 108 adult patients with T1D (58 men), aged 36 (IQR: 29-46) years, with disease duration of 21 years (IQR: 16-29) and HbA1c level of 7.8 (IQR: 7-8.8)%. The sudomotor function was evaluated using SUDOSCAN device on the basis of the electrochemical skin conduction (ESC). The Ewing battery test was performed in every participant using Proscicard III Program. The study group was subdivided into two groups based on the normal values of ESC. The accumulation of advanced glycation end products in the skin was evaluated with skin autofluorescence (AF) with AGE Reader.

RESULTS:

Abnormal sudomotor function was detected in 68 patients (63%). ROC curve analysis, used to evaluate sensitivity and specificity of particular tests for detecting CAN showed significant results for HRV index at rest (area under the curve of 0.74; $p<0.001$) with sensitivity of 47% and specificity of 95%, for breathing test (area under the curve of 0.67; $p<0.001$) with sensitivity of 49% and specificity of 85%, for Valsalva test (area under the curve of 0.68; $P=0.0006$) with sensitivity of 66% and specificity of 68% and for orthostatic test (area under the curve of 0.71; $P<0.0001$) with sensitivity of 50% and specificity of 88%.
We found positive correlation between HR at rest and HbA1c level ($Rs=0.25$, $p=0.008$), and negative correlation between patients age ($Rs=-0.19$, $p=0.045$). HRV index at rest was positively correlated with eGFR ($RS=0.21$, $p=0.03$), Feet ESC ($Rs=0.49$, $p<0.001$) and negatively with duration of diabetes ($Rs=-0.42$, $p<0.001$), patients' age ($Rs=-0.43$, $p<0.001$), skin AF ($Rs=-0.47$, $p<0.001$). The Rmax/Rmin during deep breathing, during Valsalva manoeuvre and orthostatic test was positively correlated with Feet ESC ($Rs=0.43$, $p<0.001$, $Rs=0.34$, $p<0.001$ and $Rs=0.43$, $p<0.001$ respectively) and negatively with duration of diabetes ($Rs=-0.47$, $p<0.001$, $Rs=-0.41$, $p<0.001$ and $Rs=-0.49$, $p<0.001$), patients age ($Rs=-0.51$, $p<0.001$, $Rs=-0.39$, $p<0.001$, $Rs=-0.5$, $p<0.001$), skin AF ($Rs=-0.37$, $p<0.001$, $Rs=-0.29$, $p<0.001$, $Rs=-0.41$, $p<0.001$).

CONCLUSIONS:

Diabetes duration and accumulation of advanced glycation end products have most significant impact on the development of CAN in adults with T1D. HRV index evaluated at rest is the most accurate test to exclude potential cardiac autonomic neuropathy in type 1 diabetic patients. Valsalva test has the most sensitivity among all the Ewing battery tests in diagnosis of CAN.

P27 KU-596 IMPROVES MITOCHONDRIAL BIOENERGETICS AND DECREASES OXIDATIVE STRESS IN DIABETIC SENSORY NEURONS VIA HSP70

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OBJECTIVES:

Neuronal mitochondrial dysfunction and oxidative stress are key pathophysiologic mechanisms of diabetic peripheral neuropathy (DPN). KU-596 is a small molecule drug that can reverse clinically relevant measures of DPN by modulating the expression of heat shock protein 70 (Hsp70). Mechanistically, systemic administration of KU-596 to diabetic mice improved sensory neuron mitochondrial bioenergetics (mtBE) and decreased oxidative stress in an Hsp70-dependent manner. However, it remained unclear if the drug could directly improve mtBE and decrease oxidative stress in diabetic sensory neurons. The goal of this study was to determine if treating diabetic neurons with KU-596 could directly improve mtBE by decreasing glucose-induced superoxide production in an Hsp70-dependent manner.

METHODS:

Sensory neurons were isolated from non-diabetic or 14-week diabetic wild type (WT) or Hsp70 knockout (Hsp70 KO) mice. The cells were treated ex vivo for 24 hrs with KU-596 in the presence of 26 mM glucose. mtBE were assessed using a XF96 Extracellular Flux analyzer and superoxide production was measured by immunofluorescence or electron paramagnetic resonance spectroscopy.

RESULTS:

In diabetic WT and Hsp70 KO neurons, hyperglycemia significantly increased superoxide levels, but KU-596 only decreased superoxide in WT neurons. Similarly, KU-596 significantly improved mtBE in hyperglycemically stressed diabetic WT neurons, but not in diabetic Hsp70 KO neurons. Since manganese superoxide dismutase (MnSOD) is the main mechanism to detoxify mitochondrial superoxide, we determined if knockdown of MnSOD affected the drug-induced changes in mtBE and superoxide levels. Downregulating MnSOD in diabetic WT neurons increased hyperglycemia-induced superoxide levels, which was still significantly decreased by KU-596. Surprisingly, knockdown of MnSOD increased mtBE and KU-596 had no further effect on altering mtBE.

CONCLUSIONS:

The ability of KU-596 to decrease mitochondrial superoxide levels in diabetic neurons is not necessarily dependent on the presence of MnSOD since KU-596 decreased superoxide levels following knockdown of MnSOD. This may be due to incomplete knockdown of the enzyme or other mechanisms, such as mitophagy, that can decrease superoxide by clearing damaged mitochondria. Consistent with this possibility is that mtBE increased following knockdown of MnSOD, which has previously been shown to increase mitophagy in other cell types. Given the role of Hsp70 in facilitating the translocation of parkin to promote mitophagy, the ability of KU-596 to decrease superoxide levels and improve mtBE in an Hsp70-dependent manner may be linked to the drug's ability to increase the removal of damaged mitochondria. Since KU-596 is poised to enter Phase 2 clinical trials for treating DPN, it remains important to gain insight into its mechanism of action.

P28 DIABETIC NEUROPATHY IS CHARACTERISED BY DISTAL CORNEAL NERVE FIBRE LOSS AND SMALL FIBRE DYSFUNCTION

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OBJECTIVES:

We have previously shown that distal inferior whorl length (IWL) is reduced before more proximal corneal nerve fibre density (CNFD), branch density (CNBD) and length (CNFL) (proximal) in patients with diabetic neuropathy. We have compared change in IWL, central corneal nerve parameters and other measures of neuropathy over 3-5 years.

METHODS:

30 patients; 21 with type 1 and 9 with type 2 diabetes (age: 54.36±15.21, duration: 24.29±15.10, HbA1c: 55.5±14.44) underwent assessment of neuropathy disability score (NDS), vibration perception threshold (VPT), cold (CPT) and heat (WPT) perception thresholds, peroneal motor nerve conduction velocity (PMNCV) and corneal confocal microscopy.

RESULTS:

CNBD (56.95±25.49 vs. 44.98±21.26, P=0.02), CNFL (22.21±4.58 vs. 16.0±4.29, P<0.0001), IWL (24.33±8.48 vs. 14.19±5.62, P<0.0001) and the average of CNFL and IWL (ANFL) (23.26±5.53 vs. 14.01±3.32,P<0.0001) showed a significant reduction, with no change in CNFD (27.26±7.2 vs. 26.25±6.68, P=0.4) comparing baseline to follow up. There was a significant increase in CPT (16.66±10.82 vs. 22.4±9.3,P=0.04) and reduction in WPT (44.02±4.16 vs. 41.1±4.8, P=0.02), but no change in NDS (3.9±3.9 vs. 3.3±3.7, P=0.5), VPT (13.17±8.7 vs. 13.55±8.13,P=0.7) or PMNCV (42.47±4.19 vs. 41.9±6.1,P=0.7) at follow up.

CONCLUSIONS:

Greater distal corneal nerve loss is consistent with a dying process in diabetic neuropathy, with small fibre dysfunction, but no change in proximal corneal nerves or measures of large fibre neuropathy. IWL and measures of small rather than large fibre neuropathy are optimal for assessing longitudinal change in diabetic neuropathy.

P29 THE EFFICACY OF FREQUENCY-MODULATED ELECTROMAGNETIC NEURAL STIMULATION (FREMS) IN THE MANAGEMENT OF PAINFUL DIABETIC NEUROPATHY IN REAL-LIFE SETTING: A COHORT STUDY

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OBJECTIVES:

Painful diabetic peripheral neuropathy (PDPN) is a disabling complication affecting at least 20% of patients with diabetes mellitus. The pharmacological management of PDPN remains challenging with the majority of patients requiring several medications including opiates for adequate pain control and functionality. Frequency-modulated electromagnetic neural stimulation (FREMS) is not widely used. FREMS applies modulated electrical stimuli of varying pulse frequency, duration and voltage amplitude. FREMS was assessed in 1 RCT in patients with PDPN but there is no data from real-life clinical setting. The aim of this service evaluation is to assess the efficacy of a single FREMS treatment-session in patients with PDPN.

METHODS:

The study was conducted in a single tertiary center diabetic neuropathy clinic in the UK. Patients with PDPN who failed to respond to (or did not tolerate) multiple pharmacological treatments were offered FREMS (delivered in 10 consecutive out-patients sessions, 40 minutes each). Patients with contraindications to FREMS (epilepsy, implantable device) were excluded. The following assessment were performed at day 0 (i.e. before) and day 10 (i.e. after) FREMS and 6 months post-treatment: Short-Form McGill Pain Questionnaire – 2 (SF-MPQ 2), Pain visual analogue scale (VAS), SUDOSCAN and EQ-5D-5L.

RESULTS:

Five patients were included in this analysis, but more patients will be available for the presentation in September if the abstract is selected. The mean (SD) age was 54 years (16.6); diabetes duration 26.4 years (18.9); and HbA1c 9.1% (2.5);]. 80% (n=4) were Type 1 diabetes, 40% (n=2) were on opiates.
Most SFMPQ-2 scores and pain VAS numerically improved between day 0 and 10 of FREMS treatment [Mean (SD) Total: 4.2 (2.2) vs 3.1 (2.3) p=0.1; continuous: 4.4 (1.3) vs 2.7 (1.4) p=0.1; intermittent: 3.1 (2.6) vs 3.6 (4) p=0.6; affective: 4.4 (2.8) vs 2.7 (1.6) p=0.1; neuropathic 4.8 (2.8) vs 3.5 (2.9) p=0.1; pain VAS 9.3 (1.2) vs 5 (5) p=0.2). The EQ-5D-5L VAS also numerically improved between days 0 and 10 (57.5 (10.6) vs 72.5 (3.5) p=0.4). There was no change in SUDOSCAN parameters.
Three patients completed at least 6 month follow-up (range 6-8 months). The total, neuropathic and affective SFMPQ-2 scores remained numerically lower than baseline [Total 4.6 (2.9) vs 4.1 (2.6) vs 3.9 (3.6) p=0.7; SF-MPQ-2 neuropathic 5.2 (3.9) vs 4.2 (3.7) vs 4.7 (4.4) p=0.6; SF-MPQ-2 affective 5.5 (3.0) vs 3.8 (1.1) vs 4.1 (2.5) p=0.5) for day 0, day 10 and 6 months respectively].

CONCLUSIONS:

FREMS improved quality of life and pain in patients with PDPN who had advanced disease requiring multiple pharmacotherapy agents and long diabetes duration. Further FREMS treatment sessions around 6 months post initial treatment might be needed as some of the benefits of the initial treatment started to wean off. Larger sample size and RCTs are needed to determine the place of FREMS in the PDPN treatment algorithm.

P30 THE EFFECT OF AUTONOMIC AND SENSORY NEUROPATHY ON ALL-CAUSE MORTALITY -RETROSPECTIVE COHORT STUDY

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OBJECTIVES:

Cardiovascular autonomic neuropathy is associated with increased mortality, while the natural history of sensory neuropathy is much less understood Furthermore, there is a lack of information on the association between any neuropathy and all-cause mortality.
Objectives: Our aim was to examine the effect of both autonomic and sensory neuropathy on all-cause mortality in a well-phenotyped cohort.

METHODS:

Participants: patients living in the service area of the 1st Department of Medicine, Semmel-weis University with detailed autonomic and sensory neuropathy assessments between 1997 and 2016 (n=1940). Predictors: autonomic neuropathy (≥2 positive Ewing-tests), sensory neuropathy (≥1 abnormal result of one type of nerve fibre on both sides using Neurometer). Covariants: age, sex, type and duration of diabetes, comorbidities, medication, lifestyle factors. Outcome: all-cause mortality based on data from the National Health Insurance Fund of Hungary. Statistical analysis: Kaplan–Meier survival curves and Cox-regression models.

RESULTS:

Altogether n=1940 patients had had any neuropathy examination. Full sensory assessment was available for n=1873 cases (96.5%), autonomic neuropathy for n=1692 cases (87.2%). Partici-pants were 61.8±12.0 years old at baseline, n=1311 had diabetes (type 1 diabetes n=126), 43.4% were male (n=813). Autonomic neuropathy was found in n=492 cases (29.0%), sensory neuropathy in n=673 cases (35.9%), a combination of both neuropathies in n=196 cases (12.0%). During the 1–17-year follow-up, 788 participants died (40.6%). According to models adjusted for baseline age, sex, type and duration of diabetes, and comorbidities, patients with either autonomic or sensory neuropathy had an approximately 50% increased risk of mortality (hazard ratio [HR]: 1.47, 95% CI: 1.25–1.74 and HR: 1.55, 95% CI: 1.32–1.83, respectively). When both types of neuropathy were present together the risk more than doubled (HR: 2.19, 95% CI: 1.74–2.77).

CONCLUSIONS:

Our results confirm the association between autonomic neuropathy and all-cause mortality. Furthermore, they suggest that the presence of sensory neuropathy is at least as strongly relat-ed to all-cause mortality as autonomic neuropathy, and it is not only an important determinant of quality of life.

P31 EVALUATION OF AUTONOMIC AND SENSORY NERVE FUNCTION IN WOMEN WITH POLYCYSTIC OVARY SYNDROME

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OBJECTIVES:

Dysfunction of the nervous system is well-known in diabetes but is also documented in patients with prediabetes, obesity and hypertension as well. No data are available about the alteration of the neuronal function in polycystic ovary syndrome (PCOs), although this is also accompanied with metabolic and vascular abnormalities.The aim of our study was to assess the cardiovascular autonomic and peripheral sensory function in PCOs.

METHODS:

27 women with PCOs were involved (age: 28.7±1.8 years, BMI: 29.7±2.3, fasting plasma glucose: 4.5±0.09 mmol/L, HOMA index: 2.58±0.57; mean±SE). 24 healthy women acted as controls (age: 28.1±1 years, BMI: 22.6±0.8). Autonomic neuropathy (AN) was assessed by the five standard cardiovascular reflex tests. The peripheral sensory function was defined with Neurometer. Electric stimulation was applied transcutaneously and the current perception thrhold (CPT) values were determined on the median and peroneal nerves.

RESULTS:

No significant differences were found between the PCOs patients and the control group regarding the reflex tests and the AN scores (heart rate responses to deep breathing: 24.9±1.9 vs 24.5±1.6 beats/min; Valsalva ratio: 1.68±0.07 vs 1.86±0.06; 30/15 ratio: 1.4±0.06 vs 1.49± 0.06; orthostatic systolic RR drop: 2.5±0.8 vs 2±0.8 mmHg, diastolic RR response to handgrip: 20.9±1.8 vs 22.1±2.2 mmHg, AN score: 0.42±0.24 vs 0.72±0.19; mean±SE, PCOS vs control; $p>0.05$ respectively). Decreased CPT values were found in PCOs patients at the median and peroneal nerves at all frequencies in comparison with controls: Median nerve 2000 Hz: 2.88±2 vs 1.64±1.7 mA $p<0.01$; 250 Hz: 0.73±0.08 vs 1.27±0.12 mA $p<0.01$; 5 Hz: 0.49±0.06 vs 1±0.18 mA $p<0.05$. Peroneal nerve: 2000 Hz: 3.29±0.19 vs 4.4±0.28 mA $p<0.05$; 250 Hz: 1.34±0.49 vs 2.02±0.56 mA $p<0.01$; 5 Hz: 0.83±0.09 vs 1.56±0.1 $p<0.01$ PCOS vs control).

CONCLUSIONS:

The cardiovascular autonomic nerve function was normal in PCOS-s patient, but the current perception thresholds were consequently lower in the PCOs patients at the upper and lower extremeties at all testing frequencies. Our results suggest that the early neuronal damage manifests as a sensory hyperaesthesia in PCOs patients.

P32 DIAGNOSTIC ABILITY OF SUDOMOTOR FUNCTION ASSESSED BY COLOR CHANGE PLASTER (NEUROCHECK®) FOR DETECTING CARDIAC AUTONOMIC NEUROPATHY

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OBJECTIVES:

Sudomotor function test is one of the methods assessing peripheral autonomic dysfunction. The aim of this study was to evaluate the diagnostic ability of sudomotor function assessed by color change plaster (NeuroCheck®) for detecting cardiac autonomic neuropathy.

METHODS:

One hundred and twelve patients with diabetes underwent assessment of sudomotor function with NuroCheck, a simple, non-invasive sweat indicator test. Cardiac autonomic neuropathy (CAN) was assessed using five tests according to Ewing's protocol. Each test was given a point of 0, .5 or 1 if it yielded normal, borderline or abnormal values, respectively. CAN was defined as the presence of at least two abnormal tests or a sum of autonomic neuropathy points of 2 or more. The CAN score was categorized as follows: CAN score 0 (total points 0), 1 (points 0.5-1.5), 2 (points 2-3), and 3 (points ≥3.5). The primary outcome was the sensitivity and specificity of sudomotor dysfunction assessed by NeuroCheck for the detection of CAN. Secondary outcomes were the positive and negative predictive values of sudomotor dysfunction assessed by NeuroCheck for the diagnosis of CAN.

RESULTS:

Among all participants, 84 patients (75.0%) had sudomotor dysfunction and 34 patients (30.4%) had CAN. Patients with sudomotor dysfunction had significant higher CAN score than those without sudomotor dysfunction. Meanwhile, the prevalence of sudomotor dysfuntion significantly increased according to CAN score. The odds ratio of sudomotor dysfunction for presence of CAN was 4.9 (p=0.009). Sudomotor dysfunction showed sensitivity of 91.2% for detecting CAN, but relatively low specificity of 32.1%. The positive and negative predictive values of sudomotor dysfunction for detecting CAN were 36.9 and 89.3%, respectively.

CONCLUSIONS:

Sudomotor dysfunction assessed by NeuroCheck was significantly associated with CAN. Although sudomotor dysfunction assessed by NeuroCheck showed low specificity for detecting CAN, its sensitivity was more than 90%. Therefore, if sudomotor dysfunction is detected using NeuroCheck, it would be necessary to evaluate CAN.

P33 ACUTE HYPEROXIA AND SLOW DEEP BREATHING IMPROVE BAROREFLEX SENSITIVITY IN LONG-DURATION TYPE 1 DIABETES IRRESPECTIVE OF MACROALBUMINURIA

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OBJECTIVES:

In previous studies, hyperoxia and slow deep breathing (SDB) acutely improved measures of autonomic dysfunction in young patients with type 1 diabetes (T1D) and in patients with type 2 diabetes (T2D). Such effects have not been addressed in patients with T1D and concomitant macroalbuminuria and/or existing autonomic dysfunction. The aim of this study is to examine the effect of acute oxygen inhalation and SDB on measures of autonomic dysfunction and whether these could be modified by albuminuria or existing autonomic dysfunction.

METHODS:

Fifty-four patients with T1D (57% male) were enrolled in a cross-sectional study where 29 patients had normoalbuminuria and 25 had presence of/or historical macroalbuminuria. Mean age (SD) and diabetes duration were 59.8 years (9.5) and 37.5 years (14.4) respectively. Patients were exposed to acute oxygen inhalation and SDB, while obtaining measures of autonomic function and blood oxygen saturation. Autonomic function was assessed by baroreflex sensitivity (BRS) and the standard deviation of the normal-normal intervals (SDNN).

RESULTS:

Acute oxygen inhalation was associated with an increase of 21.3% (95%CI 9.8;34) and 8.3% (95%CI 0.1;17) in BRS (ms/mmHg) and SDNN (ms) respectively. SDB was associated with an increase of 31.6% (95%CI 13.2;5) and 32.8% (95%CI 18.2;49.1) in BRS (ms/mmHg) and SDNN (ms) respectively. Combined oxygen inhalation and SDB was associated with an increase of 29.8% (9.8;53.4) and 44.2% (95%CI 27.1;63.5 in BRS (ms/mmHg) and SDNN (ms) respectively. Patients with existing autonomic dysfunction had an improved effect of combined interventions on BRS. Albuminuria or existing autonomic dysfunction did not modify any other associations.

CONCLUSIONS:

Hyperoxia and SDB improve BRS and SDNN in T1D even in the presence of macroalbuminuria and existing autonomic dysfunction. This suggests that hypoxia might be involved in the pathogenic mechanisms of autonomic dysfunction in T1D. Further studies exploring the pathological pathways causing tissue hypoxia may improve the understanding of diabetic neuropathy.

P34 FIRST CLINICAL PRESENTATION OF DIABETES AUTONOMIC NEUROPATHY AS GASTROPARESIS IN A NEWLY DIAGNOSED TYPE-2 DIABETES PATIENT

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OBJECTIVES:

Diabetic autonomic neuropathy (DAN) is a serious and common complication of diabetes, often overlooked and misdiagnosed especially in early stages when it can be asymptomatic. It has a multisystem involvement and invariably its clinical presentation is preceded by subclinical dysfunction as commonly demonstrated by tests of cardiovascular autonomic function. Gastrointestinal (GI) manifestations of DAN, though not uncommon, represent a complex spectrum with multifactorial pathogenesis. We present a 46-year old newly diagnosed male patient with type-2 diabetes (T2DM) who presented with gastroparesis prior to the development of diabetes.

METHODS:

Our patient initially presented with a three-year history of nausea, bloating, epigastric pain and vomiting but without significant weight loss. Initial biochemistry excluded a diagnosis of diabetes (fasting glucose April 2015= 5.5 mmol/l). Subsequent, GI investigations including upper and lower GI endoscopy, abdominal CT scan, barium meal follow through and malabsorption tests were all normal. Gastroparesis was diagnosed due to delayed gastric emptying time of t½ 147 min but with normal vagal function. Subsequently (September 2017), he was diagnosed to have T2DM based on HbA1c (8.0%) and fasting plasma glucose (13.3 mmol/L). Following this diagnosis, he underwent assessment for both large and small fibre neuropathy to further explore the association between his clinical diagnosis and DAN.

RESULTS:

The following neurological assessments were performed:

Neural Parameter	Method	Outcome	Interpretation
Small fibre function	Laser Doppler imager (LDI_{FLARE})	3.83cm²	Reduced
Small fibre structure	Corneal confocal microscopy - CNFD	25.12 no /mm²	Reduced
	Corneal confocal microscopy - CNBD	51.83 no/mm²	Reduced
	Corneal confocal microscopy - CNFL	11.67mm/mm²	Reduced
Large fibre modalities	Vibration perception threshold	5.5mV	Normal
	Sural nerve conduction amplitude	21.5 µV	Normal
	Sural nerve conduction velocity	46.5 m/s	Normal

CONCLUSIONS:

The development of gastroparesis prior to the development of T2DM highlights the complex and heterogeneous spectrum of DAN in patients with diabetes. The 10-year incidence of gastroparesis in type-1 and type-2 DM is 5% and 1 % respectively. Clinical manifestations are often unrecognised, often leading to delay in diagnosis and reduction in quality of life. Based on our observations, we recommend that gastroparesis should be considered in patients presenting with unexplained gastrointestinal symptoms and diabetes should be considered as a possible cause. Furthermore, tests of small fibre function and structure using the LDIFLARE and CCM may aid the earlier diagnosis of DAN in those with diabetes. It is interesting to speculate that such tests may have been of value in the prediabetes period.

P35 DIABETIC DIARRHEA: DIAGNOSIS AND TREATMENT CHALLENGES IN A PATIENT WITH SEVERE PSYCHIATRIC DISORDER – A CASE REPORT

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OBJECTIVES:

The objective of this presentation is to illustrate the challenges and the difficulties in diagnosis and treatment of diabetic diarrhea in a patient with severe psychiatric pathology.

METHODS:

A 63-year-old male, diagnosed with type 2 diabetes, without no treatment due to systematic refuse was referred via emergency department for: severe hyperglycemia (blood glucose=818mg/dl), syncope, severe asthenia and fatigue, marked weight loss, nocturnal diarrhea associated with sudden impulse to defecate and tenesmus in the last 3 years. From past medical history, patient is known to suffer from organic personality disorder secondary to head trauma and partial gastric resection for a pancreatic pseudo cyst. At admission: altered general status, moderate thinness (body mass index=16.26kg/m²), symptomatic orthostatic hypotension, anhidrosis of skin, oral thrush, anesthesia below the knee, multiple brown round lesions of various size with crusted surface at the level of the calf secondary to burn trauma.

RESULTS:

Laboratory findings revealed: mild anemia, glycosuria, hypocalcaemia, hypoproteinemia and severe glycemic disequilibrium (A1c=16.4%). From the 2nd day of admission a basal bolus regimen with Determir (once daily) associated with aspart insulin was started. Due to the poor adherence to dietary recommendations and to optimize the glycemic control, Detemir insulin was administered twice daily. The stool test and inflammatory samples performed excluded an infection. The barium exam displayed a rapid transit at the level of the gastric stump and jejunum. During hospitalization the patient received i.v. treatment with: vitamins B, vitamin C, iron, alpha lipoic acid, amino acids, Loperamid and Erythromycin with significant clinical improvement. The screening for chronic microvascular complications highlights the presence of mild non-proliferative diabetic retinopathy and stage III distal sensorimotor diabetic polineuropathy. The psychological evaluation confirmed the presence of the organic personality disorder associated with a severe cognitive deficits and recommended a psychiatric consult.

CONCLUSIONS:

Diabetic diarrhea represents a major factor of morbidity in diabetic patients due to the possible complications. The treatment must address to all the pathophysiological mechanisms and the patient adherence to the treatment is essential in improving the clinical outcome.

P36 A SIMPLE METHOD TO MEASURE BAROREFLEX SENSITIVITY AND PERIPHERAL VASCULAR REACTIVITY DURING A STANDARDIZED VALSALVA MANOEUVRE: A PROPOSAL

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OBJECTIVES:

to propose simple and reliable indices of the baroreceptors-driven response to blood pressure variations during standardized Valsalva manoeuvre.

METHODS:

The sympathetically-dependent relationship between beat to beat ratio of the ECG RR intervals and the corresponding Blood Pressure Systolic values against time (msec/mmHg/seconds) during late phase 2 and the vagally-dependent similar relationship during early phase 4 were calculated as b2 and b4 respectively

RESULTS:

b2 showed age independent values and acceptable intra-individual variability coefficient (around 16%); b4 showed age related values ($p<0.0025$) and a higher intra-individual variability coefficient (around 26%)

CONCLUSIONS:

We propose b2 and b4 as complementary indices of overall baroreflex system function using a simple noninvasive test.

P37 DECREASED VAGAL ACTIVITY AND DEVIATION TO SYMPATHETIC ACTIVITY REPRESENTED BY HEART RATE VARIABILITY CAN PREDICT DEVELOPMENT OF DIABETES IN ASIANS ADULTS

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OBJECTIVES:

This study aimed to examine whether altered Heart Rate Variability (HRV) could predict the risk of development of diabetes in Asians.

METHODS:

We investigated the medical records of 37,217 adults aged 20-65 years old who did three-minute HRV measurement while seating on a chair between 2011 and 2014 at Kangbuk Samsung Hospital, without diabetes, anemia, thyroid disease, malignancy, heart disease, and hypertension. We analyzed HRV in time domain (standard deviation of the normal-to-normal interval [SDNN, ms], root mean square difference [RMSSD, ms]), and frequency domain (total power [TP, ms2], very low-frequency [VLF, ms2], low-frequency [LF, ms2], high-frequency [HF, ms2] power, normalized LF, normalized HF, and LF/HF ratio). We compared the risk of incident diabetes between 2012 and 2016 using multivariate Cox analysis according to tertiles of HRV variables with tertile 1 as reference group.

RESULTS:

Mean age of subjects were 37.9 ± 5.7 years. During 46,134,353 person-years, 693 subjects were diagnosed with diabetes. Both time and frequency domain variables were lower in diabetes group, except LF norm and LF/HF ratio. In cox analysis, as SDNN, RMSSD, TP, HF and HF norm tertiles increased, the risk of incident diabetes decreased, whereas the risk of diabetes increased in case of LF norm and LF/HF ratio.
These tendencies observed in HF norm, LF norm, and LF/HF ratio were maintained after adjustment for age, sex, body mass index, current smoking, drinking, systolic blood pressure, serum low-density lipoprotein-cholesterol, high sensitivity c-reactive protein, and glucose levels as confounders. The hazard ratios (95% confidence intervals) of tertile 3 of were 0.76 (0.61-0.94) for HF norm, 1.40 (1.13-1.74) for LF norm, and 1.37 (1.09-1.71) for LF/HF ratio.

CONCLUSIONS:

Abnormality in HRV, especially decreased vagal activity and sympatho-vagal imbalance deviated to sympathetic activity might precede incident diabetes.

P37 DECREASED VAGAL ACTIVITY AND DEVIATION TO SYMPATHETIC ACTIVITY REPRESENTED BY HEART RATE VARIABILITY CAN PREDICT DEVELOPMENT OF DIABETES IN ASIANS ADULTS

Table. Risk of incident diabetes according to tertiles of heart rate variability measurement in total subjects

Variables	Person-years	Number of events	Mortality rate (100,000 person-years) (95% CIs)	Age and sex-adjusted HRs (95% CIs)*	Multivariate-adjusted HRs (95% CIs)*	
					Model 1	Model 2
LF norm (n.u.)						
Tertile 1 (0–37.0)	14,860,307	144	0.97 (0.82-1.14)	1 (reference)	1 (reference)	1 (reference)
Tertile 2 (37.1–57.9)	15,457,987	234	1.51 (1.33-1.72)	1.45 (1.18-1.79)	1.35 (1.08-1.70)	1.34 (1.06-1.68)
Tertile 3 (≥58.0)	15,816,059	315	1.99 (1.78-2.22)	1.79 (1.46-2.18)	1.60 (1.28-1.98)	1.40 (1.13-1.74)
p for trend				<0.001	<0.001	0.004
HF norm (n.u.)						
Tertile 1 (0–41.5)	15,770,440	309	0.96 (1.75-2.19)	1 (reference)	1 (reference)	1 (reference)
Tertile 2 (41.6–62.3)	15,381,562	239	1.55 (1.37-1.76)	0.85 (0.71-1.00)	0.89 (0.74-1.07)	0.99 (0.83-1.19)
Tertile 3 (≥62.4)	14,982,351	145	0.97 (0.82-1.14)	0.57 (0.46-0.69)	0.64 (0.52-0.80)	0.76 (0.61-0.94)
p for trend				<0.001	<0.001	0.023
LF/HF ratio						
Tertile 1 (0–0.5)	13,565,438	131	0.97 (0.81-1.15)	1 (reference)	1 (reference)	1 (reference)
Tertile 2 (0.6–1.3)	16,324,483	243	1.49 (1.31-1.69)	1.43 (1.16-1.77)	1.30 (1.03-1.64)	1.33 (1.05-1.68)
Tertile 3 (≥1.4)	16,244,432	319	1.96 (1.76-2.19)	1.76 (1.43-2.17)	1.54 (1.23-1.93)	1.37 (1.09-1.71)
p for trend				<0.001	<0.001	0.012

* Cox proportional hazard models were used to estimate HRs and 95% CIs. Right-skewed variables (LF norm, HF norm, LF/HF ratio, hs-CRP, and alcohol intake) were log transformed for the analysis. Model 1 was adjusted for age, sex, body mass index, LDL-C, hs-CRP, current smoking and alcohol intake ≥20g/day. Model 2 is the same as model 1, plus an adjustment for systolic blood pressure, and fasting plasma glucose levels.

Abbreviations: HR, hazard ratio; CI, confidence interval; LF norm, normalized low-frequency; HF norm, normalized high-frequency; hs-CRP, high-sensitivity C-reactive protein; LDL-C, low-density lipoprotein-cholesterol.

P38 EFFECT OF SGLT2 INHIBITOR ON BLOOD PRESSURE AND HEART RATE VARIABILITY IN PATIENTS WITH TYPE 2 DIABETES

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OBJECTIVES:

Little is known whether SGLT2 inhibitor could affect heart rate variability (HRV), which is significantly associated with cardiovascular complications. This study is aimed to investigate the effect of SGLT2 inhibitor on blood pressure and HRV in patients with type 2 diabetes.

METHODS:

We enrolled type 2 diabetes patients who examined HRV before and after administration of SGLT2 inhibitor. We compared biochemical data, blood pressure, and HRV parameters before and after administration of SGLT2 inhibitor.

RESULTS:

Glycemic control was improved after administration of SGLT2 inhibitor. During the follow-up, there was no difference in systolic blood pressure. However, diastolic blood pressure significantly decreased after administration of SGLT2 inhibitor. There was no significant difference in heart rate before and after SGLT2 inhibitor treatment. Regarding HRV, there were no differences in standard deviation of NN intervals (SDNN), root mean square of successive RR interval differences (RMSSD), and low frequency to high frequency ratio before and after administration of SGLT2 inhibitor. However, high frequency domain significantly increased after administration of SGLT2 inhibitor.

CONCLUSIONS:

SGLT2 inhibitor decreased diastolic blood pressure. Meanwhile, it increased high frequency of HRV during day as well as night. This suggests that SGLT2 inhibitor may modulate parasympathetic tone of heart. Further studies are needed to examine whether the beneficial effects of SGLT2 inhibitor on cardiovascular events is associated with modulation of HRV.

P39 THE ASSOCIATION OF HEART-RATE VARIABILITY AND CORONARY ARTERY DISEASE IN TYPE 2 DIABETES

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OBJECTIVES:

Reduced heart-rate variability(HRV) is associated with increased risk of coronary artery disease(CAD). It is less clear whether HRV is associated with a first CAD. We aimed to evaluate the association of heart-rate variability and CAD in type 2 diabetic patients

METHODS:

A total of 102 patients with type 2 diabetes who had a history of CAD(50) or no CAD(52) enrollment were recruited from January 2015 to February 2018. We estimated the cormorbidity, risk factors of CAD and HRV in type 2 diabetes with or without CAD.

RESULTS:

The mean age and diabetes duration in type 2 diabetes with CAD were 68.5±8.7 and 12.2±6.9 years, respectively. Type 2 diabetc patients who developed CAD also exhibited hypertension (P = 0.01), diabetic nephropathy (P = 0.01), dyslipidemia (P = 0.01) and reduced HRVP=0.01) than did patients without CAD. Multivariable Cox hazard regression analysis revealed that reduced HRV was significantly associated with an CAD (hazard ratio [HR] 2.53; 95% confidence interval [CI] 1.42−4.10; P = 0.01). There is the close association of heart-rate variability and coronary artery disease in type 2 diabetes

CONCLUSIONS:

Reduced HRV was an independent risk for CAD in patients with type 2 diabetes.

P40 ASSOCIATION BETWEEN LOW HDL CHOLESTEROL AND CARDIAC AUTONOMIC NEUROPATHY IN PATIENTS WITH TYPE 2 DIABETES

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OBJECTIVES:

Cardiac autonomic neuropathy (CAN) is a chronic microvascular complication of diabetes, which is associated with increased cardiovascular risks and mortality. Low HDL cholesterol (HDL-C) is a well-known risk factor for atherosclerosis and is a common dyslipidemic feature accompanying patients with type 2 diabetes. This study investigated the association between low HDL-C levels and the presence of CAN.

METHODS:

This cross-sectional study involved 1532 patients aged more than 30 years with type 2 diabetes (741 men and 791 women; mean age, 56.2 years). CAN was assessed by analyzing heart rate responses to deep breathing, lying to standing, and Valsalva maneuver with an automated computer-based system. The severity of CAN was categorized as normal (if there were no abnormal tests), borderline (if one test was abnormal), and definite (if two or more tests were abnormal). The subjects were stratified based on gender-specific quartiles of HDL-C levels and analyzed with respect to CAN.

RESULTS:

The prevalence of CAN was 33.2% and was slightly higher in women than in men (35.6% vs. 30.6%; P=0.037). Compared with patients within the lowest HDL-C quartile, those with highest HDL-C quartile had lower body mass index (BMI), serum triglycerides, and Framingham risk score, and were more likely to be alcohol consumers in both men and women. Across the quartiles of HDL-C, there was a trend for a decreasing prevalence of impairment in heart rate responses to deep breathing (58.4%, 42.7%, 39.2% and 35.8%, P < 0.001) and impairment in heart rate responses to Valsalva maneuver (57.3%, 41.5%, 39.9% and 37.0%, P = 0.001) among men, but not women. Mean HDL-C levels in men decreased according to the increasing severity of CAN (normal 44.3 mg/dL; early 42.8 mg/dL, definite 40.6 mg/dL; P =0.002). In a multivariate analysis adjusted for age, BMI, duration of diabetes, alcohol consumption, smoking, a history of cardiovascular disease, HbA1c level ant the use of insulin, statin, or antihypertensive medication, men in the highest HDL-C quartile had an odds ratio of 0.53 of for having CAN [95% confidence interval = 0.29-0.89; P=0.021] compared to those in the lowest quartile.

CONCLUSIONS:

Lower serum HDL-C levels were associated with an increased risk for the presence of CAN in Korean men with type 2 diabetes. Further studies are needed to validate whether reduced HDL-C level can be a useful predictor of CAN.

P41 THE ASSOCIATION BETWEEN CARDIAC AUTONOMIC NEUROPATHY AND PROGRESSION OF DIABETIC NEPHROPATHY IN TYPE 2 DIABETIC PATIENTS

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OBJECTIVES:

Cardiac autonomic neuropathy (CAN) contributes to increased morbidity and mortality in type 2 diabetic patients with chronic kidney disease (CKD). Diabetic nephropathy is the leading cause of end-stage renal disease worldwide and its interrelationship with CAN remains unclear. The aim of our study was to investigate whether CAN were associated with progression of diabetic nephropathy such as change of estimated glomerular filtration rate (eGFR) in type 2 diabetes.

METHODS:

We recruited a total of 162 type 2 diabetics: 78 men (mean age 61.5±14.0 years) and 84 women (mean age 62.1±13.1 years) with CKD (≥ stage 2) by diabetic nephropathy and followed for 1.8±1.4 years. Renal function was evaluated by serum creatinine levels, estimated eGFR (calculated by the Cockcroft-Gault equation) and urinary ACR. Baseline-to-study end changes in eGFR were calculated, and yearly change of eGFR (mL/min/year) was computed. Cardiovascular autonomic function tests were performed using the following heart rate variability parameters: expiration-to-inspiration ratio, response to Valsalva maneuver and standing.

RESULTS:

Overall, the mean age was 61.9±13.4 years, duration of diabetes 12.7±9.2 years, HbA1C 8.1±2.1%, ACR 1,136.3±648.7 mg/gCr, serum creatinine 1.8±1.4 mg/dL, and systemic blood pressure (BP) 137.2±16.7/90.4±14.1 mmHg. Mean calculated GFR was 46.3±23.6 mL/min/1.73m2. Of the study population, 41 patients (25.3%) were smokers or ex-smokers, 148 patients (91.4%) were having hypertension, and 138 patients (85.2%) were taking angiotensin converting enzyme inhibitor or angiotensin receptor blocker.
At baseline, 41.4% (n=67) of patients had definite CAN. Mean yearly change of eGFR was 8.4±12.2 mL/min/year. Patients with rapidly progressive CKD (yearly change of eGFR >10 mL/min/year) were more likely to exhibit an abnormal Valsalva ratio (P = 0.02) and posture ratio (P = 0.04). The stage of CAN was also higher in patients with rapidly progressive CKD (P = 0.01). By Univariate linear regression, abnormal Valsalva ratio showed a significant negative correlation with yearly change in the eGFR (r=-0.312, P<0.05). Univariable Cox proportional hazard regression analysis revealed that patients with definite CAN exhibited a significantly higher risk of rapidly progressive CKD ([hazard ratio] HR 1.32; 95% CI 1.10-4.12; P = 0.04).

CONCLUSIONS:

This study demonstrated that CAN, especially abnormal Valsalva ratio may be predictor of progression of diabetic nephropathy in patients with type 2 diabetes.

P42 ASSOCIATION BETWEEN SEVERITY OF CARDIAC AUTONOMIC NEUROPATHY AND HYPOGLYCEMIA UNAWARENESS IN TYPE 2 DIABETIC PATIENTS

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OBJECTIVES:

Hypoglycemia unawareness (HU) is a major limitation to achieving tight diabetes control and reduced quality of life. HU occurs in approximately 40% of people with type 1 diabetes mellitus (T1DM) and with less frequency in T2DM. Though the etiology of HU is multifactorial, possible mechanisms include chronic exposure to low blood glucose, antecedent hypoglycemia, recurrent severe hypoglycemia, autonomic neuropathy and the failure of counter-regulatory hormones. The aim of our study was to investigate whether HU were more closely associated with any tests of cardiac autonomic neuropathy (CAN) in type 2 diabetes.

METHODS:

This cross-sectional study included 48 type 2 diabetics (mean age =58.2±11.2 years; duration of diabetes = 12.5±7.2 years). Two groups were divided into patients with a clinical history of hypoglycemia within the prior 3 months with intact hypoglycemia awareness and patients with hypoglycemia unawareness. The following 5 non-invasive autonomic testing were used for evaluation: heart rate at rest and in response to active standing (30:15 ratio), deep breathing and Valsalva maneuver (indicating parasympathetic function); blood pressure response to standing (orthostatic hypotension), sustained handgrip (indicating sympathetic function).

RESULTS:

Patients with HU (n=24), as compared to patients without HU (n=24), had higher prevalence of CAN diagnosed by cardiovascular autonomic reflexes tests (two abnormal tests out of five) (62.5% vs 16.7%, respectively; p=0.005). In patients with HU, 41.7, 29.2 and 16.7% respectively had early, definite and severe CAN. Compared to patients without HU, patients with HU had ≥2 abnormal tests (i.e., CAN) (P = 0.001) which included significantly abnormal heart rate response to standing (P = 0.05), active standing (30:15 ratio) (P = 0.001), Valsalva maneuver (P = 0.001), blood pressure response to sustained grip (P = 0.01) and blood pressure response from supine to standing position (orthostatic hypotension) (P = 0.001). After adjusting for baseline clinical characteristics, orthostatic hypotension (OR: 3.85; 95% IC 1.23-12.02; p=0.020), blood pressure response to sustained grip (OR: 2.73, 95% IC 1.12-8.28; p=0.032) and Valsalva maneuver (OR: 1.53, 95% IC 1.01-6.32; p=0.05) remained independent predictors of HU.

CONCLUSIONS:

The study concluded that sympathetic autonomic dysfunctions, especially orthostatic hypotension are more associated with HU than parasympathetic dysfunctions in type 2 diabetic patients.

P43 DIAGNOSTIC USEFULNESS OF COMBINED COMPASS 31 QUESTIONNAIRE AND ELECTROCHEMICAL SWEAT CONDUCTANCE FOR CARDIOVASCULAR AUTONOMIC NEUROPATHY AND DIABETIC POLYNEUROPATHY

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OBJECTIVES:

We recently validated the questionnaire COMPASS 31 for autonomic symptoms of diabetic neuropathy and documented the diagnostic accuracy of feet and hands electrochemical skin conductance (ESC) for diabetic cardiovascular autonomic neuropathy (CAN) and diabetic polyneuropathy (DPN). Thus, we investigated the diagnostic performance for CAN and DPN of the combined use of COMPASS 31 and ESC.

METHODS:

A total of 102 participants with diabetes (age 57±14 years, diabetes duration 17±13 years) completed the COMPASS 31 before undergoing 4 cardiovascular reflex tests (CARTs), assessment of neuropathic symptoms (using the Michigan Neuropathy Screening Instrument Questionnaire), signs (using the Michigan Diabetic Neuropathy Score), vibratory perception threshold, thermal thresholds, and ESC using SUDOSCAN. We defined early and confirmed CAN in the presence of at least 1 or 2 abnormal CARTs, respectively, and DPN with at least 2 abnormalities among symptoms, signs, VPT and TT. COMPASS 31 total weighted score was abnormal if >16.44, hands and feet ESC were abnormal if <50 μS and <70 μS, respectively. We evaluated the diagnostic performance for CAN and DPN of 1) the combined abnormalities in both COMPASS 31 and ESC (COMPASS 31+ESC), and of 2) the abnormality in COMPASS 31 and/or ESC (COMPASS 31 and/or ESC).

RESULTS:

Early CAN and confirmed CAN were present in 28.1% and 12.5%, respectively, PND in 52%, abnormal COMPASS 31 in 48% and abnormal ESC in 47.4%. Both the COMPASS 31+ESC and the COMPASS 31 and/or ESC abnormality were associated with early CAN (P=0.0088 and P=0.0045), confirmed CAN (P=0.0118 and 0.0159), and DPN (P=0.0041 and P=0.0033). Table shows the diagnostic performance for CAN and DPN of COMPASS 31+ESC and COMPASS 31 and/or ESC abnormality.

CONCLUSIONS:

In a busy clinical setting, the combination of two simple and time saving tests can allow a stepwise screening strategy for CAN, by suggesting with high probability the absence of disease in the case of combined normality and prompting to standard CARTs in the case of combined abnormality in COMPASS 31 and ESC.

P43 DIAGNOSTIC USEFULNESS OF COMBINED COMPASS 31 QUESTIONNAIRE AND ELECTROCHEMICAL SWEAT CONDUCTANCE FOR CARDIOVASCULAR AUTONOMIC NEUROPATHY AND DIABETIC POLYNEUROPATHY

Condition	Abnormality	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)	LR⁺	LR⁻
Early CAN	COMPASS 31+ESC	50 (30-70)	79 (69-89)	46 (27-65)	82 (72-91)	2.43 (1.31-4.49)	0.63 (0.41-0.96)
	COMPASS 31 and/or ESC	92 (82-103)	38 (26-50)	37 (25-49)	93 (83-102)	1.49 (1.19-1.85)	0.20 (0.05-0.80)
Confirmed CAN	COMPASS 31+ESC	59 (30-86)	79 (70-88)	29 (11-47)	93 (86-99)	2.74 (1.45-5.19)	0.53 (0.27-1.04)
	COMPASS 31 and/or ESC	100 (100-100)	34 (23-44)	18 (9-28)	100 (100-100)	1.51 (1.29-1.76)	0 (0-NaN)
DPN	COMPASS 31+ESC	37 (24-50)	89 (80-98)	79 (63-95)	56 (45-67)	3.43 (1.39-8.43)	0.70 (0.56-0.89)
	COMPASS 31 and/or ESC	85 (75-94)	48 (29-58)	63 (51-74)	71 (55-88)	1.50 (1.13-1.98)	0.35 (0.17-0.72)

P44 IS THERE A LINK BETWEEN TORONTO CLINICAL NEUROPATHY SCORE AND SUDOSCAN VALUES IN PATIENTS WITH TYPE 2 DIABETES MELLITUS?

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OBJECTIVES:

Among diabetic chronic complications, neuropathy is by far the most common. For diffuse neuropathies, distal symmetric polyneuropathy (DSPN), followed by cardiovascular autonomic neuropathy (CAN) are the most studied complications. Toronto Clinical Neuropathy Score (TCNS) is generally used for the diagnostic and staging of DSPN. SUDOSCAN is a point-of-care device for screening of sudomotor function and it offers a risk score for CAN by evaluating sweat gland secretory function. Since there are no previous studies focusing on the relationship between TCNS and SUDOSCAN parameters, we aimed to evaluate the relationship between TCNS, sudomotor function and SUDOSCAN-CAN in patients with type 2 diabetes.

METHODS:

After receiving the Ethic Committee approval, we retrospectively included records of all patients with type 2 diabetes seen in a private practice between 1st January 2017 and 28th of February 2018. Exclusion criteria were: other types of diabetes, use of drugs acting on sympathetic nervous system, electrical implantable devices, seizures or epilepsy, sciatic nerve lesion, vitamin B12 deficiency. Data collected were: age, sex, TCNS, SUDOSCAN values. Spearman correlation analysis and univariate regression analysis were used to identify the relation between SUDOSCAN values and TCNS.

RESULTS:

: 50.9% of the patients included were women, mean age was 67.16 (±9.125) years, mean weight 87.29 (±16.483) kg, and mean SUDOSCAN-CAN score 36.43 (±10.57). We found negative correlations between the SUDOSCAN-CAN score and left feet conductance (r=-0.561, p=0.00), right feet conductance (r=--0.226, p=0.00), left hand conductance (r=-0.334, p=0.00), right hand conductance (r=-0.353, p=0.00). Positive correlations were detected between SUDOSCAN-CAN score and right TCNS (r=0.233, p=0.00) and left TCNS (r=0.207, p=0.002) scores.
TCNS was associated with all SUDOSCAN conductances scores, and the association remained statistically significant after adjustment for age, gender and BMI (Table).

CONCLUSIONS:

SUDOSCAN-CAN results were associated with TCNS. Future directions should focus on the cut-off value of TCNS for stratifying risk and screening of CAN.

P44 IS THERE A LINK BETWEEN TORONTO CLINICAL NEUROPATHY SCORE AND SUDOSCAN VALUES IN PATIENTS WITH TYPE 2 DIABETES MELLITUS?

	Toronto values			
	Left Side Beta (*P-value*)		Right Side Beta (*P-value*)	
	Unadjusted	Adjusted[a]	Unadjusted	Adjusted[a]
CAN value	0.207(0.002)	0.164(0.005)	0. 198 (0.003)	0.177(0.003)
Feet left conductances	-0.222(0.001)	-0.200(0.004)		
Hand left conductances	-0.164 (0.014)	-0.149 (0.03)		
Feet right conductances			-0.198(0.003)	-0.180 (0.01)
Hand right conductances			-0.190(0.004)	-0.169 (0.014)

[a]Model is adjusted for age, gender, and BMI. CAN: cardiac autonomic neuropathy; ESC: electrochemical skin conductance.

P45 RELATIONS OF VITAMIN D STATUS WITH THE COMPLICATIONS OF TYPE 2 DIABETES IN KOREA

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OBJECTIVES:

To investigate the relationship between the serum vitamin D level and diabetic complications and other clinical parameters in type 2 diabetes patients.

METHODS:

This study included 480 type 2 diabetes patients who visited Eulji Diabetes Center from January 1st 2011 until March 1st 2016. Measures of anthropometric parameters, and laboratory testing including HbA1c, lipid profile, liver and kidney function, urinary albumin excretion ratio (UAER) were undertaken. The presence of diabetic macro- and microvascular complications were investigated through medical record review. Serum 25-hydroxy vitamin D (25(OH)D) concentrations were measured using a chemiluminescent immunoassay (CLIA).

RESULTS:

The mean level of 25(OH)D was 14.8 +/- 8.3 ng/ml. 364(75.8%) patients showed vitamin D deficiency (25(OH)D < 20 ng/ml). 159 (33.1%) were in the range of severe vitamin D deficiency (25(OH)D <10 ng/mL). 25(OH)D level was significantly correlated with age, diabetic duration, microalbuminuria, total cholesterol, triglyceride, and HDL-cholesterol. We identified significant independent relationship of vitamin D deficiency with the presence of diabetic nephropathy by using logistic regression equations.

CONCLUSIONS:

- In conclusion, vitamin D deficiency is very common among Korean diabetic patients and is independently associated with increased microalbuminuria. The association with serum cholesterol, triglyceride levels were also found. Further clinical studies are needed for the establishment of solid associations.

P46 EFFECT OF DIETARY OILS ON PERIPHERAL NEUROPATHY RELATED ENDPOINTS IN TYPE 2 DIABETIC SPRAGUE-DAWLEY RATS

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OBJECTIVES:

Determine the effect of dietary oils enriched in different mono- or poly-unsaturated fatty acids (olive (18:1, oleic acid), safflower (18:2 n-6, linoleic acid), flaxseed (18:3 n-3, alpha-linolenic acid), evening primrose (18:3 n-6, gamma-linolenic acid) or menhaden (20:5/22:6 n-3 eicosapentaenoic/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 a low dose of streptozotocin in order to induce hyperglycemia. After 8 or 20 weeks the rats were fed diets with 50% of the kcal of fat derived from lard replaced by the different dietary oils. In addition, a control group fed a standard diet (4% kcal fat) and a high fat fed group (45% kcal primarily lard) was maintained. The treatment period was 12 weeks. The endpoints evaluated included motor and sensory nerve conduction velocity, thermal and corneal sensitivity and innervation of sensory nerves in the cornea and skin. Data for only the late intervention period is shown below.

RESULTS:

Our findings show that menhaden and flaxseed oil provided the greatest benefit for preventing peripheral nerve damage caused by diabetes. Similar results were obtained when we examined acetylcholine-mediated vascular relaxation of epineurial arterioles of the sciatic nerve. Enriching the diets with fatty acids derived from the other oils provided none to partial improvements.

CONCLUSIONS:

These studies further support n-3 polyunsaturated fatty acids could be an effective treatment for peripheral neuropathy.

Determination	Control	Diabetic	Diabetic + Olive Oil	Diabetic + Safflower Oil	Diabetic + Flaxseed Oil	Diabetic + Evening Primrose Oil	Diabetic + Menhaden Oil
	(8)	(10)	(10)	(12)	(9)	(10)	(11)
MNCV (m/sec)	56.6 ± 2.1	36.0 ± 1.3[a]	38.1 ± 2.1[a]	36.4 ± 1.3[a]	48.6 ± 2.3[b]	39.5 ± 2.6[a]	48.9 ± 1.0[b]
SNCV (m/sec)	29.2 ± 0.5	24.0 ± 0.6[a]	23.7 ± 0.7[a]	24.0 ± 0.7[a]	26.9 ± 1.2	24.9 ± 0.7[a]	29.1 ± 0.6[b]
IENF (profiles/mm)	18.0 ± 1.1	12.2 ± 0.6[a]	13.4 ± 1.0[a]	12.5 ± 0.4[a]	14.5 ± 0.3	14.0 ± 0.9	17.7 ± 1.0[b]
Corneal nerve fiber length (mm/mm^2)	8.9 ± 0.2	4.6 ± 0.3[a]	4.8 ± 0.4[a]	4.8 ± 0.4[a]	7.6 ± 0.7[b]	5.9 ± 0.6[a]	8.0 ± 0.3[b]
Corneal sensitivity (cm)	5.8 ± 0.1	4.3 ± 0.2[a]	4.2 ± 0.1[a]	4.2 ± 0.1[a]	5.2 ± 0.2[b]	4.7 ± 0.2[a]	5.5 ± 0.1[b]
Thermal nociception (sec)	11.7 ± 0.5	22.1 ± 0.9[a]	16.9 ± 1.3[a,b]	21.8 ± 0.6[a]	13.2 ± 0.7[b]	14.7 ± 0.8[b]	12.6 ± 0.7[b]

P47 BASELINE VIBRATION PERCEPTION THRESHOLD DOES NOT AFFECT RESPONSE TO FIRST LINE TREATMENT IN PAINFUL DIABETIC NEUROPATHY

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OBJECTIVES:

Painful neuropathy is due to dysfunction of small fibres or their central connection and large fibres are believed to modulate this. Large fibre function can be measured using vibration perception threshold (VPT) and high thresholds (≥ 25 volts) are associated with the development of foot ulcers. There have been no studies demonstrating the effect of large fibre dysfunction in the treatment for neuropathic pain. The aim of this study was to analyse if the response to painful neuropathy treatment varies in patients with or without large fibre dysfunction.

METHODS:

A list of subjects with painful neuropathy was obtained from the central database and those who had VPT recorded in baseline and treated with pharmaceutical agents were studied. Subjects were then divided into two groups depending upon their VPT at baseline (<25 or ≥ 25 volts). The response to treatment at follow up after a month was assessed. Patients who confirmed improvement in their pain and elected to stay on the same dose or were discharged after satisfactory response were grouped as responders. If treatment had to be changed or dose titrated upwards due to side effects or poor response were grouped as non-responders.

RESULTS:

86 patients had VPT recorded at baseline. 24 patients did not receive pharmacological treatment, 4 patients lost to follow up and 4 subjects who had not yet had a second review were excluded. 26 subjects had low VPT and 28 had high VPT (Table 1). The severity and characteristics of pain was similar in both groups at baseline. The standard first line treatment was pregabalin (75 mg BD), amitriptyline (30 mg ON), gabapentin (300 mg TDS) or duloxetine (60 mg OD), given in weekly titration depending upon co-existing comorbidities. Subjects who had high VPT were older [66.7 (+/- 10.5) vs 60.5 (+/- 11.6) years; p = 0.023], but there was no difference in sex, type of diabetes, HbA1c and renal function. 61.5% of low VPT group responded to the first line treatment in comparison to 46.4% of high VPT group but this was not statistically significant (p = 0.29).

CONCLUSIONS:

Our results show that VPT may not affect the response to the first line treatment for painful neuropathy of diabetes. The choice of treatment was guided by co-existing medical condition and concern of side effects. Further clinical trials are needed to see if any specific treatment may be more useful in patients with large fibre dysfunction.

P47 BASELINE VIBRATION PERCEPTION THRESHOLD DOES NOT AFFECT RESPONSE TO FIRST LINE TREATMENT IN PAINFUL DIABETIC NEUROPATHY

Table 1: Baseline Characteristics

	Low VPT (n=26)	High VPT (n=28)	P value
Age (Yrs)	60.5 (+/-11.6)	66.7 (+/-10.5)	0.023*
Female (%)	53.8%	42.9%	NS
T1DM (%)	3.8%	7.1%	NS
HbA1c mmol/mol	62.2 (+/-17.2)	71.1 (+/-24.0)	NS
eGFR	69.8 (+/-18.6)	68.9 (+/-21.8)	NS
Severity of pain on presentation	9 (+/-1.5)	9.2 (+/-1.0)	NS
LANSS score	17.4 (+/-3.6)	16.8 (+/-5.8)	NS
Mean No of Diabetic medications	1.5	1.9	NS
% on insulin	15.4%	46.4%	0.02*

P48 EFFECTS OF FLAXSEED OIL ON OXIDATIVE/ NITROSATIVE STRESS AND CONDUCTION VELOCITY IN NERVES OF STREPTOZOTOCIN-INDUCED TYPE II DIABETIC RATS

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OBJECTIVES:

Oxidative stress due to hyperglycemia is a major cause of diabetic complications. Diabetic neuropathy pain is a common chronic complication of diabetes characterized by spontaneous pain, hyperalgesia and allodynia. The aim of this study was to evaluate the effects of flaxseed oil (FO) on oxidative-nitrosative stress, motor performance, and biochemical findings of diabetic neuropathy in a streptozotocin-induced rat model of diabetes mellitus.

METHODS:

FO was subjected to GCMS for chemical analysis. Type II Diabetes mellitus was experimentally induced by streptozotocin (STZ; 65 mg/kg, i.p.). Development of neuropathy was evident from a marked hyperalgesia and allodynia; reduced motor nerve conduction velocity (MNCV) associated with increased formation of advanced glycation end products (AGEs) and reactive oxygen/nitrogen species. Chronic treatment with FO (100, 200 and 400 mg/kg, p.o.) for 30 days was started from the 60th day of STZ administration.

RESULTS:

GC-MS analysis of FO revealed the presence of different fatty acids (linoleic acid, palmitic acid and oleic acid) and heterocyclic compounds. FO significantly attenuated behavioural and biochemical changes associated with diabetic neuropathy. MNCV was markedly improved by treatment with FO mainly via regenerating the structure of nerves. Present study suggested that FO ameliorated hyperglycemia and diabetic neuropathic pain via modulation of oxidative-nitrosative stress and reduction in AGEs formation in the diabetic rats.

CONCLUSIONS:

Trans-fatty acids can act as an effective dietary strategy for the decrease in postprandial glucose responses. Our results highlight potentially relevant health benefits of Flaxseed oil by exerting anti-hyperglycemic, anti-nociceptive and anti-oxidative/nitrosative stress effects in rats with STZ-induced diabetes. Therefore, it may be considered as useful dietary supplements in diabetic patients.

P49 INFLUENCE OF TESTOSTERONE REPLACEMENT THERAPY ON METABOLIC DISORDERS AND AUTONOMIC DIABETIC NEUROPATHY IN PATIENT WITH TYPE 2 DIABETES MELLITUS AND ANDROGEN DEFICIENCY.

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OBJECTIVES:

Multiple epidemiological studies have shown that low testosterone levels are associated with and predict the future development of T2D and the metabolic syndrome.
Aim of study: The aim of study was to show the influence of testosterone replacement therapy on BMI, HbA1c level, Diabetic neuropathy, and CV-risk factors - with patient diabetes mellitus and Androgen deficiency.

METHODS:

85 subjects with 41-65 years and BMI 27,0 – 48,0 kg/m2 were randomized In placebo-controlled study, who underwent a routine physical examination and choose free testosterone examination. Also for assessment of autonomic diabetic neuropathy was used "Vegetotester" – digital instrument for vegetative nervous system study. We divided patients into two groups. In the first group we used diet, physical activity (Lifestyle intervention implies reduced calorie diet (The reduction of daily calorie intake in 800-1200 calorie, it was selected individually), patient's antidiabetic therapy and testosterone replacement therapy. In second group we used diet, physical activity (Lifestyle intervention implies reduced calorie diet (The reduction of daily calorie intake in 800-1200 calorie, it was selected individually), patient's antidiabetic therapy and placebo.

RESULTS:

After six months of treatment: We had some positive results about lipid profile in both of groups but better results was in first group. Free testosterone level increased in all groups but the best results was in I group. HbA1c decreased in both group but in I group we had the best result. BMI decreased in both groups but more reduction was in I group. also blood pressure were reduced in both group, where we found alike results. Also in first group was positive results about autonomic diabetic neuropathy.

CONCLUSIONS:

Autonomic diabetic neuropathy, Serum testosterone, HbA1c, lipid profile, BMI, Hypertansion improved in both treatment groups after 26 weeks of treatment. Our study demonstrated that it is possible to break into this vicious circle by raising testosterone levels in diabetic men and low testosterone level. Maybe low level of testosterone has some role in pathogenesis of autonomic diabetic neuropathy. Re-instituting physiological levels of testosterone in hypoandrogenic men as our small study shown, have an important role in reducing the prevalence of diabetic complication.

P50 EFFECT OF DIETARY CONTENT OF MENHADEN OIL +/- SALSALATE ON NEUROPATHIC ENDPOINTS IN A TYPE 2 DIABETIC RAT MODEL

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OBJECTIVES:

This study sought to determine whether the addition of salsalate in the diet with menhaden oil is more effect than monotherapy on diabetic neuropathy.

METHODS:

Four weeks after the onset of hyperglycemia diabetic rats were treated via the diet with 3 different amounts of menhaden oil with or without salsalate for 12 weeks. Afterwards, vascular reactivity of epineurial arterioles and neuropathy related endpoints were examined.

RESULTS:

The addition of salsalate to high fat diets enriched with 10% or 25% kcal of menhaden oil protected vascular reactivity to acetylcholine and calcium gene-related peptide, motor and sensory nerve conduction velocity, thermal nociception, intraepidermal nerve fiber density and cornea sensitivity to a greater extent than 10% or 25% menhaden oil alone. Vascular and neural function was maximally protected with diet containing 45% kcal as menhaden oil and adding salsalate did not provide any additional benefit. Salsalate alone in the high fat diet of diabetic rats provided minimal protection/ improvement of vascular and neural dysfunction.

CONCLUSIONS:

These studies imply that dietary salsalate in combination with lower amounts of menhaden oil can provide greater benefit toward diabetes-induced vascular and neural impairment than menhaden oil alone.

Condition	MNCV (m/sec)	SNCV (m/sec)	Thermal sensitivity (sec)	IENF (profiles/mm)	Corneal sensitivity (cm)	Cornea nerve fiber length (mm/mm^2)
CONTROL	55.7 ± 2.1	31.9 ± 0.5	11.9 ± 0.3	20.7 ± 0.7	5.77 ± 0.08	9.5 ± 0.5
DIABETIC	40.4 ± 1.4[a]	26.7 ± 0.6[a]	18.4 ± 0.5[a]	13.1 ± 0.8[a]	4.67 ± 0.22[a]	4.9 ± 0.4[a]
DIABETIC + SALSALATE	45.0 ± 1.9[a]	27.8 ± 0.4[a]	16.0 ± 1.0[a]	15.9 ± 0.4[a]	4.65 ± 0.20[a]	6.6 ± 0.5[a]
DIABETIC + MENHADEN OIL 10%	44.1 ± 1.8[a]	27.3 ± 0.6[a]	15.2 ± 1.0	14.5 ± 0.9[a]	4.88 ± 0.19[a]	6.4 ± 0.5[a]
DIABETIC + MENHADEN OIL 10% + SALSALATE	51.0 ± 2.0[b]	28.7 ± 0.6[a]	13.4 ± 1.2[b]	16.2 ± 0.06[a]	5.03 ± 0.22[a]	6.4 ± 0.5[a]
DIABETIC + MENHADEN OIL 25%	47.2 ± 1.4[a]	28.3 ± 0.5[a]	12.3 ± 0.6[b]	15.6 ± 1.1[a]	4.81 ± 0.16[a]	8.1 ± 0.4[b]
DIABETIC + MENHADEN OIL 25% + SALSALATE	49.2 ± 1.6[b]	29.7 ± 0.4[b]	11.2 ± 0.7[b]	18.9 ± 1.0[b]	5.58 ± 0.10[b]	8.5 ± 0.7[b]
DIABETIC + MENHADEN OIL 45%	51.6 ± 1.4[b]	30.0 ± 0.4[b]	11.3 ± 0.4[b]	19.0 ± 1.2[b]	5.54 ± 0.13[b]	9.1 ± 0.6[b]
DIABETIC + MENHADEN OIL 45% + SALSALATE	52.3 ± 1.2[b]	30.3 ± 0.5[b]	11.2 ± 0.7[b]	19.1 ± 0.6[b]	5.88 ± 0.06[b]	9.4 ± 0.6[b]

Data are presented as the mean ± S.E.M. a $P < 0.05$ compared to control. b $P < 0.05$ compared to diabetic. Number of experimental animals was 12.

P51 B6 HYPERVITAMINOSIS INCREASING THE SEVERITY OF NEUROPATHIC SYMPTOMS IN A TYPE 1 DIABETIC FEMALE ATHLETE – A CASE REPORT

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OBJECTIVES:

The objective of this presentation is to illustrate the consequences of a high vitamin B6 intake in the case of a young type 1 diabetic female athlete.

METHODS:

A 34-years old female, diagnosed with type 1 diabetes at the age of 18, under treatment with detemir and aspart insulin, was admitted in our service for: frequent hypoglycemic unawareness episodes especially in the early morning after nocturnal insulin corrections, increased appetite and intense nocturnal stabbing pain in the lower limbs – 9/10 on Visual Analog Scale (VAS) with insidious onset and lasting for few hours. 5 months before presentation in our service she was diagnosed with sensitive peripheral neuropathy for which she received treatment with a combination of Benfotiamine (100mg) and Vitamin B6 (100mg) twice daily , α-lipoic acid (600mg/day), vitamin E, sulodexide and gabapentin (300mg/day). Further questioning revealed that, in the last 3 months, in addition to her background medication she also took a multivitamin complex containing a high amount of vitamin B6, in order to improve her sport performance. At presentation: diminished vibration perception with no motor deficits or autonomic signs and symptoms.

RESULTS:

The labs findings displayed high B6 (873μg/L²; normal value: 8.7-27.2) and B12 (1542pg/ml; normal value: 197-771) levels. The treatment with the combination of Benfotiamine plus Vitamin B6 and the multivitamin complex were stopped which led to a slow improvement of the symptoms (VAS=3/10 after 1 month). The therapeutic and nutritional education was resumed and the sensibility factor was changed in order to avoid the hypoglycemic events.

CONCLUSIONS:

Due to the persistent desire of achieving better results, some athletes use different supplements which may predispose to disorders like peripheral neuropathy. Thereby, in front of typical peripheral neuropathy manifestations, the measurement of B6 levels is advised.

P52 EFFECT OF LIQUID SUCROSE IN COMBINATION WITH WESTERN DIET ON METABOLIC PROFILE IN A RAT MODEL OF TYPE 2 DIABETES

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OBJECTIVES:

Lowering plasma triglycerides (TG) reduces the incidence of diabetic peripheral neuropathy (DPN), suggesting that TG is important to the development of DPN. Only a modest increase in TGs is induced in current type 2 diabetic (T2D) rat models of DPN. Including sucrose in the drinking water has shown to increase insulin resistance and TGs. The purpose of this study was to characterize the metabolic profile of rats receiving liquid sucrose together with a Western diet and to find a suitable dose of streptozotocin (STZ) to develop a T2D model where the relationship between TGs and DPN can be investigated.

METHODS:

64 male Sprague-Dawley rats were divided into two groups: WD fed Western diet and treated with 30 mg/kg STZ after 8 weeks of diet (n=10) and WDS fed Western diet with addition of sucrose in the drinking water. After 8 weeks of diet WDS was separated into three groups distinguished by STZ dose: 30 mg/kg (WDS1, n=18), 20 mg/kg (WDS2, n=18) and 10 mg/kg (WDS3, n=18). Metabolic profile was characterized before STZ-treatment and two weeks after by measuring body weight, glucose, insulin, C-peptide and TGs. Insulin sensitivity was estimated by quantitative insulin sensitivity check index (QUICKI).

RESULTS:

Before STZ-treatment WDS [3.8±1.8mM (Mean±SD)] had higher TGs than WD [2.4±1.2mM; P=0.02]. No other differences were found at this time point. The success rate of inducing diabetes was 80%, 22%, 6% and 0% in WD, WDS1, WDS2 and WDS3, respectively. The remainder of the animals did not become diabetic (0%, 6%, 94%, 100%) or died suddenly/were euthanized due to humane endpoints (20%, 72%, 0%, 0%). Animals in WD [24±10mM] and WDS1 [28±14mM] had higher glucose levels than WDS2 [7±5mM; P<0.0001; P=0.0001] and WDS3 [6±0.5mM; P<0.0001; P<0.0001]. Lower C-peptide levels were observed in WD [742±402pM] and WDS1 [643±466pM] compared to WDS2 [1912±570pM; P=0.0001; P=0.001] and WDS3 [2353±1234pM; P=0.009; P=0.04]. Furthermore, WD [227±135pM; P=0.0007] and WDS1 [196±122pM; P=0.003] had lower insulin levels than animals in WDS2 [599±210pM]. Body weight was lower in WDS1 [551±83g] compared to WDS2 [661±56g; P=0.01] and WDS3 [683±52g; P=0.001]. No difference in TG or QUICKI was found after diabetes induction.

CONCLUSIONS:

In conclusion, Western diet and liquid sucrose may serve as a pre-diabetic model showing same level of obesity and insulin resistance as Western diet alone but with increased TGs. However, with the STZ-doses used in this study liquid sucrose does not create a T2D model with higher TGs.

P53 THERAPEUTIC ROLE OF ALL TRANS RETINOIC ACID ON TYPE 2 DIABETIC NEUROPATHY

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OBJECTIVES:

Nerve growth factor (NGF) is considered to regulate nervous system, neuronal differentiation and regeneration of damaged nerves. And retinoic acid increases the endogenous expression of NGF. The aim of our study was to investigate effects of all-trans retinoic acid (ATRA) on diabetic neuropathy.

METHODS:

Twenty Otsuka Long-Evans Tokushima Fatty (OLETF) rats were received 10 mg/kg/day ATRA p.o., and 20 OLETF and 10 Long-Evans Tokushima Otsuka (LETO) rats were received cellulose as a vehicle once a day for 16 weeks. We measured blood glucose and NGF in serum and sciatic nerve at the end of treatment. Neurometer current stimulus test was performed to examine the improvement of current stimulus thresholds. Nerve capillary density was measured in search of morphological changes secondary to neuropathy and regeneration. The effects of ATRA on neurite growth from dorsal root ganglion (DRG) cells exposed to NGF were assessed and mRNA of NGF and NGF receptors p75NGFR and trkA in response to ATRA in DRG were measured by PCR and real-time PCR.

RESULTS:

After 16 weeks of treatment, serum glucose decreased by ATRA treatment. NGF was decreased in ATRA-non-treated OLETF (683.71±169.89 pg/mL in serum and 150.0± 28.8 pg/g in nerve) but increased in ATRA-treated OLETF compared to LETO (1423.5± 503.2 pg/mL in serum and 243.2± 41.9 pg/g in nerve) and in ATRA-treated OLETF (1855.2± 667.3 pg/mL in serum and 377.9± 61.5 pg/g in nerve) (p<0.05). Threshold increased significantly in OLETF and LETO, but decreased at 2000, 250 Hz in ATRA-treated OELTF compared to ATRA-non-treated OLETF. Nerve capillary density was decreased in ATRA-non-treated OLETF (173.2± 42.4 /mm2) compared to LETO (262.78 ± 34.1 /mm2). Neurite outgrowth and length in DRG increased in NGF and ATRA dose-dependently. High glucose(>30 mM) inhibited NGF-dependent neurite formation, suggesting that high glucose inhibits neurite formation. In DRG, ATRA regulated gene expression of NGF within 24 hr dose-dependently. However, ATRA did not increase the expression of NGFR, p75NGFR and trkA mRNA levels.

CONCLUSIONS:

ATRA treatment increases serum and nerve contents of NGF in OLETF and influence nerve cell regeneration by promoting synthesis of NGF. Our results suggest that ATRA has a potential therapeutic role for diabetic neuropathy.

P54 IMPROVED DESIGN OF A RANDOMIZED, DOUBLE-BLIND, PLACEBO-CONTROLLED TRIAL EVALUATING THE EFFICACY AND SAFETY OF MIROGABALIN FOR DIABETIC PERIPHERAL NEUROPATHIC PAIN

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OBJECTIVES:

Phase 2 studies were conducted in the US and Asia to evaluate the safety and efficacy of mirogabalin—a novel potent, selective alpha-2-delta ligand—for the treatment of diabetic peripheral neuropathic pain (DPNP). The analysis presented here learned from the phase 2 studies to determine key success factors for the design of clinical studies of DPNP treatment.

METHODS:

The study design and procedures of an Asian phase 3 study were improved based on insights learned from the phase 2 studies. In the Asian phase 2 study, the primary endpoint, average daily pain score (ADPS) change from baseline, was numerically greater for mirogabalin 10, 20, and 30 mg/day groups vs placebo, but not statistically significant at week 7 (P = 0.2, 0.3, and 0.5). However, the changes from baseline in visual analog scale (VAS) and average daily sleep interference score (ADSIS) were significantly different for mirogabalin 30 mg/day vs placebo at week 7 (P = 0.009 and 0.0002). ADPS change from baseline for pregabalin 300 mg/day was similar to that of placebo. Therefore, the strong placebo effect may have masked the efficacy of mirogabalin. As the incidence of somnolence and dizziness was higher in the early phase after mirogabalin administration, it was expected that more cautious dose-titration would reduce the adverse event frequency.
The design of the phase 3 study was improved as follows: a randomization ratio of 2:1 was used for placebo vs each mirogabalin arm, similar to the US phase 2 study; exclusion of the patients with extreme pain whose distress could jeopardize the pain questionnaires; more gradual titration of dosing, starting from 5 mg twice daily.
The conduct of the phase 3 study was also improved by guiding site staff and patients on study procedures and educating staff to properly administer questionnaires.

RESULTS:

In the phase 3 study, mirogabalin 30 mg/day demonstrated significant changes from baseline in the ADPS, ADSIS, and VAS compared with placebo at week 14 (P = 0.0027, 0.0018, and <0.0001, respectively). The frequency of dizziness and somnolence with mirogabalin 30 mg/day was reduced in the phase 3 study (10.9% and 17.0%) compared with the Asian phase 2 study (16.7 and 21.1).

CONCLUSIONS:

Selecting appropriate patients, planning more gradual dose titration, and improved randomization ratio and operational strategies can optimize the study design and conduct of clinical studies in DPNP.

P55 EFFECT OF MENHADEN OIL OR RESOLVIN D1 ON DIABETIC NEUROPATHY IN FEMALE C57BL/6J MICE

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OBJECTIVES:

All of our previous studies examining the beneficial effects of menhaden oil and resolvins on diabetic peripheral neuropathy (DPN) have been done in male rodents. This study sought to determine whether menhaden oil or resolvin D1 is an effective treatment for DPN in type 2 diabetic female C57Bl/6J mice.

METHODS:

Robust hyperglycemia was induced in C57Bl/6J female mice through a combination of high fat diet and streptozotocin. Type 2 diabetic female mice after 4 weeks of hyperglycemia were treated for 8 weeks with menhaden oil or with daily injections of (1 ng/kg) resolvin D1. The endpoints evaluated included motor and sensory nerve conduction velocity, thermal and mechanical sensitivity and innervation of sensory nerves in the cornea and skin.

RESULTS:

Our findings show that menhaden oil or resolvin D1 did not improve hyperglycemia in diabetic mice. Untreated diabetic mice were thermal hypoalgesic, had mechanical allodynia, reduced motor and sensory nerve conduction velocities and decrease innervation of the cornea and skin. These endpoints were generally improved with menhaden oil or resolvin treatment.

CONCLUSIONS:

These studies in combination with our previous studies further support n-3 polyunsaturated fatty acids derived from fish oil via in part due to their metabolites could be an effective treatment for diabetic neuropathy and are effective in both female and male mice.

Effect of Menhaden Oil Dietary Enrichment or Daily Treatment with Resolvin D1 of Diabetic Female Mice on Fasting Blood Glucose, Motor and Sensory Nerve Conduction Velocity (MNCV/SNCV), Intraepidermal Nerve Fiber Density (IENF), Cornea Nerve Fiber Length, Thermal Nociception and Mechanical Allodynia

Determination	Control	Diabetic	Diabetic +Menhaden Oil	Diabetic +Resolvin D1
Fasting blood glucose (mg/dl)	204 ± 7	407 ± 25[a]	343 ± 30[a]	375 ± 31[a]
MNCV (m/sec)	34.9 ± 1.3	21.9 ± 0.9[a]	31.9 ± 1.2[b]	31.3 ± 1.4[b]
SNCV (m/sec)	17.9 ± 0.2	15.0 ± 0.5[a]	17.9 ± 0.2[b]	18.2 ± 0.3[b]
IENF (profiles/mm)	24.9 ± 0.5	15.7 ± 0.3[a]	21.5 ± 0.4[a,b]	20.8 ± 0.3[a,b]
Corneal nerve fiber length (mm/mm^2)	2.00 ± 0.11	0.93 ± 0.07[a]	1.81 ± 0.15[b]	1.70 ± 0.14[b]
Thermal nociception (sec)	4.94 ± 0.07	7.25 ± 0.13[a]	5.41 ± 0.16[b]	5.87 ± 0.14[a,b]
Mechanical allodynia (g)	2.82 ± 0.08	1.15 ± 0.03[a]	1.82 ± 0.09[a,b]	1.69 ± 0.10[a,b]

Data are presented as the mean ± S.E.M. a P < 0.05 compared to control; b P < 0.05 compared to diabetic. Number of experimental animals for each group was 15.

P56 THE ANGIOPOIETIN/TIE2 SIGNALING PATHWAY CONTRIBUTES TO THE THERAPEUTIC EFFECT OF THYMOSIN BETA 4 ON DIABETIC PERIPHERAL NEUROPATHY

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OBJECTIVES:

Angiopoietin 1 (Ang1) and its receptor Tie2 regulate vascular function. Our previous study demonstrated that thymosin beta 4 (Tβ4) ameliorates neurological function of diabetic peripheral neuropathy. Mechanisms underlying the therapeutic effect of Tβ4 on diabetic peripheral neuropathy have not been fully investigated. The present study investigated whether the Ang1/Tie2 signaling pathway is involved in Tβ4-improved neurovascular remodeling and neurological outcome in diabetic peripheral neuropathy.

METHODS:

Male BKS. Cg-m+/+Leprdb/J diabetic mice (db/db) at age 20 weeks (n=10/group) were treated with Tβ4 (30mg/kg, i.p. daily) and a biotin-conjugated neutralizing antibody against mouse Tie2 antibody (1.2μg/mouse, i.p. daily) or saline for 4 consecutive weeks. Peripheral neurovascular changes and neurological function were measured.

RESULTS:

Compare to db/db mice treated with saline, db/db mice treated with Tβ4 exhibited significant ($p<0.05$) improvement of motor (MCV, 41±2m/s vs. 30±1m/s in saline) and sensory (SCV, 39±1m/s vs. 30±2m/s in saline) conduction velocity in the sciatic nerve and thermal sensitivity (Plantar test, 8±0.2m/s vs. 11±1m/s in saline). Administration of the neutralized antibody against Tie2 abolished ($p<0.05$) the therapeutic effect of Tβ4 on nerve conduction velocity (MCV, 35±1m/s; SCV, 34±2m/s) and thermal hypoesthesia (9±1m/s). Moreover, the Tβ4 treatment substantially increased ($p<0.05$) sciatic nerve blood flow (90±5% vs. 60±7% in saline) and the density of fluorescein isothiocyanate (FITC)-dextran perfused vessels (23±2% vs. 17±2% in saline) and augmented intraepidermal nerve fiber density (IENFS, 16±1 fiber/mm vs. 13±0.4 fiber/mm in saline). However, inhibition of the Tie2 significantly ($p<0.05$) attenuated Tβ4-improved regional blood flow (63±11%), vascular density (18±2%) and IENFs density (14±1fiber/mm). Western blot analysis of sciatic nerve tissue showed that the Tβ4 treatment considerably ($p<0.05$) increased Tie2 (1.4±0.1 vs. 0.7±0.2 in saline), and reduced NFkB activity (2.4±0.1 vs. 5.7±0.1 in saline) and vascular cell adhesion molecule 1 (VACM1, 1.2±0.1 vs. 2.0±0.2 in saline), whereas the neutralized antibody significantly ($p<0.05$) reversed Tβ4-increased Tie2 (0.8±0.1), and Tβ4-decreased NFkB activation (4.3±0.1) and VCAM1 level (1.6±0.1).

CONCLUSIONS:

Tβ4 improves sciatic nerve neurovascular function, leading to amelioration of peripheral neuropathy. The Ang1/Tie2 pathway contributes to the therapeutic effect of Tβ4 on diabetic peripheral neuropathy.

P57 THE ASSOCIATION BETWEEN CEREBRAL PERFUSION AND WHITE MATTER HYPERINTENSITIES IN PATIENTS WITH TYPE 2 DIABETES MELLITUS

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OBJECTIVES:

Type 2 diabetes mellitus (T2DM) is associated with cerebral small vessel disease. The association between white matter hyperintensities (WMH) as one of the key brain MRI features of small vessel disease, and cerebral perfusion in patients with T2DM is unknown. We therefore investigated the association between WMH and cerebral perfusion in patients with T2DM.

METHODS:

We examined 91 patients with T2DM (31 males, mean age 62.2±5.5 years, diabetes duration 9.7±6.6 years). Cerebral perfusion was assessed using SPECT scans and quantified by comparison to a database of healthy individuals (expressed as a standard deviation). WMH volumes were calculated on 1.5T brain MRI scans as a percentage of total intracranial volume, by a probabilistic segmentation method. Linear regression analyses adjusted for age and gender were performed to study the association of WMH and global and regional (frontal, occipital, parietal, temporal, cerebellum, caudate nucleus, putamen, and thalamus; both left and right) cerebral perfusion.

RESULTS:

A higher WMH volume was associated with a lower perfusion in the right frontal lobe (0.046 (0.004↔0.088), p=0.030). However, a higher WMH volume was associated with a higher perfusion in the caudate nucleus (left B=-0.030 (-0.060↔-0.001), p=0.042; right -0.034 (-0.064↔-0.003), p=0.032). There were no significant associations between WMH volume and perfusion in other cerebral regions (p>0.05).

CONCLUSIONS:

In patients with T2DM, a higher WMH volume was associated with lower cerebral perfusion in the right frontal lobe. However, the exact underlying mechanisms require further investigations.

P58 ANALYSIS OF CLINICAL PHENOTYPE OF NEUROPATHIC SYMPTOMS IN PATIENTS WITH DIABETES

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OBJECTIVES:

Many patients with diabetic peripheral neuropathy (DPN) complain of various neuropathic symptoms, typically characterized as burning, tingling, electric, sharp, shooting, and numbness. The aim of this study is to cluster subgroups of DPN patients according to a composite of subjective symptoms and the clinical impacts on pain severities, sleep disturbance, quality of life and to evaluate relationship between intensities and patterns of symptoms identified by factor analysis.

METHODS:

A total of 244 patients met study eligibility criteria and were recruited between January and June 2017. We conducted the Michigan Neuropathy Screening Instrument (MNSI), painDETECT, Brief Pain Inventory (BPI)-short form, Medical outcomes study (MOS) Sleep Scale and the EuroQoL (EQ-5D). A hierarchical cluster analysis and factor analysis were performed to identify relevant subgroups of patients with DPN and symptom patterns.

RESULTS:

Patients with DPN were divided into two clusters based on results of neuropathic pain assessment tools: severe pain with sleep disturbance and decreased quality of life (cluster 1, n = 86), relatively mild symptoms (cluster 2, n = 71). Patients in cluster 1, compared with clusters 2, were characterized by higher level of mean HbA1c and fasting plasma glucose (FPG) (p =0.017), proportion of patients taking insulin with or without oral hypoglycemic agent(s) (p =0.033). The results of factor analysis based on painDETECT questionnaire items determined three factors of sensory symptoms in patients with DPN. However, new three clusters according to results of factor analysis were not revealed significant differences with pain severity, sleep disturbance and quality of life.

CONCLUSIONS:

The cluster analysis indicated that poorly controlled glycemia was associated with subjective symptoms and clinical assessment of DPN. Further studies are needed to cluster subgroups of DPN symptoms in large papulation and take into account for a more stratified and personalized approaches according to subgroup analysis of DPN.

P59 ILLUSTRATING PROBLEMS ASSOCIATED WITH DIABETIC FOOT IN GEORGIA –CLINICAL CASE STUDY

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OBJECTIVES:

Uncontrolled diabetes (T2DM) increases risk of peripheral arterial disease and neuropathy, that lead to infection, gangrene and amputation. Recent statistics show that up to 1/4 ofpeople with DM will develop foot ulcers. Still most foot lesions are preventable. Annually1500 amputations are performed in Georgia, more than half of them are due to DM. Fragmental approach is used to DFS diagnoses, treated and managed, that result in time and patient loss and avoidable amputations. There is no podiatric service or nurse-podiatrists,no regular foot checks, foot screening or educate are carried out. Target populations have limited access to specialized care.

METHODS:

Ouraim is toillustrate theeffect of proper management and education in typical clinical situation. Methods: Patient male, age64yrs, T2DM,diabetes duration 12 yrs. At entry: weight 105kg, BMI-33.7kg/m², HbA1c-10.2%, T/A - 150/90mmHg. Previous treatment- Metformin (1000 mg/aday). Nodiabetes education in the past.Neuropathy tests/neurological examination were positive. Diagnosis: uncontrolledT2DM; neuroischemiculcer on the pad of theleft foot(size -7X4cm, not healed for past 6 mnths). Treatment: Thiocticacid (ThA) (50 ml IV/a day/20 infusions; p/o 600 mg/a day/3 months); long acting insulin analog (15IUat bedtime) was added.Education on foot care/diabetes management was initiated. Patient was motivated to adhere to recommendations and treatment selected.

RESULTS:

Ulcer size was progressively diminishing (month 1 -4cm; month 2 - 2.2 cm). At month 3: HbA1c-6.7%, BMI-28.7kg/m²,T/A - 130/80 mmHg. Ulcer had healed.Treatment: insulin - 12UI, Metformin (1000 mg/twice daily). ThAp/o 600 mg/a day/3 months.Regular visits, supervision, foot care and education continued. At month 6: HbA1c-6.4%, BMI-27.5kg/m², T/A - 130/80 mmHg, no ulcer recurrenceTreatment: insulin -10UI, Metformin (1000 mg/twice daily), ThAp/o 600 mg/a day/3 months. At month 9: no ulcer recurrence, HbA1c-6.1%, BMI-26.5kg/m², T/A - 130/80 mmHg. Regular visits to podiatrist/endocrinologist and adherence to treatment regimen continues.

CONCLUSIONS:

DM prevalence for Georgia is 7.5% no doubt that burden of diabetes-related foot problems is very high. Timely and proper diagnosis, management, education and adequate treatment will reduce ulceration/ amputations rate and treatment costs. Clinical case clearly indicates that qualified podiatric service can improveDFS management in Georgia

P60 RECURRENT HYPOGLYCEMIA AND GLUCOSE FLUCTUATION INDECE APOPTOSIS AND ENHANCE OXIDATIVE STRESS THROUGH ENDOPLASMIC RETICULUM STRESS IN SCHWANN CELLS.

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OBJECTIVES:

It is suggested that 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. In this study, we investigated the effects of recurrent short-term hypoglycemia and glucose fluctuation on apoptosis and oxidative stress in Schwann cells, and the involvement of endoplasmic reticulum (ER) stress under various glucose conditions were 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 CHOP were evaluated by Western blotting. 4) Cells were treated with 4-phenyl butyric acid (4-PBA), an ER stress inhibitor.

RESULTS:

1) Not only HG, but also LG decreased cell viabilities. Furthermore, either ILG or IHG also reduced cell viabilities. 2) TBARS levels were increased by LG, HG, ILG and IHG. 3) 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. CHOP, an ER stress marker protein, were increased by high and low glucose. 4) 4-PBA ameliorated cell death and oxidative stress which were induced by LG, HG, ILG and IHG.

CONCLUSIONS:

These findings indicate that recurrent short-term hypoglycemia and glucose fluctuation induced apoptosis and oxidative stress through ER stress in Schwann cells, and that diabetic neuropathy could be initiated not only by hyperglycemia, but also by recurrent hypoglycemia and postprandial hyperglycemia.

P61 COMPARATIVE EFFECT OF A HIGH FAT WITH OR WITHOUT HIGH SUCROSE DIET ON PERIPHERAL NEUROPATHY IN C57BL/6J MICE

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OBJECTIVES:

Feeding mice a diet containing high fat and high sucrose has been promoted as a good model for type 2 diabetes. This study sought to determine the effect of feeding mice a high fat and high sucrose diet on neuropathy compared to mice fed only a high fat diet and mice fed a high diet and treated with streptozotocin.

METHODS:

C57Bl/6J mice were divided into five groups and fed the following diets for 20 weeks: Normal (Control); Sucrose enriched (Control + Sucrose), High fat (Diet-induced obesity (DIO)), High fat and high sucrose (DIO + sucrose) and high fat diet/streptozotocin treated (Diabetic). The endpoints evaluated included motor and sensory nerve conduction velocity, thermal and mechanical sensitivity and innervation of sensory nerves in the cornea and skin.

RESULTS:

DIO mice with or without sucrose and diabetic mice were hyperglycemic at the end of the study (see table) and had impaired glucose utilization (data not shown). DIO mice had slowed sensory nerve conduction velocity, mechanical allodynia and decreased innervation of the cornea and skin. DIO + sucrose and to a greater extent diabetic mice were thermal hypoalgesic, had mechanical allodynia, reduced motor and sensory nerve conduction velocities and decrease innervation of the cornea and skin.

CONCLUSIONS:

Development of peripheral neuropathy was more severe in high fat and high sucrose fed mice compared to high fat fed mice but fasting hyperglycemia and impaired glucose utilization was similar for these two models. Peripheral neuropathy was most severe in diabetic mice.

Determination	Control (12)	Control + Sucrose (12)	DIO (11)	DIO + Sucrose (10)	Diabetic (12)
Fasting blood glucose (mg/dl)	103 ± 8	94 ± 6^{b}	185 ± 12^{a,b}	175 ± 9^{a,b}	301 ± 24^{a}
MNCV (m/sec)	37.5 ± 1.6	34.5 ± 1.5^{b}	32.0 ± 1.2^{b}	31.4 ± 1.9^{a,b}	24.8 ± 0.5^{a}
SNCV (m/sec)	23.0 ± 0.6	21.6 ± 0.4^{b}	18.1 ± 0.5^{a}	18.4 ± 0.3^{a}	17.7 ± 0.5^{a}
IENF (profiles/mm)	25.5 ± 0.6	25.2 ± 0.7^{b}	19.8 ± 0.5^{a,b}	20.8 ± 0.6^{a,b}	16.1 ± 0.4^{a}
Corneal nerve fiber length (mm/mm^{2})	1.78 ± 0.05	1.64 ± 0.11^{b}	0.87 ± 0.07^{a}	0.93 ± 0.05^{a}	0.82 ± 0.05^{a}
Thermal nociception (sec)	5.1 ± 0.2	5.1 ± 0.2^{b}	6.1 ± 0.2^{b}	6.6 ± 0.3^{a,b}	8.7 ± 0.5^{a}
Mechanical allodynia (g)	2.92 ± 0.14	2.95 ± 0.09^{b}	1.71 ± 0.11^{a,b}	1.68 ± 0.11^{a,b}	1.18 ± 0.06^{a}

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

P62 MALE DIABETIC MICE DEVELOP MORE SEVERE PERIPHERAL NEUROPATHY AND COGNITION DEFICIT THAN FEMALE MICE

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OBJECTIVES:

Peripheral neuropathy and cognitive impairment are the common and disabling complications of diabetes mellitus. The present study tested the hypothesis that sex as the biological variableex, affects development of diabetic peripheral neuropathy (DPN) and cognition deficit.

METHODS:

Male and female db/db and control db/m mice aged 20 and 30 weeks (n=10/group/age) were used. Neurological functions including sciatic nerve conduction velocity, mechanical and thermal thresholds were measured. Morris water maze, social and odor-based novelty recognition tests were performed to evaluate spatial and non-spatial learning memory. Regional blood flow was measured using laser Doppler flowmetry.

RESULTS:

At age 20 and 30 weeks, both male and female db/db mice exhibited significant DPN and cognition impairment compared to age matched male and female db/m mice. Although at age of 20 weeks, there was no a significant sex difference of DPN and cognitive deficits, at age of 30 weeks male diabetic mice displayed a significantly lower blood perfusion in sciatic nerve (28±4 vs 34±6, $p<0.05$) and footpad tissues (male vs female, 12.3±3.2 vs 17.8±1.2, $p<0.05$) than those in females. Male diabetic mice also had a significant lower of motor (26.0±4.4 vs 34.0±4.3 mm/s, $p<0.05$) and sensory (25.0±5.8 vs 33.3±4.9 mm/s, $p<0.05$) nerve conduction velocity than females. Hot plate and tactile allodynia tests revealed that males exhibited a significantly higher thermal (21.5±1.2 sec vs 17.9 ±1.1 sec, $p<0.05$) and mechanical (7.4±0.8 vs 6.3±0.7, $p<0.05$) latency than females. Immunohistochemistry analysis showed significant reductions of myelin thickness (1.6±0.1 vs 1.3±0.1, $p<0.01$), axon (4.9±0.2 vs 4.5±0.2, $p<0.05$) and fiber diameters (8.1±0.4 vs 7.2±0.3, $p<0.01$), and induction of g ratio (0.60 vs 0.63) in male sciatic nerves compared with female db/db mice. Also, compared to female diabetic mice, male mice spent significant more time to locate the hidden platform in the correct quadrant assayed by water maze and less time to explore a stranger mouse assayed by social test,. We did not observe the significant differences in blood glucose levels and body weight between male and female diabetic animals (age 30 weeks), but male diabetic mice showed a higher serum total cholesterol content (148.5±12.8 mg/dl vs 160.1±11.5 mg/dl, $p<0.05$).

CONCLUSIONS:

Our data indicate that the sex affects development of neuropathy in the central and peripheral nerves with male diabetic mice having a greater extent of DPN and cognition impairment.

P63 REGIONAL BRAIN VOLUMES AND COGNITION IN TYPE-2 DIABETES

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OBJECTIVES:

Mild Cognitive Impairment (MCI) is thought to be a chronic sequelae of Type-2 Diabetes Mellitus (T2DM). Cerebral atrophy is known to be associated with cognitive decline in the context of the various types of dementia. Prodronal dementia has also been associated with changes in brain parenchymal structure. The aim of this study was to identify and compare regional brain volumes in T2DM patients with and without MCI.

METHODS:

Seventy-six age and gender matched subjects [30, T2DM+normal cognition (T2DM); 17, T2DM+MCI (T2DM/MCI) and 29 non-diabetic healthy volunteers (HV)] were recruited. All subjects underwent clinical and questionnaire (Addenbrooke's Cognitive Assessment [ACE-R]) assessments plus the acquisition of a high-resolution, 3D T1-weighted Magnetic Resonance Imaging volume of the whole brain at 3T (Ingenia, Philips Healthcare, Best, NL). Cerebral volumes were analysed using voxel based morphometry (VBM, FSL, Oxford).

RESULTS:

Demographic data indicated that all three groups were age-matched (mean age 69.3-71.5 years, ANOVA, $p = 0.164$). Group mean T2DM/MCI ACE-R score (mean+/-SD; 83+/-4) was significantly lower than those of other two groups (HV=96+/-2, T2DM=94+/-3; ANOVA, $p<0.001$). The T2DM/MCI group had significantly lower regional grey matter volumes compared to HV in the left ($p<0.0005$) and right hippocampi ($p<0.05$), left putamen ($p<0.05$), caudate ($p<0.05$) and amygdala ($p<0.05$).

CONCLUSIONS:

The current study demonstrates significantly lower cortical brain volumes in areas associated with cognition (including short-term memory-retrieval) in patients who have T2DM and mild cognitive impairment. Detailed changes in neuroanatomical make-up may help elucidate diabetes-related pathological mechanisms that lead to a change in cognition associated with T2DM.

P64 CEREBRAL PERFUSION IN PATIENTS WITH TYPE 2 DIABETES MELLITUS

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OBJECTIVES:

Patients with type 2 diabetes mellitus (T2DM) have an increased risk of cerebral small vessel disease and large vessel disease. However, only few studies have examined cerebral perfusion changes in patients with T2DM. We compared regional cerebral perfusion between patients with T2DM and control subjects.

METHODS:

Ninety-five patients with T2DM (32 males, mean age 62.2±5.5 years, diabetes duration 9.7±6.6 years) who had representative structural brain changes and 18 healthy control subjects (mean age 59.4±5.7 years) were enrolled in our study. Cerebral perfusion was assessed using SPECT scans and quantified by comparison to a database of healthy individuals (expressed as a standard deviation). Linear regression analyses adjusted for age and gender were performed to assess differences in global and regional (16 regions) cerebral perfusion between patients and control subjects.

RESULTS:

There were no statistically significant differences in either global cerebral perfusion or in most regions of cerebral perfusion (frontal, parietal, temporal, cerebellum, caudate nucleus, putamen, and thalamus; both left and right) between patients with T2DM and control subjects ($p>0.05$). However, control subjects showed a decrease in left occipital lobe perfusion compared to patients (regression B coefficient (95% CI): 0.54 (0.00 to 1.08), $p = 0.049$).

CONCLUSIONS:

Our study consisted of patients with T2DM who have representative structural brain changes. These patients did not show a lower cerebral perfusion compared to control subjects. Therefore, cerebral perfusion may not have a similarly strong relation with T2DM as other, more established markers.

P65 ROLE OF ANTI-INFLAMMATION BY DENTAL PULP STEM CELL TRANSPLANTATION ON DIABETIC POLYNEUROPATHY - PROMOTING MACROPHAGE POLARIZATION INTO M2 PHENOTYPE

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OBJECTIVES:

Stem cell transplantation is expected to be a curative therapy for diabetic polyneuropathy. However, the mechanisms of stem cell therapy are still unclear. Here, we demonstrate the immunomodulatory effects of dental pulp stem cell (DPSC) transplantation on diabetic peripheral nerves and evaluate the relationship between inflammation and diabetic polyneuropathy.

METHODS:

DPSCs were isolated and expanded from dental pulp of 6-wk old Sprague-Dawley rats. DPSCs were transplanted into the unilateral hindlimb skeletal muscles of normal and streptozotocine-induced diabetic rats. Four weeks after DPSC transplantation, neurophysiological measurements, inflammatory gene expressions and the number of macrophages in the sciatic nerves were assessed. To confirm the immunomodulatory effects of DPSCs-secreted factors, we investigated whether the injection of DPSC-conditioned media suppressed the inflammation of the sciatic nerve in the diabetic rats. Furthermore, the effects of DPSC-conditioned media on Lipopolysaccharide (LPS)-stimulated murine macrophage RAW264.7 cells were investigated.

RESULTS:

The number of macrophages and the inflammatory genes, CD68 and TNF-α, expressions were increased in the sciatic nerves of the diabetic rats. DPSC transplantation significantly decreased the number of macrophages and mRNA expressions of CD68 and TNF-α. The number of macrophages was negatively correlated with nerve conduction velocity in sciatic nerves. The injection of DPSC-conditioned media also decreased the number of macrophages and inflammatory gene expressions in the diabetic rats. The in vitro study revealed that DPSC-conditioned media significantly increased the gene expressions of IL-10 and CD206 in LPS-stimulated RAW264.7 cells.

CONCLUSIONS:

These results suggest that DPSC transplantation improved diabetic polyneuropathy at least in part by anti-inflammatory effects of DPSC-secreted factors which promoted macrophages polarization towards M2 phenotype.

P66 GLUCOSAMINE-INDUCED NEUROPATHY IN MICE; A NEW MODEL FOR EXPERIMENTAL DIABETIC NEUROPATHY

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OBJECTIVES:

Hexosamine (glucosamine; GlcN) pathway has long been considered to attribute to the development of DPN, but the mechanism of how GlcN induces peripheral nerve injury is yet to be clear. In this study, we explored the molecular mechanisms of how exogenous GlcN impairs peripheral nerve tissues and the effective means to prevent GlcN-induced peripheral nerve injury.

METHODS:

First we examined whether cultured mouse Schwann cells exposed to 10mM GlcN for 24 hours will undergo cell death. We then detected the molecular changes related to apoptosis, ER stress, and ATP synthesis. We also examined whether GlcN injection elicits neuropathic changes in healthy mice and whether the changes can be suppressed by treatment with apoptosis inhibitor (Z-VAD-FMK), ER stress inhibitor (4phenylbutyrate; 4PB), anti-oxidant (N-acetylcysteine; NAC), or ATP donor (inosine).

RESULTS:

GlcN exposure induced marked cell death of Schwann cells in a dose-dependent manner. It was associated with increased expressions of cleaved caspase 3, CHOP, and hexokinase-I with ATP depletion. These changes were suppressed by siRNA of hexokinase-I or ATP donor, inosine, but not by NAC or 4-PB. O-GlcNAcylation enhancer, PUGNAc, did not augment the GlcN neurotoxicity. Mice injected with GlcN developed nerve conduction delay, reduced Na,K-ATPase activity and lowered ATP contents in the sciatic nerve. The neuropathic changes were significantly suppressed by inosine, but not by 4PB.

CONCLUSIONS:

This study pointed to a possibility that excessive GlcN flux contributes to DPN via ATP depletion whicn may explain the salient process of the hyperglcyemia-induced peripheral nerve injury. Our results may provide a potential new target for treatment of DPN.

P67 PAINFUL DIABETIC PERIPHERAL NEUROPATHY IS CHARACTERISED BY ABNORMAL COLD DETECTION THRESHOLD AND DERMAL VASCULAR PROLIFERATION

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OBJECTIVES:

Painful diabetic peripheral neuropathy (painful-DPN) is devastating in its impact and yet the underlying pain mechanisms remain uncertain. In this study we have looked at the relationship between clinical, QST and a panel of neuronal and vascular markers to differentiate between chronic painful-DPN and painless-DPN in patients with type 2 diabetes (T2DM).

METHODS:

A total of 59 subjects [14 Painful-DPN, 15 Painless-DPN, 15 No-DPN and 15 healthy volunteers (HV)] underwent detailed clinical (DN4 and several QST parameters according to the German DFNS protocol) and neurophysiological assessments [NIS(LL)+7 tests]. All subjects underwent punch skin biopsy 10 cm above the ankle and immunohistochemistry used to quantify total Intra Epidermal Nerve Fibre (IENF) with protein gene product 9.5 (PGP9.5), growth-associated protein 43 (GAP43) for regenerating IENF, and calcitonin gene related peptide (CGRP) for peptidergic nerve fibres. In addition, sub-epithelial endothelial vascular staining was assessed using an antibody to Von Willebrand Factor (vWF).

RESULTS:

IENF density was severely decreased ($p<0.001$) in both DPN groups, with no differences for PGP9.5, GAP43, CGRP, or GAP43/PGP9.5 ratios. However, sub epithelial vascular/ endothelial staining with VWF was markedly greater for painful-DPN, and significantly higher than painless-DPN ($p<0.0001$). Cold detection threshold (CDT) was significantly lower in the painful-DPN group compared to all the others and this was related to vWF-stained dermal capillary density ($P=0.002$) and DN4 score in those with painful-DPN ($p=0.018$). Significant negative co-relations were also found between all QST parameters (except Pressure Pain Threshold) and peripheral skin biomarkers of DPN ($p<0.05$).

CONCLUSIONS:

Painful-DPN is characterised by abnormal CDT and dermal microvascular proliferation. Haemodynamic factors and hypoxia may have a role in the pathogenesis of pain in diabetic neuropathy.

P68 INVOLVEMENT OF ENDOPLASMIC RETICULUM STRESS IN GLYCOLALDEHYDE NEUROTOXICITY: A NOVEL PATHOGENETIC MECHANISM OF DIABETIC NEUROPATHY

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OBJECTIVES:

Glycolaldehyde (GA), a precursor of advanced glycation end products, has been shown to induce endoplasmic reticulum (ER) stress in cultured Schwann cells, thereby resulting in Schwann cell injury and death. This study investigated the effect of GA neurotoxicity in dorsal root ganglion (DRG) neurons and its underlying association with the pathogenesis of diabetic neuropathy.

METHODS:

DRG neurons from 8-week-old female Wistar rats were treated with different concentrations of GA (0, 10, 100, or 500 μM) in a serum-free culture medium for 48 h. The viability of neurons and expression of active caspase-3, a marker of apoptotic cell death, were determined by the trypan blue exclusion test and immunofluorescence analysis, respectively. The involvement of ER stress-related signaling pathways, including the c-Jun N-terminal kinase (JNK) and PKR-like ER kinase (PERK) pathways, in GA neurotoxicity was investigated using Western blot analysis with ND7/23, a DRG neuronal cell line.

RESULTS:

GA dose-dependently reduced the survival of DRG neurons and enhanced immunoreactivity to active caspase-3. Western blot analysis revealed that GA treatment at 500 μM for 8 h upregulates the phosphorylation of JNK and the expression of activating transcription factor 4 (ATF4), a downstream regulator of the PERK pathway, in ND7/23 cells. Moreover, GA consistently enhanced the nuclear expression of ATF4 in DRG neurons.

CONCLUSIONS:

The GA-induced apoptotic cell death of DRG neurons may be partly attributed to the activation of ER stress-related pathways. The findings of the present study in line with previously reported studies imply that the excess formation of GA under diabetic conditions induces ER stress, affecting the survival of neurons and Schwann cells and thus contributing to the development of diabetic neuropathy.

P69 PAEONIA EMODI IMPROVES THE IMPAIRED NERVE FUNCTIONS IN STZ- INDUCED DIABETIC NEUROPATHY VIA INHIBITION OF ADVANCED GLYCATION END PRODUCTS

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OBJECTIVES:

Reactive oxygen species, formation of advanced glycation end products (AGEs) and apoptosis are implicated in the pathogenesis of diabetic neuropathy. The aim of the present study was to explore the effect of Paeonia emodi L. (Family: Paeoniaceae) on thermal and mechanical hyperalgesia, allodynia, motor nerve conduction velocity (MNCV) and oxidative-nitrosative stress in streptozotocin (STZ) induced experimental diabetes.

METHODS:

Diabetes neuropathy was induced in Wistar rats by injection of STZ (65 mg/kg, i.p.) 15 min after Nicotinamide (230 mg/kg, i.p.) administration. Alcohol extract of P. emodi roots was assessed by oral administration at 100, 200 and 400 mg/kg in STZ-induced diabetic rats. Thermal hyperalgesia (Eddy's hot plate and tail immersion), mechanical hyperalgesia (Randall-Selitto) and tactile allodynia (Von Frey hair tests) were evaluated in all groups of streptozotocin diabetic rats to assess the extent of neuropathy. Diabetic rats developed neuropathy which was evident from a marked hyperalgesia and allodynia; reduced MNCV associated with increased formation of AGEs and reactive oxygen/nitrogen species.

RESULTS:

Chronic treatment with P. emodi alcohol extract (100, 200 and 400 mg/kg) for 30 days starting from the 60th day of STZ-induction significantly attenuated behavioral and biochemical changes associated with diabetic neuropathy.

CONCLUSIONS:

Present study suggested that P. emodi alcohol extract corrected the hyperglycemia and partially reversed the pain response in diabetic rats through modulation of oxidative-nitrosative stress and reduction in AGEs formation in the diabetic rats and thus it may find clinical application to treat neuropathic pain in diabetic patients.

P70 THE ASSOCIATION BETWEEN SERUM HOMOCYSTEINE CONCENTRATION AND DIABETIC PERIPHERAL POLYNEUROPATHY IN TYPE 2 DIABETIC PATIENTS

Cho H.*, Cho N., Han E., Kim H., Park C.

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OBJECTIVES:

Diabetic peripheral polyneuropathy (DPP) is one of the common complications of type 2 diabetes and can lead to foot ulcers or amputation. The pathophysiology of DPP includes several factors such as metabolic, vascular, autoimmune, oxidative stress and neurohormonal growth-factor deficiency and recent studies have suggested the use of serum homocysteine as an early marker of oxidative stress. Therefore, we investigated whether serum homocysteine concentration may be useful in predicting DPP.

METHODS:

We assessed 62 patients with type 2 diabetes who were evaluated for the presence of DPP using clinical neurologic examinations including nerve conduction velocity studies. We evaluated the association between serum homocysteine and the presence of DPP.

RESULTS:

The prevalence of DPP was 64.5% (40 cases) according to clinical neurological examinations. The serum homocysteine concentration was significantly elevated in type 2 diabetic patients with DPP compared to patients without DPP ($P = 0.005$). There were other factors significantly associated retinopathy ($P = 0.002$), diabetes duration ($P < 0.001$), MNSI ($P < 0.001$), HbA1c ($P = 0.011$), fasting glucose ($P = 0.004$), urine microalbumin/creatinine ratio ($P = 0.005$) and CRP ($P = 0.012$). Serum homocysteine was independently related with DPP according to multiple logistic analysis ($P < 0.044$).

CONCLUSIONS:

This study shows that increased levels of serum homocysteine may have important clinical implications in the presence of DPP in patients with type 2 diabetes.

P71 DIABETES, DEPRESSION AND OXIDATIVE STRESS: THE DETRIMENTAL TRIANGLE

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OBJECTIVES:

Diabetes Mellitus is a common metabolic disease. Diabetic peripheral neuropathy (DPN), a complication of the disease, has been shown to affect 50% of the patients. Depression is another complication of diabetes that occurs in some of the patients. The incidence of depression in the diabetic population is higher than that of the non-diabetic. The mechanisms underlying these two complications remain incompletely characterized. Reactive oxygen species (ROS) have been shown to cause myelin damage in the central and peripheral nervous systems in depression and DPN respectively.

METHODS:

We investigated the role of ROS generated by nicotinamide adenine dinucleotide (NADPH) oxidase enzymes (Nox) in mediating biological responses in both the brains (prefrontal cortices and hippocampi) and sciatic nerves of mice.

RESULTS:

Our results show that diabetes, depression or diabetes-associated depression cause sensory and motor defects at the level of the peripheral nerves and were associated with altered central and peripheral myelin expression. Increase in Nox1and Nox4 levels and activity were recorded resulting in elevated ROS levels. Inhibiting Nox1/Nox4, managed to downregulate ROS production, reversal in myelin injury in the brain and sciatic nerves and more importantly restored the normal sensory-motor phenotype.

CONCLUSIONS:

To our knowledge, these are the first results to indicate that diabetes associated depression cause myelin injury and sensory motor dysfunction through an NADPH-induced ROS mechanism. Our observations suggest a potential therapeutic role of the blockade of the NADPH oxidases system in diabetes and depression.

P72 REDUCED THALAMIC GABA IN PATIENTS WITH PAINLESS DIABETIC PERIPHERAL NEUROPATHY: RELATIONSHIP TO CLINICAL, NEUROPHYSIOLOGICAL AND SKIN BIOPSY MEASURES

Shillo P.*[1], Wilkinson I.[2], Greig M.[1], Gandhi R.[1], Selvarajah D.[2], Anand P.[3], Tesfaye S.[1]

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[2]*University of Sheffield ~ Sheffield ~ United Kingdom,* [3]*Imperial College ~ London ~ United Kingdom*

OBJECTIVES:

The thalamus is an important gateway for sensory information, acting as a relay to several cortical areas. Nociceptive input is modulated in the thalamus by intrinsic inhibitory mechanisms and because γ-aminobutyric acid (GABA) mediates most inhibitory actions we measured thalamic GABA, in carefully phenotyped patients with and without diabetic peripheral neuropathy (DPN) using novel H-MRS editing techniques.

METHODS:

A total of 59 subjects [14 Painful-DPN, 15 Painless-DPN, 15 No-DPN and 15 healthy volunteers (HV)] were assessed with detailed clinical (DN4 and several QST parameters according to the DFNS protocol) and neurophysiological assessments [NIS(LL)+7 tests]. All subjects underwent punch skin biopsy 10 cm above the ankle and immunohistochemistry used to quantify total Intra Epidermal Nerve Fibre (IENF) with protein gene product 9.5 (PGP9.5), growth-associated protein 43 (GAP43) for regenerating IENF, and calcitonin gene related peptide (CGRP) for peptidergic nerve fibres. Finally subjects underwent H-MRS at 3 Tesla to assess GABA relative to unsuppressed water (H20) using a single-voxel, spin-echo, spectral editing technique (MEGA-PRESS; echo time=68ms) centred over the thalami. GABA resonance signal was obtained relative to that of parenchymal water.

RESULTS:

Subjects with painless-DPN had significantly lower GABA:H20 compared to the other groups [Painless-DPN 1.47(0.23), Painful-DPN 1.61(0.33), HV 1.75(0.25) and T2DM with No-DPN 1.84(0.38); ANOVA $p<0.01$]. Post-hoc comparisons indicated significantly lower mean GABA/H20 in Painless-DPN compared to No-DPN ($p< 0.005$) and significantly lower mean GABA/H20 in Painless-DPN compared with HV ($p<0.05$). Significant co-relations were found between thalamic GABA:H20 level and the NISLL +7 score ($p=0.006$), IENFD (0.012), DN4 score ($p=0.009$), Vibration Detection Threshold ($p=0.017$), Warm Detection Threshold($p=0.016$) but not with Cold Detection Threshold and the other peripheral neuronal markers (GAP43, CGRP).

CONCLUSIONS:

The thalamus is the sensory gateway to the cerebral cortex. The lower levels of GABA:H20 in this carefully characterised cohort and the clear relationship to clinical (NISLL+7, DN4), QST parameters and skin IENFD is in keeping with our previous finding of thalamic neuronal dysfunction in painless-DPN, and may reflect reduced number of afferent impulses and central sensitisation.

P73 ROLE OF FREE FATTY ACIDS IN THE ALTERATION OF CARDIAC AUTONOMIC ACTIVITY AND ITS POSTPRANDIAL CHANGES IN OBESE PATIENTS WITH GLUCOSE INTOLERANCE

Rezki A.*, Fysekidis M., Chiheb S., Banu I., Bianchi L., Cosson E., Valensi P.

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OBJECTIVES:

Depressed cardiac vagal activity and elevated sympathetic activity have been reported in prediabetic obese patients. In healthy individuals, insulin was shown to acutely induce such changes, and free fatty acids (FFA) to enhance sympathetic activity. This study aimed to examine the relations between glycemia, insulinemia and plasma FFA with cardiac autonomic activity in obese patients with glucose intolerance.

METHODS:

We included 24 obese patients (BMI 36.6±5.0 kg/m²) with glucose intolerance, normal blood pressure, and no cardio-vascular events. Cardiac vagal (HFnu-HR) and sympathetic (LFnu-HR) activity, and sympatho-vagal balance (LF/HF-HR) were measured by spectral analysis of heart rate variations during 6 minutes of controlled breathing rate (12 cycles/minute) (Task Force Monitor®). These measurements were performed at fasting and after a standardised breakfast including 75g of carbohydrates. The changes (Δ) between fasting and 2 hours after breakfast were calculated.

RESULTS:

At fasting, age correlated positively with LFnu-HR ($p=0.02$) and negatively with HFnu-HR ($p=0.02$). There was no significant correlation between autonomic indexes and glycemia and insulinemia. At fasting, FFA correlated positively with LFnu-HR and LF/HF-HR and negatively with HFnu-HR ($p<0.04$ and <0.02, respectively); and positively with nitrotyrosine ($p=0.02$). The correlations of FFA with spectral indexes were not altered after age adjustment, but were no more significant after adjustment for nitrotyrosine. Post-prandially, ΔFFA correlated positively with ΔLFnu-HR and ΔLF/HFnu-HR and negatively with ΔHFnu-HR ($p<0.04$ to <0.02).

CONCLUSIONS:

In prediabetic obese patients, FFA (lipotoxicity) play an important role both at fasting and post-prandially in sympathetic activation and vagal depression, probably by increasing oxidative stress. These effects could increase the arrhythmogenic risk.

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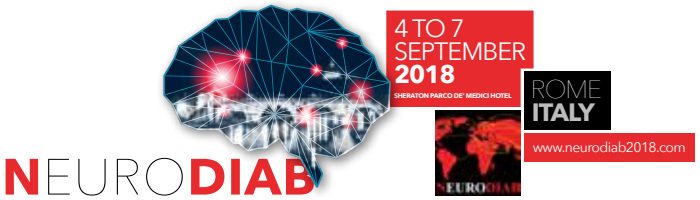
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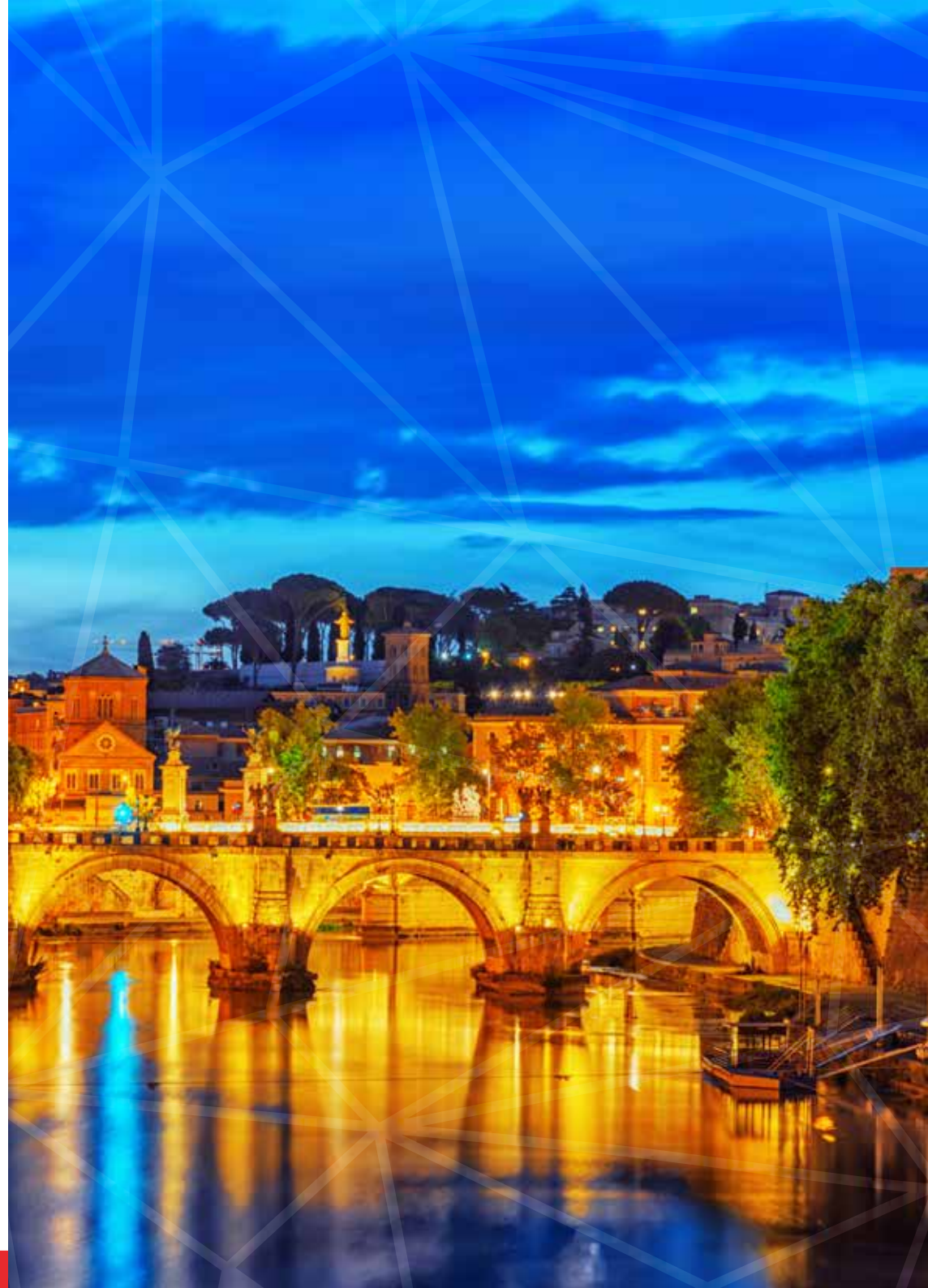

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