WELCOME

Dear Colleagues,

It is my great pleasure to welcome you to the **6th Annual Meeting of the Diabetes & Cardiovascular Disease EASD Study Group**. This year we meet in Prague at this unique event overarching diabetes and vascular disease. Despite the increasing number of experimental and clinical studies showing a narrow link between metabolic disturbancies and vascular wall pathology, we need to understand new discoveries. Such a meeting offers new insights and opens the doors to future research. The creation of new possibilities for collaboration is also one of its goals.

I wish you a nice time at the conference as well as a pleasant stay in Prague.

Jan Škrha
President of the Meeting

GENERAL INFORMATION

DATE / MEETING VENUE

October 31 – November 2, 2013

Hotel DAP
Vítězné nám. 684/4
160 00 Prague 6 | Czech Republic

ORGANIZER

Diabetes & Cardiovascular Disease EASD Study Group

LOCAL ORGANIZER

Czech Diabetes Society

PROGRAMME COMMITEE

Prof. Antonio Ceriello
Prof. Oliver Schnell
Prof. Jan Škrha

PRESIDENT OF THE LOCAL ORGANIZING COMMITTEE

Prof. Jan Škrha

LOCAL ORGANIZING COMMITTEE

Prof. Terezie Pelikánová
Prof. Zdeněk Rušavý
Prof. Jan Škrha

SECRETARIAT OF THE MEETING

AMCA, spol. s r.o.
Academic and Medical Conference Agency
Vyšehradská 320/49 | 128 00 Prague 2 | Czech Republic
Phone: 00420 221 979 351, 00420 731 496 062
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REGISTRATION HOURS

Thursday, October 31	17:00 – 20:00
Friday, November 1	7:30 – 18:20
Saturday, November 2	8:00 – 17:00

BOARD

Coffee breaks are served in hotel restaurant „Europe“ adjacent to the poster session. Buffet lunches are served in the restaurant on the second floor.

CME ACCREDITATION

The D&CVD EASD Study Group is accredited by the European Accreditation Council for Continuing Medical Education (EACCME) to provide CME activity for medical specialists. The EACCME is an institution of the European Union of Medical Specialists (UEMS), www.uems.net.

The ‚6th Annual Meeting of the D&CVD EASD Study Group' is designated for a maximum of 14 hours of European external CME credits. Each medical specialist should claim only those hours of credit that he/she actually spent in the educational activity.

Through an agreement between the European Union of Medical Specialists and the American Medical Association, physicians may convert EACCME credits to an equivalent number of AMA PRA Category 1 Credits™. Information on the process to convert EACCME credit to AMA credit can be found at www.ama-assn.org/go/internationalcme.

Live educational activities, occurring outside of Canada, recognized by the UEMS-EACCME for ECMEC credits are deemed to be Accredited Group Learning Activities (Section 1) as defined by the Maintenance of Certification Program of The Royal College of Physicians and Surgeons of Canada.

PROGRAMME AT A GLANCE

Thursday, October 31, 2013

18:00	CVD in Diabetes and Prediabetes
20:00	Welcome drink

Friday, November 1, 2013

8:30	Risk Factors of CVD in Diabetes
11:00	Diabetes Treatment and CVD
13:30	Glycemia and CVD
16:00	Endothelial Dysfunction
17:50	General assembly
20:00	Meeting dinner

Saturday, November 2, 2013

8:30	Prevention and Treatment of Other Risk Factors
11:00	State of the Art Lectures
12:00	Intervention Strategy
13:00	Posters – Discussion
15:00	Oral Presentations – Miscellaneous
17:00	Closing of the meeting

SCIENTIFIC PROGRAMME

Thursday, October 31, 2013

18:00 – 20:00 ***CVD in Diabetes and Prediabetes***
Chairmen: J. Tuomilehto, J. Škrha

18:00 – 18:30 Epidemiology of Cardiovascular Disease in Diabetes
J. Tuomilehto (FIN)

18:30 – 19:00 Cardiovascular Disease in Prediabetes
N. M. Lalic (SRB)

19:00 – 19:30 Vascular Complications in Diabetes in the Czech Republic
J. Škrha (CZE)

19:30 – 20:00 Subclinical Atherosclerosis/High CV Risk Management: What, Who, and Why? The Efficacy of Population-Based Preventive Measures
Z. Fras (SLO)

20:00 ***Welcome drink***

Friday, November 1, 2013

8:30 – 10:30 ***Risk Factors of CVD in Diabetes***
Chairmen: I. Tkáč, M. Haluzík

8:30 – 9:00 The Role of Diabetic Environment and Genetic Background in the Development of Cardiovascular Disease in Diabetes
I. Tkáč (SVK)

9:00 – 9:30 Adipose Tissue as a Source of Factors Influencing Vascular Wall
M. Haluzík (CZE)

9:30 – 9:45 Some Hemodynamic and Genetic Features of Experimental Diabetic Cardiomyopathy
A. Zhukovska (UKR)

9:45 – 10:00 Cardiac Autonomic Dysfunction and Obstructive Sleep Apnea Syndrome Are Involved in Left Ventricular Hypertrophy in Obese Patients without Known Diabetes
S. Chiheb, C. Cussac-Pillegand, I. Pham, P. Poignard, C. Barrat, M. Fysekidis, E. Cosson, P. Valensi (FRA)

10:00 – 10:15 Lipoprotein (a) in Patients with Diabetes and Peripheral Arterial Disease
L. Popovic, K. Lalic, D. Draskovic-Radojkovic, N. Rajkovic, S. Singh, L. Stosic (SRB)

10:15 – 10:30 Predicting Severe Complications in Type 1 Diabetes Patients: Development and Validation of a Prediction Rule in Large Cohort Studies from Europe and the United States
S. Soedamah-Muthu (NED)

10:30 – 11:00 Break

11:00 – 12:30 Diabetes Treatment and CVD
Chairmen: G. Schernthaner, M. Diamant

11:00 – 11:30 Classic Hypoglycaemic Drugs and CV Risk: Are Non-Insulinotropic Agents to Be Preferred?
E. Standl (GER)

11:30 – 12:00 Incretin Therapy Related to CVD in Diabetes
G. Schernthaner (AUT)

12:00 – 12:30 What Are the New Studies to Support the EASD/ADA 2012 T2DM Position Statement?
M. Diamant (NED)

12:30 – 13:30 Lunch

13:30 – 15:30 Glycemia and CVD
Chairmen: M. Hanefeld, M. Prázný

13:30 – 14:00 Hypoglycemia and Cardiovascular Disease
A. Gitt (GER)

14:00 – 14:30 Glycemic Variability, Hypoglycaemia and Cardiovascular Risk in Elderly Patients with Type 2 Diabetes
M. Hanefeld (GER)

14:30 – 15:00 Relationship of Glycemic Variability to Vascular Changes in Type 1 Diabetes

M. Prázný (CZE)

15:00 – 15:15 Prognostic Indicators of Ten-Year and Twenty-Year Mortality Following Acute Coronary Syndrome

C.J. Magri, R. Debono, N. Calleja, S. Fava (MLT)

15:15 – 15:30 Treatment of Prediabetes for the Early Prevention of Microvascular and Macrovascular Complications: The European ePREDICE Multicentric Trial

R. Gabriel (SPA), J. Tuomilehto (FIN), N.M. Lalic (SRB)

15:30 – 16:00 Break

16:00 – 17:45 Endothelial Dysfunction

Chairmen: A. Ceriello, P. Valensi

16:00 – 16:30 Endothelial Resistance to GLP-1 in Diabetes: Relevance to CVD

A. Ceriello (ESP)

16:30 – 17:00 Artery Stiffness in Diabetes

P. Valensi (FRA)

17:00 – 17:15 Acute Hemodynamic Changes after a Cold Pressure Test in Healthy Subjects and in Type 2 Diabetic Patients

M. Fysekidis, Y. Jaber, K. Takbou, M.T. Nguyen, E. Cosson, P. Valensi (FRA)

17:15 – 17:30 Coronary Microvascular Response to a Cold-Pressor Test and Diastole Duration in Asymptomatic Type 2 Diabetic Patients

M.T. Nguyen, I. Pham, E. Cosson, A. Nitenberg, P. Valensi (FRA)

17:30 – 17:45 Endothelial Function Improvement after Insulin Treatment in Poorly Controlled Type 2 Diabetic Patients. The INSUVASC Study

P. Valensi, M. Fysekidis, K. Takbou, Y. Jaber, S. Chiheb, I. Banu, A. Sutton, N. Charnaux, E. Cosson (FRA)

17:50 – 18:20 General assembly

20:00 Meeting dinner

Saturday, November 2, 2013

8:30 – 10:30	***Prevention and Treatment of Other Risk Factors*** *Chairmen: O. Schnell, P. Kempler*
8:30 – 9:00	Prevention of Cardiovascular Disease in Diabetes *O. Schnell (GER)*
9:00 – 9:30	The Role of Autonomic Neuropathy in Cardiovascular Disease in Diabetes *P. Kempler (HUN)*
9:30 – 10:00	Current Trends in the Treatment of Hypertension in Diabetes Mellitus *J. Widimský (CZE)*
10:00 – 10:30	Treatment of Dyslipidemia in Diabetic Patients for Prevention of CVD *R. Češka (CZE)*
10:30 – 11:00	Break
11:00 – 12:00	***State of the Art Lectures*** *Chairmen: A. Ceriello, J. Škrha*
11:00 – 11:30	New Insights in the Pathogenesis of Diabetes Related to CVD *M. Roden (GER)*
11:30 – 12:00	Diabetes and Cardiovascular Disease on the Crossroad – Future Goals *S. Del Prato (ITA)*
12:00 – 13:00	***Intervention Strategy*** *Chairmen: E. Standl, A. Gitt*
12:00 – 12:30	SWEETHEART Study *A. Gitt (GER)*
12:30 – 13:00	Guidelines of the European Society of Cardiology for the Treatment of Acute Coronary Syndromes in Diabetic Patients *P. Widimský (CZE)*
13:00 – 14:00	Lunch
13:00 – 15:00	***Posters – Discussion*** ***List of posters is available at the end of this programme.***

15:00 – 16:30 ***Oral Presentations – Miscellaneous***

Chairmen: N.M. Lalic, Z. Rušavý

15:00 – 15:15 Physical Activity for the Prevention of CVD
Z. Rušavý (CZE)

15:15 – 15:30 Could Health Related Quality of Life Help in Adopting Life Style?
T. Seppälä (FIN)

15:30 – 15:45 A Coronary Heart Disease Model for Type 2 Diabetes: Development and Validation
W. Ye (USA), M. Brandle (SWI), M. Brown, W. Herman (USA)

15:45 – 16:00 In Asymptomatic Type 2 Diabetic Patients, the Prevalence of Silent Myocardial Ischemia and Silent Coronary Stenoses Depends on the Number of Controlled Cardiovascular Risk Factors
E. Cosson, A. Avignon, A. Sultan, M.T. Nguyen, P. Valensi (FRA)

16:00 – 16:15 Peripheral Arterial Disease and Charcot Foot
R. Bem, A. Jirkovska, M. Dubsky, V. Fejfarova, V. Woskova, J. Skibbova (CZE)

16:15 – 16:30 Breakfast and Lunch Are Better than Six Meals a Day for Patients with Type 2 Diabetes
H. Kahleova, L. Belinova, H. Malinska, O. Oliyarnyk, J. Trnovska, V. Skop, L. Kazdova, M. Dezortova, M. Hajek (CZE), A. Tura (ITA), M. Hill, T. Pelikanova (CZE)

16:30 – 16:45 Telmisartan Improves Vascular and Cardiac Function in Particular Postprandially in Patients with Metabolic Syndrome – A Relevant Strategy for Treating a Disease Based on Eating Habits
H. von Bibra, B. Salmen, A. Pfützner, P.-M. Schumm-Draeger (GER)

16:45 – 17:00 The Beneficial Effect of Ranolazine on Cardiac Function after Myocardial Infarction Is Greater in Diabetic than Non-Diabetic Rats
I. Mourouzis, P. Matzouratou, G. Galanopoulos, E. Kostakou, A. Dhalla, L. Belardinelli, C. Pantos (GRE)

17:00 ***Closing of the meeting***

POSTERS

Posters will be displayed for the whole meeting. Discussions concerning the posters will be held on Saturday, November 2, from 13:00 – 15:00.

P1. Dietary Palmitic Interesterified Fat Promotes LDL Particle Cholesterol Enrichment in LDLr Knockout Mice Similarly to Trans Fatty Acids
M. da Silva Afonso, M.S. Ferrari Lavrador, R. de Paula Assis Bombo, V. Sutti Nunes, M. Kiyomi Koike, S. Catanozi, R. Claro da Silva, L.A. Gioielli, I. de Castro, E. Regina Nakandakare, A.M. Pita Lottenberg (BRA)

P2. Increased Beta 3 Adrenoceptor Mediated Negative Inotropic Effect in Diabetic Rat Heart
E. Arioglu-Inan, G. Kayki-Mutlu, I. Karaomerlioglu, V.M. Altan (TUR)

P3. Endothelial and Smooth Muscle Damage and Impaired No Pathway but Normal Energy Metabolism in the Female Type 2 Diabetic Goto-Kakizaki (GK) Rat Heart
M. Desrois, C. Lan, C. Dalmasso, B. Portha, D. Bailbé, P.J. Cozzone, M. Bernard (FRA)

P4. 17β Estradiol Ameliorates Mitochondrial Dysfunction and Oxidative Stress in the Heart of Ovariectomised Rats with Fructose-Induced Insulin Resistance
N. Gorbenko, O. Borikov, O. Ivanova, K. Taran, T. Zvyagina, A. Lavrenovich (UKR)

P5. Melatonin Inhibits Cardiac Apoptosis in Experimentally-Induced Diabetes Mellitus via Amelioration of Oxidative Stress, Inhibition of Caspase-3 Activation and by Regulating Anti-Apoptotic Protein Levels
A. Othman, M.A. El-Missiry, A. Amin (EGY)

P6. NOS3 Polymorphisms Are Associated with Progression of Kidney and Cardiovascular Disease in Type 2 Diabetic Patients
K. Kuricová, V. Tanhäuserová, L. Pácal, V. Bartáková, K. Kaňková (CZE)

P7. Altered Cellularity and Collagen Content in the Adventitial and Medial Layers of the Internal Mammary Artery among Patients with Type 2 Diabetes
S. Roerdam-Preil, P. Switten Nielsen, T. Steiniche, L. Melholt Rasmussen (DEN)

P8. The Level of Advanced Glycation End Products and Fibroblast Growth Factors (TGF-β, β-FGF) in Patients with Coronary Artery Disease and Diabetes Mellitus
E. Ivannikova, I. Kononenko, V. Kalashnikov, O. Smirnova (RUS)

P9. Expression of Periostin Is Reduced in Arterial Tissue from Individuals with Type 2 Diabetes
P. Soendergaard Jensen, M. Bjørling-Poulsen, V. Skov, L.P. Kristensen, L. Melholt Rasmussen (DEN)

P10. Insulin Resistance, Increased Leptin and IL-6 Levels Are Associated with Presence of Hypertension in Overweight Type 2 Diabetic Patients

L. Lukic, N.M. Lalic, A. Jotic, N. Rajkovic, K. Lalic, T. Milicic, J.P. Seferovic Mitrovic, M. Macesic, J. Stanarcic Gajovic (SRB)

P11. Ankle-Brachial Index in Type 2 Diabetes Patients and Cardiovascular Risk

B. Nussbaumerova, H. Rosolova, F. Sefrna (CZE)

P12. »Hypertriglyceridemic Waist« Phenotype in Diabetic Patients: Relationship with Oxidized LDL and Insulin Resistance

N. Rajkovic, K. Lalic, N.M. Lalic, A. Jotic, L. Lukic, T. Milicic, L. Popovic, D. Draskovic-Radojkovic, S. Singh, L. Stosic (SRB)

P13. Apolipoprotein B Is a Better Marker of Cardiovascular Risk than LDL Cholesterol in Patients with Type 2 Diabetes and Acute Myocardial Infarction

S. Singh, K. Lalic, N. Rajkovic, L. Popovic, D. Draskovic-Radojkovic, L. Stosic, M. Dajak, M. Tesic (SRB)

P14. Insulin Resistance and Inflammatory Markers in Type 2 Diabetics and Nondiabetics: Comparison between Patients with Transient Ischemic Attack and Ischemic Stroke

T. Milicic, N.M. Lalic, A. Jotic, V.S. Kostic, N. Covickovic Sternic, K. Lalic, L. Lukic, M. Mijajlovic, N. Rajkovic, M. Macesic, J.P. Seferovic Mitrovic, J. Stanarcic Gajovic (SRB)

P15. Waist Index Is the Best Surrogate Marker for Insulin Resistance in Adults with Type 2 Diabetes Mellitus

C.J. Magri, S. Fava (MLT)

P16. A Cross-Talk between Metabolic Syndrome and Alzheimer's Disease: Possible Underlying Mechanisms

M. Macesic, N.M. Lalic, V.S. Kostic, A. Jotic, E. Stefanova, K. Lalic, T. Milicic, L. Lukic, J.P. Seferovic Mitrovic, J. Stanarcic Gajovic (SRB)

P17. Characteristics of Metabolic Syndrome Existing in Patients with Antiphospholipid Syndrome

S. Jelic, L. Stojanovic, D. Marisavljevic (SRB)

P18. Associated Factors with Cardiac Structure and Function in Type 2 Diabetes

C. Cardoso, G. Salles, N. Leite (BRA)

P19. Lack of Prognostic Value of Resting Heart Rate on Cardiovascular and Renal Outcomes in T2DM Patients

K. Kankova, V. Bartakova (CZE)

P20. Ambulatory Blood Pressure in Women with Type 2: Effects of Personality and Discrimination

J. Wagner, H. Tennen, P. Finian, R. Feinn, W. White (USA)

P21. Prognostic Impact of Hemoglobin A1c in High-Risk Type 2 Diabetic Patients: The Rio De Janeiro Type 2 Diabetes (Rio-T2D) Cohort Study

C. Cardoso, G. Salles, N. Leite (BRA)

P22. Impact of Optimal Glycemic Control on Changes in Heart Rate Variability in Patients with Gestational Diabetes Mellitus

J. Charvát (CZE), E. Žákovičová (SVK)

P23. Impact of Optimal Glycemic Control on Changes in Cardiovascular System in Patients with Gestational Diabetes Mellitus Assessed by 24-Hour BP Monitoring and Echocardiography

E. Žákovičová (SVK), J. Charvát, P. Šváb (CZE)

P24. Effects of Combined Administration of N-3 Polyunsaturated Fatty Acids and Pioglitazone on Cardiovascular and Metabolic Markers in Type 2 Diabetes

J. Veleba, J. Kopecky, P. Janovska, K. Bardova, J. Kopecky (CZE), M. Bryhn (NOR), T. Pelikanova (CZE)

P25. Metformin and Myocardium: Are They Friends?

J.P. Seferović Mitrović*, N.M. Lalić, P.M. Seferović, A. Jotić, M. Tešić, V. Giga, L. Lukić, T. Miličić, M. Maćešić, J. Stanarcic Gajovic (SRB)*

P26. Nicotinamide and 1,5-Isoquinolinediol Treatments in Prevention of Diabetes-Induced Heart Dysfunctions

T. Kuchmerovska, M. Guzyk, L. Yanitska, I. Pentek, K. Diakun (UKR)

P27. Trends in the Incidence Rate and Outcomes of Acute Myocardial Infarction Hospitalization among Patients with and without Diabetes in Spain, 2004-2010

A. Lopez-de-Andres, R. Jimenez-Garcia, V. Hernandez-Barrera, I. Jimenez-Trujillo, P. Carrasco-Garrido (SPA)

P28. Prevalence of Cardiovascular Diseases and Risk Factors among Omani Type 2 Diabetes Patients

S. Al Sinani, A. Al-Mamari, N. Woodhouse, O. Al-Shafie, F. Amar, M. Al-Shafaee, M. Hassan, D. Jaju, R. Bayoumi (OMN)

P29. Association of Cerebrovascular Diseases to Diabetes and Other Risk Factors in WHO Eastern Mediterranean Countries

A. Boutayeb, W. Boutayeb, S. Boutayeb, M.E.N. Lamlili (MOR)

P30. Face Threat Sensitivity Is Associated with Heart Rate Variability and Flow Mediated Dilation among Women with Type 2 Diabetes

J. Wagner, H. Tennen (USA)

ABSTRACTS

Abstracts are listed in alphabetical order by the first author's surname.

PREVALENCE OF CARDIOVASCULAR DISEASES AND RISK FACTORS AMONG OMANI TYPE 2 DIABETES PATIENTS

S. Al Sinani[1], A. Al-Mamari[2], N. Woodhouse[2], O. Al-Shafie[2], F. Amar[2], M. Al-Shafaee[3], M. Hassan[4], D. Jaju[4], R. Bayoumi[1]

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[2]Medicine Department, Sultan Qaboos University, Muscat, Oman
[3]Family Medicine Department, Sultan Qaboos University, Muscat, Oman
[4]Physiology Department, Sultan Qaboos University, Muscat, Oman

This study aimed to estimate the prevalence of cardiovascular diseases (CVD) and risk factors among Omani type 2 diabetes (T2D) patients. A total of 986 T2D Omani patients, visited Sultan Qaboos University Hospital (SQUH), Muscat, Oman, was included in this study. History of CVD and risk factors among patients were extracted from the medical history of patients deposited in the electronic records of the hospital. The definition of CVD included coronary artery disease (CAD), cerebrovascular accident (CVA; stroke) and peripheral vascular disease (PVD). Patients underwent anthropometric and biochemical investigations (Age, sex, BMI, blood pressure, serum fasting glucose, HbA1C and serum lipids). The American Diabetes Association criterion was used to define hyperlipidemia. Twenty five percent (*n*=249) of the Omani patients had CVD, 20% (*n*=197) had CAD (15 patients had myocardial infarction), 2% (*n*=20) had PVD (9 patients had amputation) and 5% (*n*=48) had a stroke. Sixty two percent (*n*=609) of the patients were prescribed Aspirin. Hypertension was reported in 66% of the patients. In addition, 36% were overweight (BMI: 25.0 - 29.9 kg/m2) and 51% were obese (BMI: ≥30 kg/m2). Statins were prescribed to 70% (*n*=686) of the patients, but still 35% had high total cholesterol, 63% had high LDL cholesterol, 38% had high triglycerides, while 50% and 48% of the males and females, respectively, had low HDL cholesterol. A smoking was obtained from 241 randomly selected patients and only 6% (*n*=14) were active smokers. The prevalence of diabetes CVD and risk factors among Omani T2D patients were not different from other populations.

INCREASED BETA 3 ADRENOCEPTOR MEDIATED NEGATIVE INOTROPIC EFFECT IN DIABETIC RAT HEART

E. Arioglu-Inan, G. Kayki-Mutlu, I. Karaomerlioglu, V.M. Altan

Department of Pharmacology, Ankara University, Faculty of Pharmacy, Ankara, Turkey

Aims: Diabetic cardiovascular complications are the most important causes of morbidity and mortality. The change in β1- and β2-adrenoceptor mediated responses in diabetes is well known. However, the role of β3-adrenoceptor in this pathology is unclear. Thus, the aim of this study was to determine the role and signaling pathway of β3-adrenoceptors in chronic diabetic rat heart.

Methods: 8-week-old male Sprague-Dawley rats were used in this study. Diabetes was induced by streptozotocin injection (40mg/kg, sc). At the end of 8th-week,-diabetic rats were treated with insulin (5-20U/kg/day, sc) for 2 weeks. Basal cardiac function and β3-adrenoceptor-mediated cardiac effects were studied in Langendorff-perfused heart preparations. Cardiac β3-AR, eNOS and phosphorylated eNOS protein expressions were determined by western blotting.

Results: Cardiac dysfunction induced by 10-week-STZ-diabetes was verified by the results of *in vitro* basal hemodynamics. Left ventricular developed pressure (LVDP), rate of contraction (+dP/dt) and relaxation (–dP/dt) values were decreased in diabetes. These values, on the other hand, were almost restored to control values with 2 week-insulin treatment. Using Langendorff perfused hearts the effects of β3-AR stimulation on cardiac performance was studied. Selective β3-adrenoceptor agonist, CL 316,243 induced a dose-dependent decrease in LVDP, +dP/dt and –dP/dt in control hearts. On the other hand, the effects of CL 316,243 on LVDP, +dP/dt and –dP/dt were significantly increased in diabetic hearts. Insulin treatment did not change CL 316,243 mediated responses on cardiac contractility. These effects of CL 316,243 were abolished by L-NAME, a NOS inhibitor, in all groups. Protein levels of beta 3 adrenoceptors were found to be increased in diabetic rat heart. After 2-week-insulin treatment, this upregulation was normalized. Total eNOS protein levels were decreased in diabetic group to some extent but it was not statistically significant. On the other hand, phosphorylated (serin 1177) eNOS to total eNOS protein ratio was increased markedly in diabetic group and was still high after insulin treatment.

Conclusion: Our results show that β3-adrenoceptor mediated negative inotropic effect was increased in diabetic state. This data is consistent with the upregulation of β3-adrenoceptors. Since β3-adrenoceptor mediated negative inotropic effect was abolished in all groups in the presence of L-NAME, it is likely that β3-adrenoceptors mediate negative inotropic effect through NOS pathway. Although insulin treatment normalized β3-adrenoceptor protein levels, negative inotropic effect was not totally restored to control values in diabetic rats However, increased serin 1177 phosphorylation of eNOS in both diabetic and insulin treated diabetic rats could explain the increased beta 3 adrenoceptor mediated responses in these groups.

Grant support: This study was supported by a grant from TUBITAK (110S179)

PERIPHERAL ARTHERIAL DISEASE AND CHARCOT FOOT

R. Bem, A. Jirkovska, M. Dubsky, V. Fejfarova, V. Woskova, J. Skibbova

Diabetes Centre, Institute for Clinical and Experimental Medicine , Prague, Czech Republic

Aims: To investigate the association between peripheral arterial disease (PAD) and ulcerated Charcot neuropathic osteoarthropathy (CNO) and assess the role of lower limb angiography with the respect to pathological findings and possibility of vascular interventions.
Methods: The presence of PAD was compared between a group of 82 patients with ulcerated CNO and 100 consecutive patients presenting with a new diabetic foot ulcer, but without CNO (Controls) treated in foot clinic between 2003 and 2012. The diagnosis of PAD was based on clinical examination and verified by transcutaneous oxygen tension measurement (TcpO2) and by angiography.
Results: No significant difference in the presence of PAD between ulcerated CNO and Controls (35.4% vs. 48%; p=0.12), was found. In 58.6% of CNO patients with PAD, the revascularization (angioplasty or bypass) predated the manifestation of active CNO and it could be its prerequisite. In PAD patients, a significant difference between the groups was only in the presence of most severe findings; 69% of CNO patients and 89.7% of Controls had one or no patent crural artery ($p<0.05$). Revascularization rate based on angiographic findings was comparable between groups (89.7% of CNO patients vs. 87.5% of Controls).
Conclusions: This study suggests that PAD is not rare in patient with ulcerated CNO. Revascularization is a potential risk factor for manifestation of active CNO. Our results indicate that patients with CNO and non-healing ulcer may have benefit from lower limb angiography, because it leads to equaly frequent revascularization as for non-CNO patients.

ASSOCIATION OF CEREBROVASCULAR DISEASES TO DIABETES AND OTHER RISK FACTORS IN WHO EASTERN MEDITERRANEAN COUNTRIES

A. Boutayeb[1]*, W. Boutayeb[1], S. Boutayeb[2], M.E.N. Lamlili[1]

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[2]*Department of Medical Oncology, National Institute of Oncology, Rabat, Morocco*

*Corresponding author, member of EASD research group

Background: In 2008, non communicable diseases caused 2.3 million deaths in WHO Eastern Mediterranean countries, representing 53% of the regional annual mortality. Cardiovascular diseases, cancer, respiratory diseases and diabetes caused 55%, 14%, 9%

and 5% of deaths respectively. According to the WHO statistics, stroke is the second killer in the world with 6.2 million deaths per year, representing 11.4% of the 54.6 deaths that occurred in 2011.

According to the data released by the International Diabetes Federation in 2011, the Middle East and North Africa region has the highest comparative prevalence of diabetes (11%). Six of the top 10 countries with the highest prevalence of diabetes (in adults aged 20 to 79 years) are in this region: Kuwait (21.1%), Lebanon (20.2%), Qatar (20.2%), Saudi Arabia (20.0), Bahrain (19.9%) and UAE (19.2%).

This review is dedicated to the association between cerebrovascular diseases (stroke) and diabetes mellitus in the WHO Eastern Mediterranean region. Association with other risk factors is also considered.

Method:

- This is a systematic review on cerebrovascular diseases and known associated risk factors in WHO Eastern Mediterranean countries. Medline/PubMed, EMBASE and other sources were used to get peer reviewed papers dealing with the review theme.
- The words/strings used for search and inclusion criteria were: stroke, cerebrovascular disease, Arab and name of countries belonging to the WHO Eastern Mediterranean Region and risk factors. The search was limited to publications between 1990 and 2013(30th June).
- For a paper to be included in the review, five criteria were jointly required 1) Stroke, cerebrovascular diseases, 2) WHO Eastern Mediterranean region, 3) Diabetes as risk factor and eventually other risk factors: Hypertension, hyperlipedaemia, smoking 4) Availability of abstract in English or French, 5) The study is not devoted to childhood disease. When more than a paper was selected with the same authors and the same topic, only one paper was included in the review.

Results and discussion: According to the inclusion criteria, 36 papers were included in the present review, from Bahrain(1), Egypt(1), Jordan(1), Iraq(2), Iran(6), Kuwait(3), Libya(1), Qatar(3), Palestine(2), Pakistan(9), Saudi Arabia(5), Sudan(1), UAE(1). Diabetes mellitus represents a high risk factor in stroke patients. As indicated in the table below, the prevalence of diabetes was less than 25% in ten studies, between 25% and 50% in 19 studies and grater than 50% in 7 studies. In 26 studies, the prevalence of hypertension was greater than 50%. Smoking was indicated in 23 studies and varied from 1.6% to 47.34% whereas hyperlipidaemia was less indicated and varied from 2.55% to 57%. It should also be stressed that, geographically, only two contributions were issued from North African countries.

Table

Country	Number of publications	Dates of publication	DM prevalence (%)	HBP prevalence (%)
Bahrain	1	2000	20	52
Egypt	1	2013	38.9	66
Jordan	1	2004	44	76

Irak	2	2003, 2005	25, 28	76.1, 34
Iran	6	From 2005 to 2011	13.5 to 55.7	36.6 to 60.4
Kuwait	3	1997, 2003, 2013	42, 69.4, 56.3	53, 72, 68.9
Libya	1	1995	24.6	51
Pakistan	9	From 2000 to 2010	18 to 50	55.54 to 78
Palestine	2	2008, 2009	45.8 , 45.2	66.1, 69.9
Qatar	3	2001, 2007, 2008	45.5, 51, 46.6	66, 69, 76
Saudi Arabia	5	From 1991 to 2000	11.6 to 41	24.9 to 61
Sudan	1	2002	14.6	46.9
UAE	1	2002	55	75

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PROGNOSTIC IMPACT OF HEMOGLOBIN A1C IN HIGH-RISK TYPE 2 DIABETIC PATIENTS: THE RIO DE JANEIRO TYPE 2 DIABETES (RIO-T2D) COHORT STUDY

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Aims and background: The prognostic importance of glycated hemoglobin in type 2 diabetes for cardiovascular prognosis after full adjustment for potential confounders remains debatable. The aim was to evaluate the prognostic impact of hemoglobin A1c for cardiovascular morbidity and all-cause mortality in a cohort of 569 high-risk type 2 diabetic patients.

Materials and methods: Clinical, laboratory, ambulatory blood pressure (BP) monitoring data were obtained at baseline. The primary endpoints were a composite of fatal and non-fatal major cardiovascular events and all-cause mortality. Multiple Cox survival analysis assessed the associations between hemoglobin A1c, as a continuous variable and categorized at (<7%, ≥7% <8%, ≥8%) and the endpoints. Hemoglobin A1c values obtained at entry, mean of first year of follow up, and time varying were used for the analysis.

Results: After a median follow-up of 6.25 years, 96 total cardiovascular events and 92 all-cause deaths occurred. After adjustments for potential cardiovascular risk factors(age, sex, BMI, diabetes duration, smoking status, physical activity, number of anti-hypertensive drugs in use, presence of macrovascular and microvascular complications at baseline, 24-hour ambulatory bold pressures, HDL- and LDL-cholesterol, statins and aspirin use),

hemoglobin A1c was predictive of the composite endpoint and of all-cause mortality. It was a predictor of the composite endpoint as a continuous variable (HR: 1.20; 95% CI: 1.03-1.38; p=0.018, for increments of 1% of mean HbA 1c of the first year of follow up). For all-cause mortality, both baseline and mean of first year of follow up were predictive at categorized values (HbA 1c ≥7 <8% HR: 1.98 95%CI 1.16-3.40 p=0.013; HbA 1c >8% HR:1.83 95%CI 1.04-3.23 p=0.037; HbA 1c ≥7 <8% HR: 1.93 95%CI 1.12-3.30 p=0.017; HbA 1c >8% HR:1.85 95%CI 1.04-3.32 p=0.038, respectively) in relation to reference value <7%, with similar hazards ratios. In the analysis, excluding all patients with the presence of macrovascular complications at baseline, mean of first year of follow up and time varying Hb A1C, as continuous variables, were independent predictors of composite endpoint. As a categorized variable, mean first year follow up HbA 1c values > 8% showed an increased risk for composite endpoint (HR:2.82 95%CI 1.22-6.53 p=0.015).
Conclusions: Hemoglobin A1c provides cardiovascular risk prediction independent of standard risk factors, degenerative complications and ambulatory blood pressures, and improves cardiovascular risk stratification in high-risk type 2 diabetes, particularly, in those patients without macrovascular complications.

ASSOCIATED FACTORS WITH CARDIAC STRUCTURE AND FUNCTION IN TYPE 2 DIABETES

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Background and objectives: Relationships between left ventricular mass/hypertrophy and diastolic dysfunction with less traditional risk markers, such as ambulatory blood pressures, aortic stiffness, common carotid intima media thickness and extra-cranial carotid artery atherosclerosis and biomarkers have not been investigated in type 2 diabetes. We aimed to investigate associations between LVMI and diastolic dysfunction in type 2 diabetes and more recent risk factors.
Patients and methods: Clinical, laboratory, 24-hour ambulatory blood pressure monitoring, aortic pulse wave velocity and carotid ultrasonographic data were obtained in 613 type 2 diabetic patients. Two-dimensional transthoracic echocardiography (Sonoline G60S, Siemens, Munich, Germany) was performed by the same experienced observer. Left ventricular mass was calculated and indexed to height 2.7 (LVMI). Left ventricular hypertrophy (LVH) was defined as LVMI >44g/m2.7 in women and >48g/m2.7 in men. Left ventricular diastolic function was also assessed using the mitral inflow Doppler pattern using standard criteria. Associations were assessed by bivariate tests and multivariate linear and logistic regressions.
Results: Six point four per cent of diabetic patients were obese, 86.6% were hypertensive, 73% had LVH criteria and 79% presented diastolic dysfunction**.** On the multivariate linear analysis, age, body mass index (BMI), 24-hour systolic blood pressure (SBP), number of anti-hypertensive drugs in use, log10 UAE were the variables associated with LVMI2.7.

Abdominal circumference was also independently associated with LVMI, but with a lower correlation coefficient than BMI, 24-hour pulse pressure was also associated independently with LVM when substituted for 24-hour SBP in the model. On logistic multivariate analysis, the same variables were associated with the presence of left ventricular hypertrophy except for log 10UAE. (age:or=1.05 95%CI :1.03-1.07 p<0.001; female gender: or= 0.43 95%CI: 0.29-0.64 p<0.001; BMI: or=1.12 95%CI: 1.06-1.18 p<0.001; 24-hour SBP: or= 1.03 95%CI: 1.02-1.05 p<0.001, number of antihypertensive drugs in use: or=1.28 95%CI: 1.10-1.49 p=0.001). On logistic analysis, age, female gender and 24-SBP or PP were the variables independently associated with diastolic dysfunction. In 250 diabetic patients we performed measurement of adiponectin, tumor necrosis factor-a, transforming growth factor (TGF)-b1, interleukin(IL)-6, -8 and -10. On multivariate analysis, in this subgroup of diabetic patients, log 10 of adiponectin was independently and inversely associated with the presence of diastolic dysfunction (or=0.27 95 % CI : 0.084-0.850 p=0.026) besides older age.
Conclusions: Age, body mass index/abdominal circumference, ambulatory blood pressures and urinary albumin excretion were the variables independently related to left ventricular mass or hypertrophy in type 2 diabetic patients. Age, ambulatory blood pressures were the variables related to diastolic dysfunction. Adiponectin was inversely associated with diastolic dysfunction; adipocyte dysfunction may be related to abnormal cardiac function in type 2 diabetes.

IMPACT OF OPTIMAL GLYCEMIC CONTROL ON CHANGES IN HEART RATE VARIABILITY IN PATIENTS WITH GESTATIONAL DIABETES MELLITUS

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Objective: The aim of the present study was to evaluate changes in heart rate variability in normotensive patients with gestational diabetes mellitus (GDM), who had optimal glycemic control throughout pregnancy.
Methods: 34 pregnant women with GDM with optimal glycemic control achieved by intensive therapy were enrolled in the study. Target values were fasting glycemia under 5.6 mmol/l, two hours postprandial glycemia below 6.7 mmol/l and HbA1c levels below 45 mmol/l. In this study group, at 36 weeks of gestation, heart rate variability was evaluated at rest in the morning, while fasting, using VariaCardioTF4 device during 3 consecutive intervals (supine, standing, lying - every interval about 5 minutes apart). Measured values were compared with a control group of healthy pregnant women tested at the same gestational age. Mann-Whitney test and t-test were used for statistical analysis.
Results: Mean age of 34 women with GDM was 32 ± 3.2 years, compared with 25 women of the control group 30.2 ± 4.5 years (NS).
Parasympathetic activity assessed as power HF (high frequency) in 3 consecutive intervals

was 230 ± 343, 151 ± 155, 212 ± 280 ms^2 in the control group, which was comparable to 234 ± 341, 170 ± 271, 216 ± 277 ms^2 in women with GDM.
Sympathetic activity assessed as power ratio LF/HF (low frequency/high frequency) in 3 consecutive intervals was 1.9 ± 1.7, 1.9 ± 1.6, 1.7 ± 1.9 in the control group, which was comparable to 2.1 ± 1.7, 3.6 ± 3.9 and 2.1 ± 2.3 in women with GDM. The sum of all three intervals representing parasympathetic activity (power H1 + H2 + H3) was 632 ± 511 ms^2 in the control group and 621 ± 790 ms^2 in the GDM group (NS). Total sympathetic activity assessed by the sum of the ratios LF/HF in all three intervals (power LF1/HF1 + LF2/HF2 + LF3/HF3) was 5.5 ± 4.1 in the control group compared with 7.9 ± 6.0 in the group of women with GDM (NS).
Conclusion: Trend towards higher sympathetic activity in women with GDM was observed. However, no significant differences in heart rate variability were observed when compared to healthy pregnant women.

CARDIAC AUTONOMIC DYSFUNCTION AND OBSTRUCTIVE SLEEP APNEA SYNDROME ARE INVOLVED IN LEFT VENTRICULAR HYPERTROPHY IN OBESE PATIENTS WITHOUT KNOWN DIABETES

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Aim: Left ventricular hypertrophy (LVH) is often found in the patients with obstructive sleep apnea syndrome (OSAS). Cardiac autonomic neuropathy was also shown to be associated with LVH in diabetic patients. Cardiac autonomic dysfunction (CAD) often affects non diabetic obese patients. The aim was to examine in non diabetic obese patients the role of OSAS and CAD in LVH.
Patients and methods: We included 92 obese patients, BMI 43.5±5.1 kg/m2, free of known glycemic disorder. The apnea/hypopnea index (AHI) was determined in 47 patients who had signs suggesting OSAS and confirmed the diagnosis in 23 of them. CAD was assessed using 3 tests of heart rate variations mostly dependent on vagal control (Valsalva, deep-breathing, lying-to-standing) which were interpreted according to age. CAD was defined as ≥1 abnormal test. Dysglycemia was detected by oral glucose tolerance test (WHO criteria). An echocardiographic examination was performed with calculation of left ventricular mass (LVM) according to ASE convention.
Results: Five patients had diabetes and 23 had prediabetes (fasting hyperglycemia and/or glucose intolerance). CAD was found in 26 patients of the 39 patients tested, 2 with diabetes and 24 without. LVM/height2.7 was higher in the patients with OSAS than in those without (52.1±11.8 vs 44.5±11.1 g/m2.7; p=0.007), and in the patients with CAD than in those without (49.7±11.8 vs 39.7±11.4 g/m2.7; p=0.02). LVM/height2.7 correlated negatively with deep breathing (p=0.01) and lying-to-standing (p=0.04) tests, systolic blood pressure (p<0.001), body weight (p=0.05) and fasting plasma glucose (p=0.01).

LVH (defined as LVM/height2.7 >50 or 47 g/m2.7, respectively in men and women) was diagnosed in 40%, 52.1% and 60% of the patients with normal glycemia, prediabetes and diabetes, respectively. There was a trend to a higher rate of LVH in patients with OSAS (14/23) than without (26/66) (p=0.07). In multivariate regression analysis including OSAS, systolic blood pressure, body weight and glycemic status, LVH was still associated with OSAS (p=0.04). In another model where glycemic status was replaced by CAD, LVH was associated only with CAD (p=0.02).

Conclusions: LVH is a highly prevalent condition in massively obese patients without known diabetes. LVH is associated with OSAS and CAD. Altogether our data suggest that sympathetic predominance may contribute to increase LV mass.

IN ASYMPTOMATIC TYPE 2 DIABETIC PATIENTS, THE PREVALENCE OF SILENT MYOCARDIAL ISCHEMIA AND SILENT CORONARY STENOSES DEPENDS ON THE NUMBER OF CONTROLLED CARDIOVASCULAR RISK FACTORS

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Silent myocardial ischemia (SMI) is a common complication of diabetes. SMI may be due to functional coronary disorders and/or coronary stenoses (CS). We hypothesized that control of cardiovascular risk factors (CVRF) at the time of investigation would be associated with a lower prevalence of SMI.

A total of 1627 asymptomatic type 2 diabetic patients with at least one additional CVRF were screened for SMI with stress and/or dipyridamole myocardial scintigraphy. SMI was detected in 412 patients (25.3%); a coronary angiography was performed in 298 of those with SMI and found CS in 131 patients (44%). The patients were classified according to control of blood pressure (≤140/90 mmHg), HbA1c (≤7.5%), LDL cholesterol (≤2.6 mmol/l) and triglycerides (≤2.3 mmol/l).

SMI prevalence was inversely associated with the number of controlled CVRF (39.6%, 35.7% 24.7%, 19.8%, 17.7% in patients with none, 1, 2, 3 or 4 controlled CVRF, respectively; p<0.001). In multivariate analysis taking into account the number of controlled CVRF (3 or 4 vs 0-2), age, diabetes duration, gender, retinopathy, nephropathy, smoking, HDL cholesterol, peripheral vascular disease, SMI was associated with a lower number of controlled CVRF (odds ratio 0.53[95CI 0.39-0.74]), male gender (2.4[1.8-3.3]) and peripheral vascular disease (1.6[1.02-2.5]). Among the patients with SMI, the prevalence of CS was lower in the patients with 3-4 controlled CVRF than in those with 0-2 controlled CVRF (34.5 vs 47.7%, p<0.05), even after multivariate analysis.

In conclusion, in patients with type 2 diabetes, SMI is markedly lower and is less concordant with CS when the number of controlled CVRF is higher, even after adjustment on confounders. This strongly suggests the preventive efficacy of CVRF control on silent coronary artery disease.

DIETARY PALMITIC INTERESTERIFIED FAT PROMOTES LDL PARTICLE CHOLESTEROL ENRICHMENT IN LDLr KNOCKOUT MICE SIMILARLY TO TRANS FATTY ACIDS

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Introduction: Interesterified fats have been used as an alternative to trans fatty acids in the diet, however its impact on plasma lipoprotein composition is not yet elucidated in the literature. Therefore, the aim of this study is to evaluate the effect of interesterified fats containing stearic and palmitic acids on the plasma lipid and lipoprotein profile in LDLr knockout (LDLr-KO) mice.
Methods: Weaning male LDLr-KO mice were randomly divided into six groups (n=15-20) fed with a high fat diet (40% of energy as fat) containing polyunsaturated fatty acids (PUFA), trans fatty acids (TRANS), palmitic acid (PALM), palmitic interesterified fat (PALM INTER), stearic acid (STEAR) or stearic interesterified fat (STEAR INTER) during 16 weeks. We evaluated dietary intake, body weight gain and measured plasma total cholesterol and triglycerides concentrations by enzymatic method. Lipoproteins composition was determined by fasting protein liquid chromatography (FPLC).
Results: There was no difference in dietary intake among the groups studied however, animals fed with PALM INTER diet presented a significant weight gain as compared to the other groups. No difference in plasma cholesterol concentrations was observed between groups PALM *vs* PALM INTER and STEAR *vs* STEAR INTER. PALM and PALM INTER groups presented lower total plasma cholesterol and triglycerides concentrations as compared to TRANS. Although PALM INTER induced an increase in cholesterol concentration in LDL particle similarly to TRANS, HDL-C was not reduced. STEAR and STEAR INTER did not increase plasma lipids concentration when compared to the PUFA group that was lower as compared to PALM, PALM INTER and TRANS groups (Table).
Conclusion: Our results demonstrated that PALM INTER promotes cholesterol accumulation in LDL particles similarly to TRANS. without inducing the same increase in cholesterolemia.

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Table. Plasma lipoprotein cholesterol and triglycerides concentrations and lipoprotein profile[1,2]

	PUFA	TRANS	PALM	PALM INTER	STEAR	STEAR INTER
Total cholesterol (mg/dL)	321 ± 13[a]	669 ± 20[b]	499 ± 23[c]	527 ± 21[c]	343 ± 22[a]	364 ± 22.5[a]
VLDL-C (mg/dL)	60 ± 7[a]	363 ± 18[b]	190 ± 23[c]	189 ± 22[c]	108 ± 18[a]	121 ± 15.2[a]
LDL-C (mg/dL)	157 ± 10[a]	266 ± 17[b]	219 ± 10[c]	248 ± 9[bc]	145 ± 9[a]	175 ± 14.9[a]
HDL-C (mg/dL)	90 ± 7[a]	40 ± 5[b]	91 ± 8[a]	91 ± 7[a]	91 ± 5[a]	80 ± 6[a]
Triglycerides (mg/dL)	130 ± 12[a]	541 ± 67[b]	309 ±49[c]	303 ± 33[c]	239 ± 28[a]	237 ± 27[ac]
VLDL-TG (mg/dL)	89 ± 12[a]	481 ± 60[b]	209 ± 39[ac]	214 ± 28[ac]	146 ± 19[ac]	163 ± 21[ac]
LDL-TG (mg/dL)	32 ± 3[a]	141 ± 20[b]	48 ± 7[a]	70 ± 11[a]	66 ± 12[a]	57 ± 9[a]
HDL-TG (mg/dL)	18 ± 3[a]	24 ± 5[a]	20± 4[a]	13 ± 2[a]	15 ± 3[a]	14 ± 2[a]

1 Data are presented as mean ± SEM (n=14-20). Means in a row without a common letter differ (P<0.05). Statistical analysis for the data that passed the normality test was performed using 1-way ANOVA followed by the post hoc Newman-Keuls multiple comparison test. VLDL-c, VLDL-TG, LDL-TG, HDL-TG were analyzed by nonparametric Dunn multiple comparison test.
2 The cholesterol and TG distribution was calculated as the area under the peaks of the fast protein liquid chromatography profiles of individual plasma samples and converted to absolute numbers

ENDOTHELIAL AND SMOOTH MUSCLE DAMAGE AND IMPAIRED NO PATHWAY BUT NORMAL ENERGY METABOLISM IN THE FEMALE TYPE 2 DIABETIC GOTO-KAKIZAKI (GK) RAT HEART

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Background: Cardiovascular disease is a long-term complication of type 2 diabetes mellitus, with a two-fold increased risk of heart failure, and greater mortality after myocardial infarction than non-diabetic patients. In addition, aging and diabetes in women increase their susceptibility to myocardial ischemic injury but the molecular mechanisms involved are not well understood. Consequently, we have investigated the effect of gender on cardiac function, energy metabolism, endothelial function and NO pathway in the aging type 2 diabetic Goto-Kakizaki (GK) rat heart.
Materials and Methods: Age-matched (8 months) Control Wistar (male n=11, female n=9) and GK (male n=11, female n=12) isolated rat hearts were perfused during 28 min with a physiological Krebs-Henseleit buffer containing 0.4 mM palmitate, 3% albumin, 11 mM glucose, 3U/L insulin, 0.8 mM lactate and 0.2 mM pyruvate before freeze-clamping for biochemical assays. High energy phosphate compounds and intracellular pH (pHi) were followed using 31P magnetic resonance spectroscopy with simultaneous measurement of contractile function. Tissue water content, creatine kinase and lactate dehydrogenase activities were used as markers of intracellular oedema and cellular integrity, respectively. NO pathway was studied by total nitrate concentration (NOx) as well as total level and phosphorylation of eNOS and Akt. In parallel, endothelium-dependent and independent vasodilatations were measured in other hearts (male Control n=8, male GK n=8, female Control n=10, female GK n=11), using 5-hydroxytryptamine and papaverine to assess

endothelial and smooth muscle functions.
Results: Phosphocreatine, ATP, PME and Pi contents were not significantly different in Control and diabetic groups. Intracellular pH was similar in the four groups. Total pool of creatine (creatine and phosphocreatine) and adenine nucleotides was similar in all groups. Myocardial function as expressed by the rate pressure product was significantly impaired in male and female diabetic versus Control groups ($p<0.05$). Endothelium-dependent and independent vasodilatations were not different in male Control and GK rat hearts. By contrast, endothelium-dependent and independent vasodilatations were significantly impaired in female GK compared with male GK ($p<0.05$) and female Control ($p<0.05$) rat hearts. Ratio Akt/actine was similar in all groups. NO production was up-regulated in diabetic groups but to a less extent in female GK rat hearts ($p<0.05$).
Conclusion: We reported here both endothelial and smooth muscle damage and impaired NO pathway but normal energy metabolism in the female GK rat hearts. These results could be related to gender differences in susceptibility to ischemic injury of the aging type 2 diabetic heart.

ACUTE HEMODYNAMIC CHANGES AFTER A COLD PRESSURE TEST IN HEALTHY SUBJECTS AND IN TYPE 2 DIABETIC PATIENTS

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Background and aims: Sympathetic activation during a cold pressure test (CPT) has been shown to induce an immediate increase in arterial stiffness and aortic systolic blood pressure (AoSBP). This study aimed to examine the effects of CPT both in aorta and in peripheral arteries and to determine whether these effects are different in type 2 diabetic patients (T2D).
Subjects and methods: We recruited 41 subjects (16 females; mean age 42.4 ±12.5 years): 25 were healthy controls (HC) and 16 had T2D, 9 with normal blood pressure (T2D-NT) and 7 with hypertension (T2D-HT). After a 15-minute supine rest, radial and aortic systolic (SBP) and pulse (PP) pressure and the augmentation index (AIx) were measured by applanation tonometry (Sphygmocor®), twice at baseline (5 minutes and just before CPT: T-5,T0), and once for the next 2, 4 and 6 minutes (T2,T4,T6) after a two-minute left hand immersion in ice.
Results: The double product (DP: heart rate x SBP) and AIx did not differ between HC, T2D-NT, T2D-HT at baseline nor after CPT. In the overall series DP and AIx increased from T0 to T2 ($p=0.002$) and then decreased 4 minutes after the beginning of the test ($p< 0.001$). The increase in SBP was greater in aorta than in radial artery ($p=0.004$). DP increase (%) was negatively correlated with the subendocardial myocardial viability ratio from T0 to T2 ($p=0.006$) and positively with basal AoSBP ($p=0.001$). The reflection time of the incident wave was negatively correlated to DP, AoSBP, aortic PP and to heart rate ($p<0.01$) and similarly after CPT.

Conclusion: Sympathetic nervous system activation provokes a greater increase in central than peripheral SBP, with a decrease in subendocardial myocardial viability and arterial compliance. This effect may have important consequences in stressful situations in high cardiovascular risk patients.

TREATMENT OF PREDIABETES FOR THE EARLY PREVENTION OF MICROVASCULAR AND MACROVASCULAR COMPLICATIONS: THE EUROPEAN ePREDICE MULTICENTRIC TRIAL

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Background: A significant proportion of pre-diabetic individuals in population-based studies, show already macro and micro vascular complications associated with hyperglycaemia. Although many trials have demonstrated the efficacy of lifestyle and pharmaceutical interventions in the prevention or postponing the onset of diabetes, No trial has evaluated the extent to which mid- and long-term complications can be prevented by early interventions on hyperglycaemia.
Objective: To assess the long-term effects on multiple complications of hyperglycaemia of early intensive management of hyperglycaemia with sitagliptin, metformin or their combination added to lifestyle intervention (diet and physical activity), compared with lifestyle intervention alone in adults with non-diabetic intermediate hyperglycaemia (IFG, IGT or IFG plus IGT).
Design: Long-term, multi-centre, randomised, single blinded, placebo controlled, phase-IIIb clinical trial with prospective blinded outcome evaluation. Participants will be randomised to four parallel arms: 1) Lifestyle intervention + two placebo tablets/day; 2) Lifestyle intervention + two *Metformin* tablet 850 mg/day; 3) Lifestyle intervention + DDPIV; 4) Lifestyle intervention + 2 tablets of a fixed-dose combination of *DPPIV* and *Metformin* 850mg /day. Active intervention will last for at least 3 years, and additional follow-up up to 5 years. Main outcomes will be determined at baseline.
Setting and population: Males and Females with pre-diabetes (IFG, IGT or both) aged 45 to 74 years selected from ongoing primary care screening programs in 15 clinical centres from 12 different countries: Australia, Austria, Bulgaria, Germany, Greece, Italy, Lithuania, Poland, Serbia, Spain, Switzerland and Turkey. The initial sample size estimated: 3000 participants.
Main Outcomes: The primary endpoint is a combined continuous variable: ***"the microvascular complication index" (MCI*)** composed by a linear combination of the Early Treatment Diabetic Retinopathy Study Scale (ETDRS) score (based on retinograms), the level of urinary albumin to creatinine ratio, and a measure of distal small fibre neuropathy (sudomotor test by SUDOSCAN), measured during the 36th and 60th month visits after randomisation. Besides the main primary outcome, this project will include

the evaluation of a broad spectrum of early novel serological biomarkers of systemic inflammation, early micro-vascular damage, non-alcoholic fatty liver disease (NAFLD), insulin sensitivity and insulin secretion, and measures of quality of life, sleep quality (somnograms) and neuropsychological evaluation. Vascular function and structure will be evaluated in a subset of participants (n=1000), including Carotid Intima Media thickness, microvascular endothelial function measured (EndoPAT).
Expected results: Evaluating the effect of aggressive treatments in pre-diabetes for the early prevention of diabetes complication, this project has the potential of changing the current paradigm of early management of hyperglycaemia. The ultimate goal is the development of a standardized core protocol for the early prevention of microvascular and other complications, the leading cause of blindness, renal end-stage disease and non-traumatic lower limb amputations in Europe, impacting social cost as a result not only in health care, but also in disabilities at work.

17β ESTRADIOL AMELIORATES MITOCHONDRIAL DYSFUNCTION AND OXIDATIVE STRESS IN THE HEART OF OVARIECTOMISED RATS WITH FRUCTOSE-INDUCED INSULIN RESISTANCE

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Background and aims: It is believed that premenopausal females have a reduced incidence of cardiovascular disease. Much of this protection is attributed to beneficial effects of estrogen on the lipid profile and endothelial cell function, but recent data have suggested that estrogen also can protect cardiomyocytes and mitochondria are a major target of cardioprotective signaling. The aim of the study was to assess the effects of 17β-estradiol (E2) on mitochondrial respiratory chain activity and oxidative status in the heart of ovariectomised rats with fructose-induced insulin resistance.
Materials and methods: Female Wistar rats were divided into four groups: control intact rats (C, n=8), ovariectomised rats fed on a regular diet (OVX, n=8), OVX rats which had free access to 250 g/L solutions of fructose for 8 weeks (OVX+HFD, n=8), and OVX rats treated with E2 (20 μg/kg/day per os) during 2 months of HFD feeding (OVX+HFD+E2). Mitochondria were isolated by differential centrifugation from the hearts of rats. Oxygen consumption rate was measured polarographically at 37°C using a Clark-type oxygen electrode with either glutamate/malate or succinate as energy substrates of Complex I or II, respectively. Levels of lipid hydroperoxides, reduced glutathione (GSH), superoxide dismutase (Mn-SOD) and cytochrome c oxidase activity were determined in mitochondrial preparations.
Results: Respiration studies on isolated heart mitochondria revealed that estrogen deficiency decreased the respiratory control index (RCI; state 3/state 4) for Complexes I and II by 26 % and 34%, respectively, ($p<0.05$) and cytochrome c oxidase activity

(OVX: 6.85±0.62 vs C: 11.01±0.56 μmol/min/ mg of protein, p<0.05) compared to intact control. HFD feeding induced a greater decrease of RCI (44%; p<0.05) for Complex I in OVX animals, but did not significantly affect succinate oxidation (Complex II) in the state 3 and the state 4 of respiration. Administration of E2 increased RCI for Complex I (OVX+HFD+E2: 7.27±0.51 vs OVX+HFD: 4.99±0.24; C: 8.90±0.59 p<0.05), normalised the ratio of state 3 to state 4 respiration at Complex II and cytochrome c oxidase activity. In addition, E2 provided also 50% reduction in lipid hydroperoxides contents (p<0.01), enhanced Mn-SOD activity (OVX+HFD+E2: 32.16±2.31 vs OVX+HFD: 22.94±2.10; OVX: 29.75±1.46; C: 44.90±1.17 U/mg of protein, (p<0.02) and normalised GSH level in heart mitochondria of ovariectomised rats with fructose-induced insulin resistance.
Conclusion: These data demonstrate that combination of estrogen deficiency with high-fructose diet induced additional disturbances in the mitochondrial coupling of respiration and oxidative phosphorylation at Complex I. 17β-Estradiol replacement inhibited the development of mitochondrial dysfunction and oxidative stress in the heart of ovariectomised rats with fructose-induced insulin resistance.

THE LEVEL OF ADVANCED GLYCATION END PRODUCTS AND FIBROBLAST GROWTH FACTORS (TGF-β, β-FGF) IN PATIENTS WITH CORONARY ARTERY DISEASE AND DIABETES MELLITUS

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Introduction: Chronic hyperglycemia activates pathological mechanisms restructuring the connective tissue, including the vascular wall. Fibroblasts are the main cellular component of connective tissue. Activation of the transforming growth factor (TGFβ1), basic fibroblast growth factor (β-FGF), produced by fibroblasts, advanced glycation endproducts (AGE) and their receptors (rAGE), may have important prognostic value.
Objective: To assess the level of AGE, TGFβ1 and β-FGF in patients with coronary artery disease (CAD) in comparison with normoglycemic controls and patients with DM.
Material and methods: The study involved two groups of patients with CAD: 55 patients with normal blood glucose (1) and 61 patients with type 2 DM (2). The extent of coronary atherosclerosis was determined by coronary angiography (CAG) in all patients. Blood samples were collected during CAG from aorta and cubital vein simultaneously, immediately centrifuged (15000g*min) (supernatants were stored at –70*C until analyses were performed). Serum TGFβ1 and β-FGF levels were analyzed by ELISA (IFA). The critical significance level (p) for statistical hypothesis testing was set at <0.05.
Results: Average TGFβ1 in the second group was significantly higher (7838.7 [2715.07;13813.5] pg/ml and 5818.2 [2884.4;10599.1] pg/ml, respectively). Elevation of AGE and TGFβ1 levels positively correlated with low-density lipoproteins and triglycerides (p<0.005). We observed a significant correlation between the levels of AGE, TGFβ1 and β-FGF with DM duration (p=0.009), and a direct association with HbA1c

(p=0.006). AGE, TGFβ1 and β-FGF levels were significantly higher in aortic blood than in peripheral venous blood p<0,005). Patients with DM had three-vessel disease more often (73%) than patients without glycemic disorders (r = 0.621), which was in direct correlation with the level of TGFβ1 (r = 0.523).
Discussion: Elevation of AGE, TGFβ1 and positive correlation with atherogenic lipids may highlight the role of connective tissue remodeling in pathogenesis of the coronary atherosclerosis. An increase in AGE and TGFβ1 levels positively correlated with duration of DM, indicating a pathological effect of hyperglycemia on vascular walls. Statistically significant elevation of AGE, TGFβ1 and β-FGF levels in aorta above those in peripheral blood suggest the involvement of cardiomyocytes in these growth factors metabolism.
Conclusion: DM and CAD comorbidity was characterized by higher AGE and TGFβ1 levels, which was in direct correlation with atherogenic dyslipidemia.

CHARACTERISTICS OF METABOLIC SYNDROME EXISTING IN PATIENTS WITH ANTIPHOSPHOLIPID SYNDROME

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Metabolic syndrome (MetS) and antiphospholipid syndrome (APS) are among most prevalent syndromes. As both of them represent prothrombotic and proatherogenic states, their coexistence has recently started to attract attention of researchers.
The aim of our research was to assess the characteristics of MetS coexisting with antiphospholipid syndrome (APS), primary (PAPS) and associated with rheumatic diseases (sAPS). The International Diabetes Federation (IDF) clinical definition of MetS was used.
Study included 68 patients with PAPS (59 females, 9 males, mean age 43.51+10.58 years), 69 patients with sAPS (61 females, 8 males, mean age 47.83+15.67 years) and 50 MetS patients (35 females, 15 males, mean age 47.68+11.66 years).
Prevalence of MetS was 36.76% in PAPS and even 42.03% in sAPS. When compared with MetS patients, waist circumference (WC) in patients with PAPS and SAPS did not differ significantly (MetS: 93.67+14.36 cm, PAPS: 90.73+9.18 cm; sAPS: 88.53+11.91 cm; F=2.77, *p*=0.065). Most prevalent characteristic of MetS among PAPS patients was atherogenic dislipidemia, while in sAPS patients arterial hypertension was also present in high percent of patients. It was interesting to observe low prevalence of hyperglicemic disorders (i.e. impaired fasting glyceamia, glucose intolerance or diabetes) among patients with APS. Compared with MetS patients in whom hyperglycemic disorders were present in as much as 36%, these disorders were observed in only 5.88% of PAPS patients (*p*=0.0001) and 4.35% of sAPS patients (*p*<0.0001).

By identification of MetS in APS patients, we could be able to identify those high risk patients in whom strict control of modifiable cardiovascular risk factors is mostly needed.

BREAKFAST AND LUNCH ARE BETTER THAN SIX MEALS A DAY FOR PATIENTS WITH TYPE 2 DIABETES

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Background: The impact of meal frequency on body weight and glucose homeostasis in patients with type 2 diabetes (T2D) remains unclear.
Methods: In a randomized, crossover study, we assigned 54 patients with T2D to follow two regimens of a hypocaloric diet (-500 kcal/day), each for 12 weeks: six meals (A6), and two meals a day, breakfast and lunch (B2). The diet in both regimens had the same macronutrient and energy content. The procedures were performed at weeks 0, 12 and 24. Hepatic fat content (HFC) was measured by the proton magnetic resonance spectroscopy performed by 3T MR scanner. Whole body insulin sensitivity was measured by isoglycemic hyperinsulinemic clamp as metabolic clearance rate of glucose (MCR) and calculated by mathematical modeling as oral glucose insulin sensitivity (OGIS). β-cell function was assessed during standard meal tests by C-peptide deconvolution and was quantified with a mathematical model. For statistical analysis, 2x2 crossover ANOVA was used.
Results: Body weight decreased in both regimens ($p<0.001$), more in B2 (-2.3; 95% CI -2.7 to -2.0 kg in A6 vs. -3.7; 95% CI -4.1 to -3.4 kg in B2; $p<0.001$). HFC decreased in response to both regimens ($p<0.001$), more in B2 (-0.03; 95% CI -0.033 to -0.027 % in A6 vs. -0.04; 95% CI -0.041 to -0.035% in B2; $p=0.009$). Fasting plasma glucose and C-peptide decreased in both regimens ($p<0.001$), more in B2 ($p=0.004$ and $p=0.04$, respectively). Fasting plasma glucagon decreased in B2 ($p<0.001$), while it increased ($p=0.04$) in A6 ($p<0.001$). Hb1Ac decreased ($p<0.001$) and MCR increased ($p<0.001$) comparably in both regimens. OGIS increased in both regimens ($p<0.01$), more in B2 ($p=0.01$). Insulin secretion at the reference level and glucose sensitivity increased ($p<0.05$) comparably in both regimens.
Conclusions: Two meals a day reduced body weight, HFC, fasting plasma glucose, C-peptide and glucagon and increased OGIS more than a diet with the same caloric restriction divided in six more frequent meals. MCR and β-cell function improved comparably in both regimens. Our data suggest that eating larger breakfast and lunch may be more beneficial for patients with T2D than six smaller meals during the day.

(ClinicalTrials.gov number, NCT01277471)

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LACK OF PROGNOSTIC VALUE OF RESTING HEART RATE ON CARDIOVASCULAR AND RENAL OUTCOMES IN T2DM PATIENTS

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Background and aims: Elevated resting heart rate (RHR) has been associated with increased risk of mortality and cardiovascular (CV) events in healthy subjects as well as those with pre-existing CV disease (CVD). Limited data are available on the RHR effect on CV and renal morbidity and mortality in type 2 diabetic (T2DM) subjects. Aims of our study was to study and eventually replicate previous sporadic positive findings on whether RHR can be considered as a simple and reliable predictor of serious disease outcomes such as CV and renal disease progression and death in T2DM patients.
Materials and methods: A total of 300 T2DM patients (50% of men, age 67 [IQR 60 – 75], median DM duration 13 years [IQR 8 – 20]) with variable stage of diabetic kidney disease (DKD) at baseline were prospectively followed for a median of 38 [21 – 65] months. RHR at baseline was determined either by 1 minute radial artery palpation or from ECG records. Following end-points were considered: (1) progression of DKD, i.e. decline of GFR <60ml/min during the follow-up period for those with GFR >60 at baseline or progression of CKD by at least stage for those with GFR <60ml/min at baseline or development of overt proteinuria in normo- and microalbuminuric subjects at baseline, (2) CV event (fatal or non-fatal myocardial infarction or stroke, lower limb arterial disease with claudication or amputation) and (3) all-cause mortality. A history of the CVD was present in 209 (70%) patients at baseline, DKD (GFR<60ml/min or proteinuria was present in 244 (81%) at baseline. Time-to-event analysis (Kaplan-Meier) was used to analyze the effect of RHR categories (< and > actual median RHR and arbitrary cut-off 70bpm) on studied outcomes.
Results: Cumulative incidence of DKD progression, CV event and all-cause mortality were 41%, 19% and 23%, respectively, in the whole group. Median RHR was 74 bpm. Although RHR was not significantly higher in subjects with CVD or DKD at baseline (b+) (P>0.05 in both groups, Mann-Whitney), analyses were still performed for both (i) whole group and (ii) CVD-b+ and (iii) DKD-b+ subgroups. Using time-to-event analyses significant differences in the cumulative incidence of the three studied outcomes between RHR </>70 or 74bpm were found neither in the whole group nor in the CVD-b+ or DKD-b+ subgroups (P>0.05, log-rank test).
Conclusion: Unlike recent study in T2DM (Miot A et sl., Diabetes Care 2012) we have not been able to replicate any predictive effect of the RHR for the renal or CV outcomes in

type 2 diabetic population of Czech Republic. Given similar settings of our study one of the possible explanations might be smaller sample size and slightly shorter follow-up. Additional studies are therefore required for the definitive conclusions regarding RHR, otherwise smart, cheap and widely applicable risk marker.

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NICOTINAMIDE AND 1,5-ISOQUINOLINEDIOL TREATMENTS IN PREVENTION OF DIABETES-INDUCED HEART DYSFUNCTIONS

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Backgrounds and aims: The heart is known to be abnormally susceptible to oxidative damage from high ambient oxidant levels associated with diabetes. However, the exact mechanism by which oxidative stress could contribute to and accelerate the development of heart dysfunctions in diabetes is not clear. Intensification of oxidative stress induces of DNA damage and consequent activation of the nuclear enzyme poly(ADP-ribose) polymerase-1 (PARP-1). The study was designed to investigate the impact of experimental diabetes on the pathophysiological processes development in heart. We also tested whether PARP-1 inhibitors nicotinamide (NAm) and 1,5-*isoquinolinediol (*ISO) may exert beneficial effect against heart dysfunctions.

Material and methods: All studies were carried out after 10 wk of STZ-induced diabetes in male Wistar rats (55 mg/kg body weight, i.p.). NAm and ISO treatment was started after 8 wk of diabetes for 2 wk in dose 100 and 3 mg/kg b.w., i.p. respectively. The activities of an ethanol-inducible cytochrome P450 (CYP 2E1) and PARP-1 were assessed by electrophoresis and immunoblotting.

Results: After 10 wk diabetic animals had lost weight compared with control and NAm and ISO treatment did not affect it, $p<0.05$. At the end of term blood glucose level was increased about 5.1-fold in diabetic rats as compared with control. ISO administration to diabetic rats had no effect on blood glucose level while NAm caused a slight lowering effect. TBARS, an indicator of oxidative stress, in diabetic heart were more than 2-fold increased (15.9±1.4 μmol/mg protein) vs control (7.5±0.8). NAm reduced the level of TBARS in diabetic group to 9.2±0.9, while ISO only to 12.7±1.1. As result of weakening of antioxidant system SOD activity in diabetic heart was reduced by 40.3±3.5 % as compared to control ($p<0.05$) and NAm and ISO treatment only partly increased it, $p<0.05$. Diabetes was accompanied by reduction levels of NAD+, substrate of poly-ADP-ribosylation, by 37.5±3.9 % vs control, $p<0.05$. NAD+ levels were partly reversed in response to NAm but not ISO treatment. Western blot analysis of whole heart tissue extracts with anti-PARP-1 antibody did not reveal reliable activation of PARP-1 cleavage in diabetes as compared to control. It was found that diabetes induced more than 2.5 fold increase in mean hepatic

CYP 2E1 expression in diabetic rats and treated with ISO as compared to control, but influence of NAm was less extent, $p<0.05$. It is not excluded that diabetes-induced CYP 2E1 can be responsible not only for liver injury but also for heart impairments. Moreover, we have shown that development of diabetes in rats accompanied by a significant decrease in the viability of blood leukocytes and changes in the redistribution between their two main types. These alterations suggest the intensification of inflammatory processes in diabetes which were partly attenuated by NAm and stronger by ISO.
Conclusion: The findings suggest that diabetes-induced oxidative stress may cause physiologically drastic failures in heart functioning. Our data imply that NAm and ISO are involved in improvements of heart functions not only as PARP-1 inhibitors but through multiple other mechanisms.

NOS3 POLYMORPHISMS ARE ASSOCIATED WITH PROGRESSION OF KIDNEY AND CARDIOVASCULAR DISEASE IN TYPE 2 DIABETIC PATIENTS

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Background and aims: We have previously identified association of 6 single nucleotide polymorphisms (SNP) with diabetic nephropathy (DN) in type 2 diabetes mellitus (T2DM) using multi-locus analysis in a case – control study comprising 419 type 2 diabetics and 228 healthy subjects genotyped for 45 SNPs in 20 candidate genes for DN. We identified SNPs in four genes – *AGER* (-429T>C and 2184A>G), *EDN1* (8002G>A) and *LTA* (252A>G) on chromosome 6p and *NOS3* (774C>T and 894G>T) on chromosome 7q - associated with DN in T2DM. In the present study we genotyped the same SNPs in the independent cohort of prospectively followed T2DM patients with aim to investigate their possible role in the progression of DN and development of morbidity and mortality associated with diabetes.
Methods: 311 T2DM subjects (157 men and 154 women) with defined stage of DN and chronic kidney disease at baseline were enrolled in the study and followed up for a median of 38 [21 - 65] months. SNPs were detected using PCR. Three end-points were considered: (i) progression of DN (i.e. transition from any given baseline DN stage to a more advanced stage of albuminuria or to ESRD), (ii) major cardiovascular event (non-fatal or fatal myocardial infarction or stroke, limb amputation) and (iii) all-cause mortality. Kaplan-Meier curves with log-rank testing were applied to time-to-event analysis.
Results: At the end of the follow-up period, the cumulative incidence of DN progression, CV event and all-cause mortality reached 26.5 %, 19.9 % and 23.8 %, respectively. Significant differences between genotypes of *NOS3* SNPs 774C>T and 894G>T were ascertained for the progression of DN ($P = 0.00972$ and $P = 0.01402$, respectively) and in case of the 894G>T for the major cardiovascular event ($P = 0.03907$).
Conclusions: In conclusion, using the prospective cohort of T2DM subjects with defined

stage of diabetic kidney disease (both in terms of event. proteinuria and renal function) we demonstrated association of *NOS3* variants with DN progression (774C>T and 894G>T) and major cardiovascular event (894G>T).

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TRENDS IN THE INCIDENCE RATE AND OUTCOMES OF ACUTE MYOCARDIAL INFARCTION HOSPITALIZATION AMONG PATIENTS WITH AND WITHOUT DIABETES IN SPAIN, 2004-2010

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Background: Acute myocardial infarction (AMI) is one of the most frequent reasons for diabetic patients being admitted to hospital, and there are reports that show that the long-term prognosis after an AMI is much worse in the patients than in non-diabetics patients. This study aims to describe trends in the incidence rate and outcomes of AMI hospitalization among patients with and without diabetes in Spain in the period 2004-2010.
Methods: We selected all patients with a discharge of AMI using the Spanish national hospital discharge data. Discharges were grouped by diabetes status: type 2 diabetes and no diabetes. The incidence of discharges attributed to AMI were calculated overall and stratified by diabetes status and year. As hospitalization outcomes we calculated length of stay (LOS) and in-hospital mortality (IHM). Multivariate analysis for time trends was adjusted by age, sex, year and comorbidity (Charlson comorbidity Index).
Results: From 2004 to 2010, 363,558 discharges with AMI were identified. Patients with type 2 diabetes accounted for 31.2% of the total. The estimated incidence due to AMI in diabetes patients decreased from 71 cases per 100,000 inhabitants in 2004 to 61.9 in 2010. Diabetic patients had significantly higher IHM and LOS than those without diabetes in all the years analyzed (Table 1).
Conclusion: AMI hospitalization rates decreased slowly in patients with type 2 diabetes from 2004 to 2010. Diabetic patients have higher IHM and LOS after an AMI than non-diabetics patients.

Table 1. Incidence and outcomes of hospitalizations due to acute myocardial infarction among patients with and without type 2 diabetes in Spain, 2004-2010.

	2004	2005	2006	2007	2008	2009	2010	
Type 2 Diabetes	Total	16396	16608	15754	16082	16221	16390	16171
Incidence*	71	70.4	65.4	65.3	64.6	63.9	61.9	
LOS (SD)	10(8.3)	9.8(8.4)	9.6(8.7)	9.2(8.6)	9.2(8.3)	8.9(9.6)	8.6(9)	
%IHM	11.8	12.1	11.2	11.0	10.6	9.8	9.8	
Without diabetes	Total	36550	36187	35566	35537	35799	35309	34988
Incidence*	158.3	153.4	147.5	144.4	142.5	137.7	133.8	
LOS (SD)	9.1(10.3)	8.8(8.8)	8.5(8.4)	8.3(8.9)	8.1(8.7)	7.8(8.3)	7.7(9.5)	
%IHM	9.7	9.2	8.5	8.5	8.3	7.9	7.7	

*Incidence per 100,000. Incidence was calculated using the Spanish National Statistics Institute census projections . LOS (SD): Mean length of stay (standard deviation). %IHM: In-Hospital Mortality

INSULIN RESISTANCE, INCREASED LEPTIN AND IL-6 LEVELS ARE ASSOCIATED WITH PRESENCE OF HYPERTENSION IN OVERWEIGHT TYPE 2 DIABETIC PATIENTS

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Aims: It has been shown that adipocytokines, together with proinflammatory cytokines, associated with insulin resistance (IR), represents a well established risk factor for development of hypertension in type 2 diabetes (T2D). We analyzed the levels of (1) IR, (2) adipocytokines (leptin and adiponectin) and proinflammatory cytokines (IL-6 and TNF-alpha) in: overweight T2D with hypertension (group A, n=48, 30≤BMI≥25kg/m2), overweight T2D without hypertension (group B, n=43, 30≤BMI≥25kg/m2) and overweight nondiabetics without hypertension (group C, n=40, 30≤BMI≥25kg/m2).
Materials and methods: Hypertension was defined as systolic BP ≥140 and diastolic BP ≥ 90mmHg measured by sphygmomanometer, or by established use of antihypertensives. Insulin sensitivity were measured with two complementary methods: (a) homeostasis model assessment of IR (HOMA-IR) from fasting plasma glucose and insulin levels (b) a 75 g oral glucose tolerance test using oral glucose insulin sensitivity (OGIS) index. Fasting plasma insulin (PI) and leptin levels were measured by RIA method. Fasting levels of total adiponectin, IL-6 and TNF-alpha were measured by ELISA method.
Results: We have found significantly higher PI levels in group A (A:31.05+/-8.24; B:17.23+/-3.23;C:11.12+/-2.69 mIU/ml, A vs B $p<0.05$ and A, B vs C $p<0.01$), together with lower OGIS as measurement of peripheral insulin resistance (A:267±35.42; B:342.89±32.0; C:496.80±63.35 A vs B $p<0.01$ and A, B vs C $p<0.01$) and higher HOMA-IR, reflecting hepatic insulin sensitivity (A:8.43+/-4.69; B:6.52+/-3.04; C:2.36+/-0.71 A vs B $p<0.05$ and A, B vs

C p<0.01). The highest levels of leptin were in group A (A: 11.61+/-4.41; B: 7.53+/-2.42; C:5.81+/-1.72 pg/ml A vs B p<0.05; A vs C p<0.01 and B vs C p<0.05). However, there were no significant differences in the levels of adiponectin between diabetics (A: 3.70+/-1.32; B: 3.37+/-1.27; C:7.67+/-1.27 ng/ml, A vs B p=NS; A vs C and B vs C p<0.01). Significant differences was only in IL-6 levels (A: 15.46+/-5.15; B: 11.77+/-6.09; C:3.48+/-1.48 pg/ml, A vs B p<0.05; A, B vs C p<0.01).), but not in the levels of TNF-alpha between diabetics (A: 1.54+/-0.41; B: 1.53+/-0.42; C:0.71+/-0.30 pg/ml, A vs B p=NS; A, B vs C p<0.01). However, adiponectin correlate with all parameters of IR (PI: r= -0.480; HOMA-IR: r=-0.466, and OGIS: r=0.601; p<0.01, respectively) while an increased leptin levels negatively correlate with OGIS only (r=-0.347; p<0.05). In addition, we have found a significant correlation between both cytokines with PI, HOMA-IR and OGIS (IL-6: r=0.456; r=0.400, r= -0.441, p<0.01, TNF-alpha: r=0.474; r=0.390, r=-0.607, p<0.01 respectively), among diabetics.
Conclusion: Our results have demonstrated that hypertension in overweight T2D patients is associated with increases in insulin resistance and changes in adipo- and pro-inflammatory cytokine levels. However, decreased levels of adiponectin were linked more with insulin resistance and T2D than with hypertension, while increases in both: leptin and IL-6 levels stronger influence the presence of hypertension in overweight T2D patients.

A CROSS-TALK BETWEEN METABOLIC SYNDROME AND ALZHEIMER'S DISEASE: POSSIBLE UNDERLYING MECHANISMS

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Background and aims: There is growing body of epidemiological evidence suggested that metabolic syndrome (MetS) and Mets components may be important in the development of Alzheimer's disease (AD), most common form of age-related non vascular dementia. Previous studies have suggested that decreased insulin sensitivity and dyslipidemia are consistently indicated as essential in the pathophysiology, and possibly the pathogenesis of AD. On the other hand, the study on the large autopsy series have demonstrated that individuals with cardiovascular disease (CAD) often have demonstrable AD-like Ab (amiloid) deposits within neurons in the brain and that cerebral atherosclerosis is strongly associated with an increased frequency of neuritic plaques. As CAD and MetS have been linked to changes in cholesterol profiles, many studies have tried to characterize the relationships between cholesterol metabolism, MetS and AD, but they produced conflicting results. So, the aim of this study was to analyze in patient with AD the levels of (a) insulin sensitivity (IS), (b) plasma insulin (PI), (c) waist circumference (Wsc) and (d) lipid parameters comprising total cholesterol (Ch),

low-density (LDL) and high density (HDL) Ch, triglycerides and apolipoproteins (apoAI, apoAII, apoB, Lp(a) and apoE) potentially involved the pathogenesis of the disease.
Patients and methods: In the study we included 40 normoglycemic non obese patients with AD (group A; BMI: 23,76 +/- 0.83 kg/m^2, mean age of 71,25+/-8,71 years) and 40 matched controls (group B; BMI: 24,43 +/- 0,68 kg/m^2, mean age of 68,53+/-7,85 years). IS was evaluated by using euglycemic hyperinsulinemic clamp technique with insulin infusion rate of 1 mU/kgbw/min during 120 min. PI levels were determined by radioimmunossay and PG levels by glucose oxidase method. Wsc measurement is done in a standing position at the level of the umbilicus. Total cholesterol, HDL-Ch, and triglycerides levels were determined by using enzymatic method, and LDL-Ch was calculated using the formula of Friedewald. Apolipoproteins ApoAI, ApoAII, Lp(a), ApoB and ApoE were determined by using nephelometry method.
Results: We found that total glucose uptake was significantly lower in group A compared to group B (6,43 +/- 0,62 vs 8,15 +/- 0,38 mg/min/kg, p<0.01). In addition, basal PI levels were higher in group A compared to group B (15,59 +/- 2,13 vs 7,52+/-1,04 mU/l, p<0.01), while basal PG levels did not differ between the groups. Also, Wsc did not differ significantly between the groups in both gender. Moreover, the levels of total Ch and LDL-Ch were significantly higher in group A in comparison to group B (6,45 +/- 0,25 vs 5,75 +/- 0,21; 4,43 +/- 0,17 vs 3,55 +/- 0,16 mmol/l, respectively, p<0.01), while the HDL-Ch levels were significantly lower in group A than in group B (1,20 +/- 0,06 vs 1,41 +/- 0,33 mmol/l, p<0.01). In addition, the levels of ApoAI were significantly lower in group A in comparison to group B (1,497+/-0,062 vs 2,031+/-0,036 g/l, p<0.01), while the levels of triglycerides and other apolipoproteins (ApoAII, ApoB, Lp(a) and ApoE) did not differ significantly between the groups.
Conclusions: Our results have demonstrated that the presence of AD in normoglycemic patients was associated with decreased IS and increases in peripheral insulin levels. Moreover, our results has been suggested overlap in patogenic influence of factors like insulin resistance and abnormal cholesterol metabolism, especially the increases in LDL-Ch, decreases in HDL-Ch and ApoAI levels in cognitive decline, which emphasise that vascular risk factor management could be decisive in delaying the onset of dementia syndromes or in preventing the progression of predementia syndromes.

WAIST INDEX IS THE BEST SURROGATE MARKER FOR INSULIN RESISTANCE IN ADULTS WITH TYPE 2 DIABETES MELLITUS

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Background: Insulin resistance is an important predictor of increased cardiovascular morbidity and mortality in the general population as well as in subjects with type 2 diabetes mellitus. It can be assessed using complex reference techniques, such as

clamp or frequently sampled intravenous glucose tolerance test. Alternatively, insulin resistance can be estimated using simple indices derived from fasting insulin and glucose concentrations. Nonetheless, insulin levels are not widely measured in routine clinical practice. The aim of the present study was to assess how markers of central obesity, atherogenic dyslipidaemia and vascular dysregulation are associated with insulin resistance in adults with type 2 diabetes mellitus.

Methods: This cross-sectional study included 194 patients (112 male, 82 female) with type 2 diabetes mellitus of mean ± standard deviation (SD) age 64.8 ± 9.8 years, diabetes duration 18.4 ± 9.4 years, body mass index (BMI) 31.7 ± 5.4 and waist index (WI) 1.19 ± 0.17. All subjects were tested for fasting glucose and insulin levels and fasting lipid profile. Correlation anaylses of fasting plasma insulin, fasting glucose to insulin ratio (FGIR), fasting glucose insulin product (FGIP), homeostatic model assessment (HOMA-IR) and quantitative insulin check index (QUICKI) to BMI, WI, triglyceride levels, 1/ high-density lipoprotein (HDL) and triglyceride/HDL were performed. Logarithmic transformation was performed when variables were not normally distributed. Linear regression analysis was consequently performed to identify independent predictors of the various indices of insulin resistance mentioned above. Furthermore, the sensitivity and specificity of metabolic syndrome (according to the definition of the International Diabetes Federation) was also estimated. Statistical analysis was performed with SPSS version 21.0.

Results: In the study population, WI correlated more strongly with log insulin levels (r=0.435, P<0.001), log FGIR (r=-0.381, p<0.001), log FGIP (r=0.449, p<0.001), HOMA-IR (r=0.449, p<0.001) and QUICKI (r=-0.457, p<0.001) than did any other index. In linear regression analysis, WI also emerged as the strongest independent predictor of all the insulin indices studied. Thus significant predictors of log insulin were WI (B=1.377, 95% CI 0.98-1.771, p<0.001) and log1/HDL (B=0.711, 95% CI 0.195-1.228, p=0.007), of log FGIR were WI (B= -1.257, 95% CI -1.687- -0.828, p<0.001), log 1/HDL (B= -0.674, 95% CI -1.249 - -0.098, p=0.022) and log uric acid (B= -0.508, 95% CI -0.971- -0.044, p=0.032), and of log FGIP were WI (B=1.412, 95% CI 0.993-1.832, p<0.001) and log triglyceride/HDL (B=0.257, 95% CI 0.014-0.5, p=0.038). Similarly WI and log triglyceride/HDL were found to be independent predictors of log HOMA-IR (WI: B=1.412, 95% CI 0.993-1.832, p<0.001, and log triglyceride/HDL 0.257, 95% CI 0.014-0.5, p=0.038) and log QUICKI (WI: B= -0.203, 95% CI -0.262- -0.144, p<0.001, and log triglyceride/HDL: B=-0.036, 95% CI -0.07- -0.001, p=0.042). Furthermore, when ROC analysis was performed to assess whether WI, triglyceride/HDL levels or the product of WI and triglyceride is the best indicator of insulin resistance, WI was again the strongest indicator. When HOMA-IR was used as indicator of insulin resistance, a cut-off of 1.11 for WI exhibited 79% sensitivity and 60% specificity for predicting insulin resistance (area under Curve (AUC) 0.796 (95% CI 0.734-0.859), p <0.001). Similarly, when QUICKI was used as indicator of insulin resistance, a cut-off of 1.11 for WI showed 75% sensitivity and 67% specificity for predicting insulin resistance (AUC: 0.796 (95% CI 0.730-0.862), p <0.001). WI was also shown to be a better indicator of insulin resistance than the presence of metabolic syndrome; the latter exhibited a sensitivity of 66.27% and specificity of 75% when HOMA-IR was used as indicator of insulin resistance, while a sensitivity of 77.71% and specificity of 53.71% was shown when QUICKI was used as indicator of insulin resistance.

Conclusion: In subjects with type 2 diabetes mellitus of long duration, waist index was shown to be the best predictor of insulin resistance with a cut-off of 1.11. Waist index is an easily measurable and reproducible parameter in clinical practice and should thus be assessed regularly in the management of diabetic subjects.

PROGNOSTIC INDICATORS OF TEN-YEAR AND TWENTY-YEAR MORTALITY FOLLOWING ACUTE CORONARY SYNDROME

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Background: Diabetes mellitus (DM) is a well-established cardiovascular risk factor and adverse short-term prognosticator following acute coronary syndrome (ACS). However, there is little long-term mortality data following ACS and its relation to DM. The objective of this study was to identify independent predictors of mortality at 10 years and 20 years following admission with ACS and its relation to DM and other patient characteristics at baseline.
Methods: Patients who were hospitalized with ACS from December 1990 till June 1994 were recruited. Baseline data were recorded and patients were followed up through 31st December 2012 to assess their mortality rates. Univariate analysis followed by Cox regression analysis was performed to identify independent predictors of mortality at 10 and 20 years. Variables were entered into the regression model if their p value was <0.1 in univariate analysis. All data were analysed using SPSS version 21.0.
Results: The study followed 881 patients (mean age 64.3 years, 66.2% men) for 10 years and 712 patients (mean age 65.8 years, 64.3% men) for 20 years. Using Cox regression analysis, 10- year all-cause mortality was associated with age (hazard ratio (HR) 1.077, 95% confidence interval (CI) 1.055-1.099, P<0.001) and DM at baseline (HR 2.475, 95% CI 1.733-3.546, P<0.001). Similar results were obtained for 10- year cardiovascular disease (CVD) mortality whereby both age (HR 1.089, 95% CI 1.065-1.115, p<0.001) and DM at baseline (HR 2.801, 95%CI 1.876-4.184, p<0.001) were significant predictors, while age (HR 1.077, 95%CI 1.045-1.110, p<0.001), DM at baseline (HR 1.949, 95% CI 1.145-3.322, p=0.014) and presence of proliferative diabetic retinopathy (HR 2.858, 95%CI 1.27-6.435, p=0.011) were associated with 10-year cardiac mortality. With regards subjects who were followed up for 20 years, all-cause mortality was associated with ST-elevation myocardial infarction (STEMI) in the index admission (HR 1.631, 95% CI 1.333-1.938, p<0.001), age (HR 1.056, 95% CI 1.044-1.069, p<0.001), and DM at baseline (HR 1.594, 95% CI 1.304-1.949, p<0.001) using Cox regression analysis. Twenty-year CVD mortality was associated with STEMI in the index admission (HR 2.717, 95% CI 1.515-4.878, p=0.001), age (HR 1.071, 95% CI 1.047-1.096, p<0.001), DM at baseline (HR 2.326, 95% CI 1.466-3.69, p<0.001), baseline creatinine phosphoskinase (CPK) (HR 1.001, 95% CI 1.00-1.002,

p=0.03) and total cholesterol levels (HR 1.003, 95% CI 1.001-1.005), while 20-year cardiac mortality was associated with STEMI in the index admission (HR 1.763, 95% CI 1.34-2.326, p<0.001), male gender (HR 1.362, 95% CI 1.045-1.775, p=0.022), age (HR 1.063, 95%CI 1.046-1.08, p<0.001), DM at baseline (HR 1.658, 95% CI 1.276-2.155, p<0.001) and history of coronary artery disease (HR 1.473, 95% CI 1.11-1.953, p=0.007).

Conclusions: In this cohort of ACS patients with very long follow-up period, the occurrence of DM emerged as an independent and significant predictor of 10-year and 20-year all-cause, CVD, and cardiac mortality. These data further substantiate the importance of targeting good glycaemic control not only for short-term prognostic benefit but more importantly for long-term increased survival. Risk equation models will ensue to quantify the mortality risk attributed with presence of DM.

INSULIN RESISTANCE AND INFLAMMATORY MARKERS IN TYPE 2 DIABETICS AND NONDIABETICS: COMPARISON BETWEEN PATIENTS WITH TRANSIENT ISCHEMIC ATTACK AND ISCHEMIC STROKE

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Background and aims: Previous studies have shown that insulin resistance (IR) and inflammation have important role in atherosclerosis progression, but their effect on occurrence of cerebral ischemic events with different intensity, transient ischemic attack (TIA) or ischemic stroke in type 2 diabetics (T2D) and nondiabetics, has not yet been elucidated. Our study was aimed to analyze (a) IR and plasma insulin (PI) (b) inflammatory markers, hs-C reactive protein (hs CRP) and interleukin-6 (IL-6) levels in T2D patients and nondiabetics with TIA or with ischemic stroke.

Material and methods: The study groups were included 26 T2D patients with TIA (group A), 30 T2D with ischemic stroke (group B), 22 nondiabetics with TIA (group C) and 28 nondiabetics with ischemic stroke (group D). TIA and ischemic stroke was confirmed by duration of neurological sings and simptoms, and neuroimaging criteria. IR was determined by 2 complementary methods: homeostasis assesment model (HOMA-IR) and frequently sampled intravenous glucose tolerance (FSIGT) test with minimal model analysis (Si index). PI levels were determined by RIA. Hs-CRP was determined by Olympus Analyzer and interleukin 6 (IL-6) levels were measured by ELISA method.

Results: We found that HOMA-IR was significantly higher while Si levels were significantly lower in group B compared to A (7.98±0.32 vs 4.92±0.20, 1.00+/-0.32 vs 1.77+/-0.70 $min^{-1}/mU/lx10^4$; p<0.05) and in group D compared to C, respectively (3.67 ± 0.15 vs 2.42±0.12, 2.66+/-0.40 vs 3.80+/-0.65 $min^{-1}/mU/lx10^4$; p<0.05). PI levels were higher in group B than in group A (23.12+/-1.62 vs 16.04+/-0.68 mU/l; p<0.01) and in group D compared to C

(19.22+/-8.76 vs 12.06+/-2.31 mU/l; p <0.001). Simultaneously, hs CRP and IL-6 levels were significantly higher in B vs A (17.35±2.98 vs 10.22 ±1.89 g/l p<0.05; 22.24±4.00 vs 15.92+/-5.56 pg/ml p<0.05) and D vs C (6.93±0.78 vs 2.44±0.38 g/l p<0.01; 10.89±5.98 vs 3.05+/-1.40 pg/ml, p<0.01).

Conclusion: Our results signify that onset of ischemic stroke in comparison with TIA was strongly associated with pronounced IR and increased PI levels both in T2D patients and nondiabetics. The results imply that IR and compensatory hyperinsulinemia might exert their atherogenic influence in severity of occurrence of ischemic cerebrovascular event through the low grade inflammation.

THE BENEFICIAL EFFECT OF RANOLAZINE ON CARDIAC FUNCTION AFTER MYOCARDIAL INFARCTION IS GREATER IN DIABETIC THAN NON-DIABETIC RATS

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Objectives: Ischemic heart disease is a common co-morbidity of patients with type II diabetes mellitus (DM). Ranolazine (RAN), an inhibitor of late sodium current, is known to exert both anti-ischemic and anti-diabetic actions. Based on these dual beneficial effects of ranolazine, we hypothesized that the drug would have greater cardioprotective effects in diabetic than non-diabetic rat hearts following myocardial infarction (MI).

Methods: MI was induced in non-diabetic (MI, n=14) and diabetic (streptozotocin induced) (DM-MI, n=13) Wistar rats by permanent ligation of the left coronary artery. Cardiac function was evaluated at 4 weeks post-MI in anesthetized rats using echocardiography (ejection fraction, LVEF%) and in isolated heart preparations by measuring LVDP and ±dp/dt.RAN (20 mg/kg, i.p.) was administered for 4 weeks after MI to non-diabetic (MI+RAN, n=17) and diabetic rats (DM-MI+RAN, n=15). The ratio of wet lung weight to body weight was used to assess pulmonary congestion.

Results: RAN improved LVEF% in both non-diabetic and diabetic animals but this effect was greater in the DM-MI+RAN group (table). In isolated perfused hearts, improvements in LVDP and –dP/dt were also greater in DM-MI+RAN group.A marked reduction in pulmonary congestion was observed in DM-MI+RAN group (table). RAN increased insulin levels from 3.1±0.4 ng/ml in DM-MI to 5.5± 0.5 in DM-MI+RAN(p<0.05) and reduced serum glucose levels from 142 ± 6.7 mg/dL in DM-MI to 118 ± 4.0 in DM-MI+RAN(p<0.05). Thus, RAN resulted in 1.6 fold increase in Akt activation and 2.0 fold increase in mTOR and AMPK activation in the diabetic MI hearts. This response was associated with reduced accumulation of myocardial glycogen (7.9 ± 0.5 μmol/g in DM-MI+RAN vs. 10.2 ±0.5 in DM-MI, p<0.05), and a 2.3 fold increase in the ratio of SERCA/ Phospholamban expression in the myocardium.

	Non-diabetic	Diabetic				
	MI	MI+RAN	% Change	DM-MI	DM-MI+RAN	% Change
LVEF %	30.5 ± 1.7	38.1± 1.8#	24.9%	32 ±1.5	41 ±1.4 *	28.1%
LVDP (mmHg)	57 ±6.5	78±7.2	53%	54 ±7.3	87 ±3.3 *	69%
+dP/dt (mmHg/sec)	1940±243	2280±200	19%	1808±320	2818±144	60%†
-dP/dt (mmHg/sec)	1110 ±144	1541 ±132	38%	1056 ±143	1712 ±74 *	71%†
Pulmonary Congestion (%)	28%	18%	35.7%	53.8%	20%*	62.8%†

Values are Mean ± SEM.# p=0.07 vs MI, *p<0.05 different from DM-MI,†p<0.05 vs. % change in non-diabetic rats. LVEF, left ventricular ejection fraction; LVDP, left ventricular developed pressure; +dp/dt, rate of increase of LVDP; -dp/dt, rate of decrease of LVDP

Conclusion: The beneficial effect of ranolazine on cardiac function after myocardial infarction is greater in diabetic than non-diabetic rats. This response was associated with insulin-regulated Akt/mTOR activation and activation of AMPK. These data provide a possible explanation of the results of the recently published TERISA trial, indicating a better effect of RAN in patients with DM and coronary artery disease (CAD).

CORONARY MICROVASCULAR RESPONSE TO A COLD-PRESSOR TEST AND DIASTOLE DURATION IN ASYMPTOMATIC TYPE 2 DIABETIC PATIENTS

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Background and aims: The cold-pressor test (CPT) by inducing sympathetic stimulation and a subsequent rise in myocardial oxygen demand induces an increase in coronary blood flow and a dilation of normal epicardial coronary arteries. Coronary perfusion is enhanced during diastole. The aim of this study was in type 2 diabetic patients (T2Ds) to examine the influence of diastole duration (DD), which depends on heart rate and presumably autonomic activity, on the coronary response to CPT measured with a non invasive method based on trans-thoracic echography-doppler (NCT00685984).

Materials and methods: We prospectively screened 118 T2Ds, without any cardiac history and fulfilling the criteria of the French guidelines, for silent myocardial ischemia (SMI: abnormal stress myocardial scintigraphy and/or echocardiography). The distal inter-ventricular anterior coronary velocity (CV) was measured by trans-thoracic echo-

doppler before and after CPT (two hands immersed in crushed ice for 120 s). Left ventricle DD was measured from tissue doppler images at mitral annulus using the formula [RR interval – (ejection time + isovolumetric contraction time)], and the percentage of DD was calculated [DD% = (DD/duration of heart period) x100].
Results: Both CV before and after CPT and DD% could be measured reliably in 34 T2Ds, 21 with SMI and 13 without. Before CPT, DD% correlated negatively with heart rate (r=-0.451, p=0.008) and did not correlate with CV. DD% before CPT correlated with CV changes, *i.e.* related to microcirculation (r=0.394, p=0.02) and with rate-pressure product changes (r=0.395, p=0.02) during CPT whereas CV changes did not correlate with heart rate before CPT. In multivariate analysis CV changes were associated with DD% (p=0.01) independently from rate-pressure product changes and SMI status.
Conclusion: In T2Ds the changes of coronary velocity during sympathetic stimulation induced by CPT depend mostly on basal DD. A shorter DD that may indicate a higher basal sympathetic tone seems to reduce the positive effect of further sympathetic stimulation on the microcirculation. These data afford an additional argument in favor of the role of cardiac autonomic activity on coronary microcirculation.

ANKLE – BRACHIAL INDEX IN TYPE 2 DIABETES PATIENTS AND CARDIOVASCULAR RISK

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Purpose: The ankle – brachial index (ABI), i.e. the ratio of systolic blood pressure (SBP) measured on the ankle and on the arm, is considered the diagnostic parameter for the peripheral occlusive artery disease and the marker of cardiovascular (CV) risk. We measured ABI in patients with type 2 diabetes (DM2) and evaluated its impact on the CV risk.
Method: A sample of 253 DM2 patients (135 males, 118 females, average age 66 ± 9 y.) was examined. The supine ankle SBP was measured with the Doppler ultrasonography sond after a 5 minutes rest, with the 2 mmHg accuracy, SBP on the identical arm was measured the same way with the same accuracy by the mercury sphygmomanometer. The ABI < 0,9 suggests the arterial occlusion, on the contrary the ABI ≥1,2 is nondiagnostic and suspected of mediocalcinosis. The CV risk was evaluated according to up-to-date guidelines; as the high risk patients were considered the patients with manifested CV diseases (information from the patients´ documentation), with elevated coronary calcium score (CAC) evaluated by the Agatston´s score (101-400 high risk, ≥401 very high risk) or according to the global CV Risk Score ≥ 5%. Used statistical method: Wilcoxon´s unpaired test, $\chi 2$ test, Spearman´s correlation, multiple logistic regression.
Results: The ABI < 0,9 was found unilateral in 20 DM2 (8 %), bilateral in 27 (11 %), thus the ABI was decreased in 47 (19 %) DM2. Other 168 DM2 (66%) showed the normal ABI and

38 (15 %) the nondiagnostic ABI. There was no significant difference in the characteristics of DM2 patients with the normal and the nondiagnostic ABI. The DM2 patients with the ABI ≤ 0,9 compared to the rest of the sample were older males with elevated total cholesterol, total homocystein and CAC and with the history of CV diseases. Many CV and metabolic risk factors correlated significantly positively with ABI < 0,9: age, glycaemia, total homocystein, CAC ($p < 0,05$), LDL-cholesterol ($p < 0,01$) and SBP ($p < 0,01$). The ABI < 0,9 was significantly and independently associated with age ($p < 0,001$), smoking ($p < 0,01$), LDL-cholesterol, total homocystein and CAC ($p < 0,05$). The decreased ABI was a strong significant predictor of ischemic stroke and symptomatic carotid stenosis for the next 3 years ($p < 0,001$). The ABI < 0,9 correlated significantly neither with ultrasensitive C-reactive protein nor with presence of the metabolic syndrome in DM2.
Conclusion: Decreased ABI < 0,9 was found in 19 % of DM2 patients. It was in a significant and independent association with age, smoking, LDL-cholesterol, total homocystein and CAC. We evaluated ABI < 0,9 as a strong predictor of ischemic stroke and symptomatic carotid artery stenosis. That is why these patients need an individual, complex and intensive intervention. Nondiagnostic ABI values were found in 15 % of the sample; a high prevalence of mediocalcinosis in DM2 patients is suspected.

MELATONIN INHIBITS CARDIAC APOPTOSIS IN EXPERIMENTALLY-INDUCED DIABETES MELLITUS VIA AMELIORATION OF OXIDATIVE STRESS, INHIBITION OF CASPASE-3 ACTIVATION AND BY REGULATING ANTI-APOPTOTIC PROTEIN LEVELS

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Background and aims: Hyperglycemia induces various cardiovascular complications, which have become the main cause of morbidity and mortality in the diabetic population. Diabetes and its complications are associated with increased oxidative stress. Cell death, as a major result of myocardial abnormalities, is an important cause of various cardiomyopathies. Recent studies showed that the incidence of apoptosis increases in the heart of diabetic patients and STZ-induced diabetic animals. Hyperglycemia induced myocardial apoptosis is mediated, at least in part, by activation of the cytochrome c–activated caspase-3 pathway, which may be triggered by reactive oxygen species (ROS) derived from high levels of glucose. A correlation between ROS generation and the pathogenesis of various diabetic complications has been observed. Therefore, it is possible that ROS accumulation occurs in diabetic myocardium, in which apoptosis may take place and lead to cardiomyopathy. At this point, melatonin seems unique among several antioxidants because of its physical and chemical properties, allowing it to easily cross biological membranes and reach the cytosol, nucleus, and mitochondria. Consequently, the present study was designed to investigate the effects of melatonin treatment against Diabetic-induced cardiac death in experimentally induced DM.
Materials and methods: Experimental T2DM was induced in male rats by a single ip

injection of 50 mg/kg streptozotocin. All experimental groups received the melatonin orally and individually at a dose of 10mg/kg/day.
Results: Diabetic rats showed a significant ($p < 0.05$) decrease in serum insulin level, hyperglycemia, elevated HBA1c and altered lipid profile. Concurrent with these changes, there was an increase in the concentration of the oxidative stress markers in the heart. In addition, increased apoptosis with downregulation of Bcl-2 and activation of caspase-8 and caspase-3 were demonstrated. The treatment with melatonin ameliorated hyperglycemia-evoked heart oxidative stress through modulating the levels of glutathione, superoxide dismutase and catalase as well as malondialdehyde concentrations in heart. The treatment of diabetic rats with melatonin protected myocytes viability as evidenced by the significant increase in viable cells associated with a significant decrease in apoptotic and necrotic cells compared to diabetic rats. Melatonin also controlled Bcl-2 expression and decreased the activation of caspase-8&3.
Conclusion: Melatonin normalized apoptotic regulating proteins and consequently protected myocytes against apoptosis. These data suggest that melatonin attenuated steps in the mitochondrial apoptotic pathway through its redox control properties. Thus, melatonin may be a promising pharmacological agent for preventing the potential cardiotoxicity associated with diabetes.

LIPOPROTEIN (a) IN PATIENTS WITH DIABETES AND PERIPHERAL ARTERIAL DISEASE

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Background: Several cross-sectional, case-control and cross- sectional cohort studies have found an association between elevated Lp(a) levels and PAD in various populations, and one prospective longitudinal observational study found Lp(a) to be an independent predictor of progression of PAD (as determined by a decrease in ABI over 4.6 ± 2.5 years). In contrast to this results The Physicians's Health Study did not find Lp(a) levels to be predictive of symptomatic PAD.
Aim: to determine the importance of Lp (a) in patients with PAD type 2 diabetes.
Methodology: the study included 80 patients, nonsmokers with type 2 diabetes and disease duration of 8 ± 2 years, 47.5% with PAD, group A, and 52.5% without a PAD, group B. Edimburgh claudication questionnaire, and Anle-Brachial Index (ABI) measurement have been used for PAD diagnosis. Lp (a) have been analyzed by nephelomery.
Results: the average age of examined patients in group A and group B was comparable (64.6±6 vs. 62.7±7 yrs, p=0.358). The average diabetes duration of 8±2 years was the same in both groups. Similar number of examined patients in group A and group B had hypertension (78.9% vs. 69.6%, p=0.315). Claudication was more frequent in group A than in group B (60.6% vs. 28.6%, p=0.004). After five years of follow up we found that 21.05% of patients in group A have progression of PAD (subgroup A1), while 52.38% of patients

in Group B have developed PAD (subgroup B1). When compared Lp(a) values between group A and B no difference have been found at the begining of examination as well as at the control exam (0.30±0.35 vs. 0.23±0.22, p=0.31; 0.30±.36 vs. 0.23±0.21, p=0.26). When compared Lp(a) values in subroups A1, A2, B1 and B2 there was no difference also (A1 vs A2: 0.29±0.73 vs 0.31±0.38, p=0.89; 0.29±0.25 vs. 0.30±0.381, p=0.97), (B1 vs. B2: 0.23±0.20 vs. 0.23±0.21, p=0.97; 0.23±0.19 vs. 0.23±0.27, p=0.97). Finally when compared patients who had or developed PAD (subgroups A1, A2 and B1, n=60) with those who did not have nor have developed PAD in this five years follow up (subroup B2, n=20), no difeerence in Lp(a) values have been found also (0.28±0.31 vs. 0.23±0.21, p=0.54; 0.28±0.30 vs. 0.24±0.27, p=0.59). The ROC analysis for Lp (a) between subgroups A1, A2, and B1 versus subrop B2 (AUC= 0.49, SE=0.07, 95%CI=0.35-0.63, p=0.89), and logistic regression analysis (B=0.53, Exp(B)=1.69, 95%CI=0.08-34.55, p=0.73), confirmed that Lp(a) value could not be used as a predictor for PAD.

Conclusion: Alhough patients who did not have and who did not develop PAD had the lowest Lp(a) values, considering the complexity of atherosclerotic vascular disease, we conclude that Lp(a) could not be used as a single marker for significant predictive or prognostic information for PAD in patients with type 2 diabetes.

»HYPERTRIGLYCERIDEMIC WAIST« PHENOTYPE IN DIABETIC PATIENTS: RELATIONSHIP WITH OXIDIZED LDL AND INSULIN RESISTANCE

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Background and aim: The excess of cardiovascular events observed in patients with type 2 diabetes (T2D). It was reported that "hypertriglyceridemic waist" (HW) phenotype (abdominal obesity defined by the presence of waist girth ≥90cm in men and ≥85cm in women, simultaneously with plasma triglycerides (Tg) concentration ≥2mmol/l) could be a good predictor of increased risk for coronary atherosclerosis. Also, oxidized LDL (oxLDL) levels were found to be another important risk marker for atherosclerosis. The aim of our study was to analyze the relationship between the levels of oxLDL, insulin resistance (IR) and other related metabolic risk factors in patients with HW phenotype and T2D.

Material and methods: The following groups of patients were included in the study: T2D patients with abdominal obesity and Tg≥2mmol/l (Group A, N=30), T2D with abdominal obesity and Tg<2mmol/l (group B, N=30), T2D patients without abdominal obesity and Tg≥2mmol/l (group C, N=25) and T2D patients without abdominal obesity and Tg<2mmol/ (group D, N=25). Patients were aged 40-70 years, matched by gender, duration of diabetes, smoking habit and hypertension. OxLDL levels were measured by ELISA methods (Mercodia), total cholesterol (TCh), HDL-Ch, LDL-Ch and TG by enzymatic

methods, glycated hemoglobin levels (HbA1c) by immuno-inhibition and insulin resistance was evaluated by homeostasis model assessment (HOMA-IR).
Results: We found that the levels of oxLDL were the highest in the group A and were significantly higher compared to group B, C and D (A: 117.2±22.0; B: 105.9±10.2; C: 100±9.7; D: 79±5.4IU/l, AvsB, C, D p<0, 01). Simultaneously, the HOMA-IR values were significantly higher in groups with abdominal obesity, A and B (9.3±1.8 and 7.1±1.5 Avs B p=NS) in comparison to groups without abdominal obesity, C and D (4.7±1.0 and 2.4±0.4; C vs D p=NS, A vs C: p<0.05; B vs D: p<0.01). There were no differences in the levels of TCh, HDL-Ch and LDL-Ch, as well as in the HbA1c level between the groups. However, the ratio TG/HDL were increased both in groups A and C (A: 3.5±0.8 and C: 2.19± 0.9) being higher than in groups B and D (B: 1.35±0.5. and D: 1.22±0.3; A,C vs B,D: p<0.05, A vs C p<0.01 B vs D p=NS). We found significant correlation of HOMA-IR with TG level (r=0.376, p<0.05), also with TG/HDL ratio (r=0.405, p<0.01) and with increased oxLDL (r=0.535, p<0.01). To adjust for potential confounders, we did multivariate regression models and we found that correlation is dependent of waist girth (R^2 0, 88).
Conclusion: Our results have shown that in T2D patients with HW phenotype atherosclerotic risk has been associated with higher IR, increased oxLDL levels as well as with higher TG/HDL ratio.

ALTERED CELLULARITY AND COLLAGEN CONTENT IN THE ADVENTITIAL AND MEDIAL LAYERS OF THE INTERNAL MAMMARY ARTERY AMONG PATIENTS WITH TYPE 2 DIABETES

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Background: As an element of the normal aging, arterial stiffness occurs. This is believed to be caused by accumulation of collagen and degradation of elastin. Arterial stiffening is accelerated among patients with diabetes, and this phenomenon is believed to partly explain the increased incidence of cardiovascular diseases. If increased arterial stiffening is due to accumulation of collagen or degradation of elastin in the arterial wall in diabetes has not been examined in human arteries. Moreover, changes in arterial matrix and remodeling could be due to altered cellular content of the arterial wall. We hypothesized that the arterial amount of collagen and elastin, and putatively also the number of vascular cells are changed in type 2 diabetes in areas of the vessel wall without atherosclerosis.
Methods: Internal mammary arteries (repair arteries) were collected from coronary bypass operations from 32 patients with diabetes and 32 patients without diabetes, formalin-fixed, and paraffin-embedded. The groups were matched according to age, gender, and blood pressure. Every patient was treated with statins and all tissue was

without atherosclerotic lesions. The paraffin blocks were cut and stained for macrophages (CD68), elastin (Weigert), collagen (Masson trichrome), and smooth muscle cells (SMC α-actin). Three areas of the vascular wall were investigated: intima, media, and adventitia. The area fraction for collagen and elastin and the number of smooth muscle cells were determined by histomorphometric software.

Results: There were no infiltrations of macrophages in any arterial layer in either patient group. Counting of smooth muscle cells revealed significantly fewer smooth muscle cells in the adventitia of patients with diabetes vs. patients without diabetes (5*10-4cells/mm2 vs. 8*10-4cells/mm2, $P<0.05$). There were no altered cellularity in media and intima in diabetes. The masson trichrome staining showed that the diabetic group had a larger volume fraction of collagen in the intima and media layer than the control group ($P<0.05$). No differences in the volume fraction of elastin were observed, and there was no change in the number of breaks of elastica interna in patients with diabetes than in non-diabetic patients.

Conclusion: There were fewer smooth muscle cells in the adventitia layer and more collagen in media and intima among patients with type 2 diabetes than among patients without diabetes 2. No gross changes in diabetes were, however, observed when elastin amount and elastic membrane breaks were considered.

METFORMIN AND MYOCARDIUM: ARE THEY FRIENDS?

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Background and aims: Numerous studies revealed that hyperglycaemia and insulin resistance are strongly involved in the development and progression of myocardial impairment, from asymptomatic left ventricular dysfunction to heart failure. Diabetic cardiomiopathy (DC) is an early complication of type 2 diabetes (T2D), defined as left ventricular diastolic dysfunction (LVDD) in the absence of hypertension or other cardiovascular disease. Recent studies suggest that metformin improves myocardial function and reduces cardiovascular mortality in T2D patients. The aim of the study was to determine the influence of antihyperglycaemic treatment (metformin alone/plus other treatment) on the development of DC.

Design and methods: We investigated 78 T2D patients, without hypertension and coronary artery disease. They underwent high-resolution transthoracic echocardiography including tissue Doppler and exercise stress-echocardiography. LVDD was diagnosed when E/E' ratio (early mitral valve flow velocity/early diastolic lengthening velocity) was ≥15. If E/E' ranged from 8-15, higher values of one of the additional diagnostic criteria were required.

Results: DC was detected in 10.3% of the study group. Patients with DC used metformin less frequently in comparison to patients without DC (χ=10.786; p=0.001). Metformin therapy was identified as statistically significant (p=0.016) by univariant, and furthermore, as independent predictor of DC, using multiple linear regression analysis (p= 0.002).
Conclusion: Patients with DC used metformin less frequently. Furthermore, less frequent use of metformin therapy was recognized as independent predictor of DC. These results, as well as the results of other investigations, emphasize that metformin, by ameliorating insulin resistance improves myocardial function in patients with T2D.

COULD HEALTH RELATED QUALITY OF LIFE HELP IN ADOPTING LIFE STYLE?

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Background: The worldwide epidemic of obesity has influenced the explosion of diabetes and its precursors, impaired fasting glucose (IFG) and impaired glucose tolerance (IGT). The Finnish diabetes prevention study (DPS) and its follow-up study confirmed that one can prevent diabetes or at least postpone it with intensive life style changes.[1,2] Also in general practice setting minor life style changes had beneficial influences on the risk of diabetes.[3]
What are the means by which we can permanently change our ways of living? Health related quality of life means different things to different people. Also a seriously ill person can feel his/her quality of life well although the disease could be incurable if he/she is adapted to the situation.[4] The situation may be the same with significantly obese people. They have adapted obesity and it is difficult to give up the pleasant things connected to overweight. On the other hand, good things that have been left out of life because of obesity may have lost their significance.
Methods: We examined health related quality of life in a population study carried out in Western Finland in 2005- 2006. The 1469 subjects were 45-70 years old and had at least one cardiovascular risk factor but no long-lasting diseases. A study nurse measured all subjects' waist circumference, weight, height and blood pressure. Laboratory tests were determined with blood tests obtained after 12 hours fasting. Oral glucose tolerance test (OGTT) was performed. Study subjects filled extensive questionnaire concerning sosiodemographic factors, employment status, smoking, physical activity, depressive symptoms and health related quality of life with Short Form-36, SF-36, questionnaire.[5]
Results: Of the study subjects, 1383 filled the questionnaires adequately. Their mean age was 57.7±6.9 years, 57% were women. According to OGTT 11% had IFG, 12% had IGT and 7% had new type 2 diabetes (NDM). Body mass index (BMI) increased so that it was 28.0 kg/m^2 with normal glucose tolerance group, 28.8 kg/m^2 with IFG group, 29.6 kg/m^2 with IGT group and 32.9 kg/m^2 with NDM group (p=<0.001). Prediabetes didn't influence health related quality of life. Subjects with NDM had significantly worse scores in physical functioning, general health and emotional role than other study groups.

Conclusion: Our results suggest that people with NDM experienced poor physical functioning limiting their everyday physical life. Their general health had deteriorated and emotional problems restricted their working and family life. On the basis of this cross-sectional study it cannot be confirmed whether these results depend only on diabetes or on life style. There are, however, other studies in which it is confirmed the fact that impaired glucose tolerance deteriorates health related quality of life.[6,7,8]

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APOLIPOPROTEIN B IS A BETTER MARKER OF CARDIOVASCULAR RISK THAN LDL CHOLESTEROL IN PATIENTS WITH TYPE 2 DIABETES AND ACUTE MYOCARDIAL INFARCTION

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Background and aims: Studies have shown that in patients with type 2 diabetes (T2D), acute myocardial infarction (AMI) is often more severe, and is associated with poor prognosis. Disorders of lipid metabolism may play an important role in this connection,

especially disorders of LDL particles, but the detailed mechanisms are still not clear. The aim of this study was to explore the association between the changes in lipid parameters: total cholesterol (ch), LDL-ch, HDL-ch, triglycerides (Tg), Tg/HDL-ch ratio as an indicator of LDL particles size and apoliporotein (apo) A-I and B with: (a) the occurrence of AMI in patients with T2D and (b) the level of cardiac enzymes as indicators of the size of the infarct zone in the same patients.
Materials and methods: The study included 20 patients with AMI and T2D (group A) and 40 patients with AMI without T2D (group B) in which at the admission to the coronary care unit total cholesterol level, HDL-ch, Tg where determined (spectrophotometry), as well as levels of apoA-I and B (immunonephelometry) and the levels of creatine kinase (CK) and CK-MB (spectrophotometry). LDL-ch was calculated using Friedewald's formula.
Results: Our results showed that the level of apo B was significantly higher in group A than in group B (1.12 ± 0.06 vs. 0.96 ± 0.05 g / L, P <0.05), while levels of apo A-I had no significant difference between the groups (1.20 ± 0.07 vs. 1.32 ± 0.04 g / L, P> 0.05). At the same time, we found no difference in levels of total cholesterol, its subfractions (HDL-ch and LDL-ch) and Tg comparing the two groups (p = NS). However, the level of Tg/HDL-ch ratio was significantly higher in group A compared to group B (2.60 ± 1.20 vs. 2.10 ± 0.30, P <.05). In addition, we found significantly higher levels of cardiac enzymes, CK (315.50 ± 157.53 vs. 277.10 ± 65.0 U / L, P <0.05) and CK-MB (50.0 ± 22, 63 vs. 34.40 ± 8.43 U / L, P <0.05) in group A compared to group B.
Conclusion: The results indicate that the estimation of LDL particles size (determined by the level of apo B and Tg/HDL ratio) is a better indicator of cardiovascular risk and the size of the infarct zone than LDL-ch in patients with T2D and AIM.

PREDICTING SEVERE COMPLICATIONS IN TYPE 1 DIABETES PATIENTS: DEVELOPMENT AND VALIDATION OF A PREDICTION RULE IN LARGE COHORT STUDIES FROM EUROPE AND THE UNITED STATES

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Background: Type 1 diabetes mellitus is associated with the development of severe complications affecting cardiovascular and peripheral systems, kidneys and eyes. A reliable prediction of complications early in the disease process is of great clinical relevance. We developed a simple clinical prediction rule and studied its external validity.
Methods: Data from 1973 individual patients (52% men, mean age 30 years) with type 1 diabetes from the EURODIAB Prospective Complications Study, a European prospective cohort study with 7 years follow-up. Severe complications included major coronary heart disease (fatal coronary heart disease, non-fatal myocardial infarction, and major Q waves on Minnesota coded ECGs), stroke, end-stage renal failure, amputations, blindness and death. Strong predictive factors of severe complications were selected with Weibull regression analyses. External validity of the prediction rule was assessed in three

prospective cohort studies: the Pittsburgh Epidemiology of Diabetes Complications (EDC, n=554) study, Finnish Diabetic Nephropathy study (FinnDiane, n=3919) and Coronary Artery Calcification in Type 1 Diabetes study (CACTI, n=580).

Results: During follow-up 95 (5%) patients from EURODIAB developed severe complications. The following predictors were considered: age, diabetes duration, glycated haemoglobin, smoking status, albumin/creatinine ratio, fasting triglycerides, HDL, non-HDL and LDL cholesterol, waist-hip ratio, body mass index, systolic and diastolic blood pressure, antihypertensive medication and fibrinogen. Strong predictors of severe complications were age, waist-hip ratio, glycated haemoglobin, albumin/creatinine ratio and HDL cholesterol. A high risk group (n=457[23%]) could be identified with a risk of severe complications of 15% at 3-years, 24% at 5-years and 32% at 7-years. Discriminative ability of the rule was adequate with a concordance (c) statistic of 0.74. External validation confirmed the good performance (c-statistic was 0.79 (EDC), 0.81(FinnDiane) and 0.73 (CACTI). Outcomes were systematically worse than predicted for patients from EDC and FinnDiane.

Conclusions: The clinical prediction rule provides adequate discrimination of type 1 diabetes patients that do or do not develop severe complications. The rule is widely generalizable and may help clinicians to target patients with type 1 diabetes effectively.

EXPRESSION OF PERIOSTIN IS REDUCED IN ARTERIAL TISSUE FROM INDIVIDUALS WITH TYPE 2 DIABETES

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Generalized arterial alterations, such as endothelial dysfunction, matrix accumulations and calcifications are associated with type 2 diabetes. However, the molecular characteristics of such diffuse pre-atherosclerotic changes in diabetes are only superficially known.

To identify molecular alterations of arterial disease in type 2 diabetes, we first applied Affymetrix high-density oligonucleotide array analysis to RNA, isolated from normal-appearing, non- atherosclerotic internal mammary arterial tissue from individual samples from 10 diabetic and 11 age- matched non-diabetic men, undergoing coronary artery bypass graft surgery. Single gene analysis demonstrated that one of the most downregulated genes in diabetic patients was periostin, with a fold change of 0.55 ($p<0.05$, t-test without correct. for mult.test). Furthermore, we also found periostin as a downregulated candidate at the protein level in mammarian arterial tissue from patients with T2DM in a global proteomics approach: proteins were extracted from intima-media sections of internal mammary arteries from 13 T2D patients and 8 non-diabetic

individuals. Pools of extracted proteins from each group were subjected to dimethyl labeling and orbitrap-LC/MS analysis, and periostin was found to be 50% reduced in the pool from diabetic patients. Finally, the individual protein extracts were subjected to western blot analysis and a tendency towards reduced expression of periostin in arterial extracts from patients with T2D was observed (fold change=0.75, p=0.08).
Our findings indicate that the matrix molecule periostin may be reduced in non-atherosclerotic arterial tissue from patients with T2D. This molecule has previously been shown to be involved in the development of arterial diseases and it is possible that dysregulated periostin also plays a role in diabetic arterial disease.

ENDOTHELIAL FUNCTION IMPROVEMENT AFTER INSULIN TREATMENT IN POORLY CONTROLLED TYPE 2 DIABETIC PATIENTS. THE INSUVASC STUDY

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Background and aims: Insulin is known to acutely improve endothelium-dependent vasodilatation. The aim was to examine the effect of insulin treatment on endothelial function and artery compliance in poorly controlled Type 2 Diabetics (T2Ds), at fasting and postprandially after a standardised breakfast.
Patients and methods: The INSUVASC study was a unicenter pilot, randomised, open label study. We included 42 T2Ds (HbA1c: 7.1-12 %) poorly controlled despite maximal oral antidiabetic treatment. During the first visit (V1) patients took only metformin after having breakfast. Endothelial function was measured non invasively with reactive hyperaemia peripheral arterial tonometry (PAT) that uses 2 finger probes to assess digital volume changes accompanying pulses and the augmentation index (AIx) was determined. All tests were conducted according to a prespecified protocol (Clinical Trials ID:NCT01022658). Test periods included fasting (H0) and a 2-hour post-prandial period (H1, H2) after a standardised breakfast that provided 75gr of carbohydrates. After V1 patients were randomly assigned to receive three different insulin regimens (Aspart, Detemir or both, n=14 for each group) in addition to metformin, The same measurements were repeated after a 4- to 5- week treatment (V2).
Results: Among the 40 patients who completed the study, 18 were treated for hypertension and 18 for dyslipidemia, mean age was 53±9 years, diabetes duration 10.0±5.5 years, HbA1c 9.0 ±1.4%. At V1 the reactive hyperaemia index (RHI) increased from H0 to H2 (1.80±0.01 vs 2.10±0.08, p=0.017). At V2, RHI increased rapidly from H0 to H1 and remained high at H2 (1.80±0.01 vs 2.04±0.09 (p=0.02) and 2.03±0.15 (p=0.184)). There were no significant differences between the three insulin regimens. RHI at fasting was inversely correlated with fasting blood glucose at V1 (r=-0.393, p=0.018) and this association disappeared at V2. AIx decreased after breakfast only after insulin treatment (H0:20.9±2.7%, H1:16.5±2.9%, H2:16.5±2.9%, p=0.014) but the effect was no longer

significant after adjustment for heart rate (AIx@75: p=0.086). At fasting, markers of oxidative stress (oxidized LDL p=0.028; nitrotyrosine NS) and of endothelial function (serum E-Selectin and VCAM-1; p=0.002 and p=0.02, respectively) decreased after insulin treatment, with no change in inflammation markers (CRP, IL6).
Conclusion: In poorly controlled T2Ds, both an earlier postprandial RHI response and the decrease in adhesion molecules suggest an improvement of endothelium function induced by 4-week insulin treatment possibly through a decrease in oxidative stress.

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EFFECTS OF COMBINED ADMINISTRATION OF N-3 POLYUNSATURATED FATTY ACIDS AND PIOGLITAZONE ON CARDIOVASCULAR AND METABOLIC MARKERS IN TYPE 2 DIABETES

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Background and aims: By many clinical trials are documented several beneficial effects of n-3 polyunsaturated fatty acids (n3PUFA) administration on parameters of lipid metabolism and cardiovascular risk indicators. In mice, n-3 polyunsaturated fatty acids (n3PUFA) have moreover positive effect on glucose metabolism and were observed additive effects of combination treatment with n3PUFA and glitazones in both prevention and regression of insulin resistance, dyslipidemia and liver steatosis. Combination of low-dose pioglitazone and n-3PUFA also led to lower body weight. At current clinical setting, pioglitazone is used to treat type 2 diabetes (T2DM). Aim of the study was to confirm the effect of 6-months treatment with n3PUFA alone and as an additive effect to pioglitazone treatment on insulin resistance, body weight, serum lipid concentrations and compensation of diabetes in patients with T2DM treated by metformin.
Materials and methods: Placebo controlled, parallel study group of 6 month duration. 68 subjects included, 65 finished the study. Randomised into 4 branches: n3PUFA (n=17); placebo (n=14); n3PUFA + pioglitazon (n=16); placebo + pioglitazon (n=18). Compound used: n-3PUFA concentrate (EPAX 1050TG, EPAX AS, Norway; composition: 10% EPA, 50% DHA) dose of 5 g/day); placebo: n6FA concentrate (EPAX AS, Norway; composition: corn oil), dose of 5 g/day; pioglitazon (Actos 15 mg, Takeda Global Research and Development Centre, Europe), dose of 15mg/day. At the beginning and after 6-month intervention period selected laboratory, metabolic and anthropometric measures including insulin resistance by hyperinsulinemic (1mU/kg.min, 3h) isoglycemic clamp method and selected serum metabolites after standard breakfast were evaluated.
Results: Pioglitazone treatment has led to expected significant improvement in diabetes

compensation as evaluated by HbA1C (p=0.022) and to an elevation of HDL cholesterol (p=0.001) although there was weight gain (p=0.001) and enlargement of body waist circumference (p=0.04). N3PUFA usage significantly decreased serum triglyceride concentrations (p=0.012) but was also accompanied by worsening T2DM compensation (p=0.012). First data from indirect calorimetry indicate that n3 PUFA may contribute to improvement metabolic flexibility. Pioglitazone and n3PUFA in combination treatment had additive beneficial effect on total cholesterol (p=0.013). Markers of insulin resistance (glucose utilisation and total metabolic clearance of glucose) were not significantly altered by combination treatment, same for blood glucose and insulin secretion after standardised breakfast, LDL and HDL cholesterol, triglycerides, nonesterified fatty acids and weight. Combination treatment did show positive trend in T2DM compensation and additive normalisation of markers of lipid metabolism.
Conclusion: Apart from lowering of total cholesterol, the study was not able to demonstrate additive beneficial effects of n3PUFA and pioglitazone on insulin resistance, body weight, blood glucose control and serum lipid levels in patients with type 2 diabetes treated by metformin. The results further indicate that deeper analyses with the inclusion of supplementary clinical and laboratory data could reveal positive interactions between n3PUFA and glitazones on metabolic pathways in patients with diabetes.

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TELMISARTAN IMPROVES VASCULAR AND CARDIAC FUNCTION IN PARTICULAR POSTPRANDIALLY IN PATIENTS WITH METABOLIC SYNDROME – A RELEVANT STRATEGY FOR TREATING A DISEASE BASED ON EATING HABITS

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Background and aims: The angiotensin II receptor antagonist telmisartan (T) has demonstrated bifunctional effects on the hemodynamic, vascular and also metabolic features of patients with metabolic syndrome (MS). Accordingly, we tested the hypothesis, that antihypertensive therapy with T vs. amlodipine (A) improves diastolic myocardial function, vascular function and metabolic characteristics in MS with a focus also on the postprandial state (pp).
Material and methods: This randomised cross-over study investigated 19 MS patients (BMI 36±6 kgm-2) with mild-moderate hypertension before and after 3 months therapy with T vs. A. Laboratory and ultrasound data were taken in the fasting state and 2 hours after a test meal (48 g carbohydrates). Cardiac function was assessed by tissue Doppler as systolic (S') and diastolic myocardial velocity (E'), central vascular function (common

carotid artery) and peripheral function (brachial artery) as elasticity modulus and pulse wave velocity. Laboratory measurements included glucose, insulin and nitrotyrosine.
Results: After 3 months with T, fasting systolic blood pressure was reduced by 10±12 mmHg ($p<0.002$) and pp by 12±16 mmHg ($p<0.003$) vs A (5±10 mmHg ($p< 0,04$) fasting and insignificant 3±10 mmHg ($p<0.05$ vs T) pp). With T but not with A, diastolic pressure dropped by 9±11 ($p< 0,003$) fasting and pp ($p<0.006$). With T but not with A, E' increased fasting and pp by 0.6±1.2 ($p=0.04$) and 0.8±1.2 cm/s ($p=0.01$) and so did S' ($p<0.001$ and 0.03). Similarly, pp central elasticity modulus was reduced by 29±34 kPa ($p<0.002$) and so was pp pulse wave velocity but peripheral vascular function improved both fasting and pp ($p<0.003$ and $p<0.001$). With T alone, significant correlations were observed for the therapy induced changes of pp systolic blood pressure with those of pp pulse wave velocity, nitrotyrosine and of insulin.
Conclusion: In MS patients, mild to moderate hypertension and without cardiac disease, monotherapy with telmisartan but not with amlodipine improved cardiac and vascular function in particular postprandially in spite of a comparable reduction of fasting systolic blood pressure. This amelioration of cardiovascular risk appears relevant for therapeutic decision making in MS.

FACE THREAT SENSITIVITY IS ASSOCIATED WITH HEART RATE VARIABILITY AND FLOW MEDIATED DILATION AMONG WOMEN WITH TYPE 2 DIABETES

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The majority of morbidity and mortality in type 2 diabetes (T2D) is related to cardiovascular disease. It is well established that stressful social interactions affect cardiovascular functioning. Face threat sensitivity (FST) is the degree to which an individual reacts negatively to stressful interactions that challenge his/her public self-image. FST is a stable but potentially modifiable psychological trait. We conducted two cross-sectional studies in which separate samples of women with T2D completed a brief paper-and-pencil measure of FST (White et al., 2004) and underwent cardiovascular testing.
Study #1 examined FST and high frequency heart rate variability (HF-HRV). Adult women with T2D and no psychiatric disorder were recruited from the community. Ambulatory ECGs (Holters) were recorded on GE Medical (Milwaukee, WI) Marquette Series 8500 direct (amplitude-modulated) recorders and scanned by an experienced technician, manually processed and edited. The power spectrum was computed using a fast Fourier transform; HF was defined as 0.15 to 0.40 Hz. Thirty-three women participated; 65% White, mean (SD) age = 55.2 (11.3) years, A1c NGSP = 6.9 (1.3), body mass index (BMI) = 37.9 (9.4), 39% using insulin. In regression analysis, after controlling for age, race, insulin use, and same day fasting glucose, higher FST scores were associated with lower HF-HRV

*p < .05. Participants in the top half of FST scores had significantly lower HF-HRV (3.7, [0.4]) compared to those in the bottom half, (4.7, [1.5]), F(1,32) = 4.47, *p < .05.
Study #2 examined the relationship between FST and endothelial functioning. Naturally postmenopausal women with T2D and no known vascular disease or psychiatric disorder were recruited from the community. Flow mediated dilation (FMD) was measured with ultrasound by occluding the brachial artery with an inflated blood pressure cuff for 5 minutes and then releasing. FMD was calculated as percent change in artery diameter from baseline. Sixty-seven women participated; 52% White, age = 62.9 (8.1) years, A1c = 6.7 (1.4), BMI = 33.6 (6.3), 12% using insulin. In regression analysis, after controlling for age, race, insulin use, and same day fasting glucose, higher FST scores were marginally associated with lower FMD, p = .08. Participants in the top half of FST scores had a significantly lower mean FMD [0 .001, [.004]), compared to those in the bottom half [0.51, (0.61)], F(1,58) = 7.22, *p < .01. Zero order correlations showed no significant associations between FMD and HRV and other psychological vulnerabilities including neuroticism or hostility.
Findings from these two studies suggest that FST is a unique psychological vulnerability associated with decreased endothelial function and dampened parasympathetic tone. We speculate that people high on FST may be threat vigilant and may perceive repeated psychological insults. The neural circuits that regulate these psychological factors also influence vascular tone, autonomic function, and inflammation. Mechanisms linking FST to cardiovascular function should be explored.

AMBULATORY BLOOD PRESSURE IN WOMEN WITH TYPE 2: EFFECTS OF PERSONALITY AND DISCRIMINATION

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Background: Elevated blood pressure (BP) increases cardiovascular risk in type 2 diabetes. Diabetic women have higher risk for heart disease than diabetic men. African Americans have higher rates of hypertension than Whites. In the United States and other cultures, exposure to racial discrimination is a common stressor, especially for racial and ethnic minorities, and women have been shown to find it more stressful then men. Racial discrimination and the personality trait of neuroticism are both associated with elevated BP levels, but have not been examined in concert. This study investigated self-reported racial discrimination, neuroticism, and ambulatory BP in African American and White

women with type 2 diabetes.
Methods: Thirty-nine Black and 38 White women with type 2 diabetes in the United States completed the Schedule of Racist Events (modified for a multi-racial sample); blood pressure levels and variability were evaluated using ambulatory monitoring devices. Ambulatory systolic and diastolic blood pressure (SBP, DBP) were measured at 30 minute intervals during waking hours, and at 60 minute intervals during overnight hours, for 24 hours using the Spacelabs 90207 monitor with the display turned off to avoid potential reactivity. Actigraphy and diaries were used to document times of sleep and wakefulness. A series of linear regression analyses were conducted to predict awake and asleep SBP and DBP from discrimination, neuroticism, and their interaction, in unadjusted models and after controlling for covariates. Latent growth curve modeling was conducted to predict 24-hour SBP and DBP from discrimination, neuroticism, and their interaction, in unadjusted models and after controlling for covariates.
Results: In linear regressions, after controlling for race, age, antihypertensive medication use, body mass index, and educational attainment, racial discrimination interacted with neuroticism to significantly predict SBP and DBP both while awake and during sleep. For each, the influence of racist events was stronger at lower levels of neuroticism. Results of latent growth curve analyses showed the same pattern of results for 24-hour SBP and DBP.
Discussion: We found associations for both SBP and DBP, suggesting that racial discrimination may effect multiple mechanisms of hemodynamics thought to be related to stress reactivity and active coping, as well to increased vigilance. Mechanisms linking racial discrimination and cardiovascular functioning might include neural circuitry related to anger, fear, social exclusion, and dissappointment.
Conclusion: Racial discrimination is associated with higher levels of 24 hour BP in diabetic women, especially those low in neuroticism.

A CORONARY HEART DISEASE MODEL FOR TYPE 2 DIABETES: DEVELOPMENT AND VALIDATION

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Background: Coronary heart disease (CHD) is a major cause of morbidity and cost and the leading cause of death among people with type 2 diabetes. Approximately one in two people with type 2 diabetes die from heart disease. In the past decade, the medical and surgical management of diabetes, hypertension, dyslipidemia, and cardiovascular disease have changed dramatically. It is essential that computer simulation models reflect these changes in clinical practice. We have updated and validated the CHD sub-model of the Michigan Diabetes Model to reflect these changes.

Methods: We incorporated risk equations from the United Kingdom Prospective Diabetes Study (UKPDS) Outcomes Model for incident heart disease, myocardial infarction, and fatality after MI. We modified the structure of the CHD model to accommodate revascularization procedures before and after the first myocardial infarction (MI), allows for repeat MIs and revascularization procedures, and includes heart failure as the most severe stage of CHD. We also modified the model to adjust for the direct benefits of beta-blockers, ACE-inhibitors, ARBs, statins, and aspirin. We then calibrated all the model parameters (including baseline hazard parameters in the UKPDS outcome model equations) to accurately predict the clinical outcomes reported in more recently published studies.
To assess the validity of this new CHD model, we performed internal and external validation. We ran three sets of simple linear regression models to evaluate how well our model was able to predict the published outcomes from clinical trials and observational studies: one for the studies used to develop the model (internal validation), one for studies not used to develop the model (external validation), and one for studies not used to develop the model that did not report heart failure incidence (external validation).
Results: For the 23 outcomes in the six studies of the internal validation exercise, the R2 was 0.981 and the slope of the regression line was 1.035. For the 13 non-CHF outcomes in the five studies of the external validation exercise, the R2 was 0.869 and the slope of the regression line was 0.897. When we included CHF in the regression model for the external validation exercise, we obtained a R2 of 0.688 and the slope of the regression line was 0.767. This is likely due to the fact that our model models the incidence of hospitalization due to CHF rather than the incidence of CHF or worsening of CHF as reported in most clinical trials.

IMPACT OF OPTIMAL GLYCEMIC CONTROL ON CHANGES IN CARDIOVASCULAR SYSTEM IN PATIENTS WITH GESTATIONAL DIABETES MELLITUS ASSESSED BY 24-HOUR BP MONITORING AND ECHOCARDIOGRAPHY

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Background: According to some recent works, present changes in diurnal variation in blood pressure, increase of left ventricular mass index and its alteration in diastolic function in women with gestational diabetes mellitus (GDM) compared to healthy pregnant women has been detected. The importance of optimal glycemic compensation in women with GDM has not already been assessed.
Objective: The aim of the present study was to evaluate the changes in 24-hour ambulatory blood pressure monitoring (ABPM) and left ventricular mass index in

normotensive patients with gestational diabetes mellitus, who had optimal glycemic control throughout pregnancy.
Methods: 34 pregnant women with GDM who were optimally compensated by intensive therapy were admitted to the study. Target value of fasting glycaemia was under 5.6 mmol / l, postprandial glycaemia two hours after eating below 6.7 mmol / l and HbA1c levels below 45 mmol / mol. These women´s blood pressure has been examined for 24-hours by ABPM and two-dimensional and tissue echocardiography has been performed in 36 gestational week. Their findings were compared with a group of healthy pregnant women tested in the same gestational period.
Results: The average age of 34 women with GDM was 32 ± 3.2 years, compared to 30.2 ± 3.5 years (NS) in 31 healthy women. Fasting blood glucose in women with GDM was 5.0 ± 0.5 mmol /l compared to 4.6 ± 0.3 mmol /l in healthy pregnant women (p = 0.002). HOMA index in GDM patients was 2.6 ± 2.0 compared to 1.7 ± 0.7 in control group. 24 women with GDM were treated with diet, 2 with diet and conventional insulin regimen and 8 with diet and intensified insulin regimen.
Mean 24-hour blood pressure was 84 ± 6.5 compared to 86.5 ± 8 mm Hg in the control group (NS). Mean blood pressure during daytime hours was 86 ± 5 in GDM women and 87.5 ± 5.2 mm Hg in the control group (NS) and during nightime hours 74 ± 5.7 in GDM and 77 ± 5.8 mm Hg in the control group (NS). Diurnal variability less than 10% was present in 2 women with GDM but also in 2 in the control group.
Left ventricular mass index was 82 ± 14 in GDM patients and 79 ± 11 g/m2 in healthy pregnant women (NS). Significant differences between women with GDM and controls were not detected in any of the following parameters evaluating left ventricular diastolic function: E / A, E,, A', E / E,, E' / A,.
Conclusion: Gestational diabetes mellitus with optimal glycemic control compared to normal pregnancy, seems not to have significant differences in the results of the 24-hour monitoring of blood pressure, left ventricular mass index and other parameters evaluating diastolic function.

SOME HEMODYNAMIC AND GENETIC FEATURES OF EXPERIMENTAL DIABETIC CARDIOMYOPATHY

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Features of the development of diabetic cardiomyopathy (DC) have attracted the attention of researchers since the 70s of the last century, although scientists still have different views on the hemodynamic characteristics of heart disease in diabetes. The genetic characteristics of an individual undoubtedly plays an important role in the development of diabetic cardiomyopathy. In this regard, we delivered the following objective: to study the parameters of cardiac hemodynamics and genetic factors in the development of diabetic cardiomyopathy.
Methods: We used Wistar male rats for experiments. Rats were divided into two groups:

I - control, II - rats with diabetes. Diabetes was induced by a single intraperitoneal injection of 50 mg / kg streptozotocin. Subsequently, using an ultra catheter and system „Millar Instruments", we performed the *in vivo* registration and evaluation (ChartTM v.5.4.2 software) of the basal parameters of cardiohemodynamics, and parameters after vena porta occlusion in the animals of both groups. Further we performed extraction of RNA from the heart tissue was using a set of Trizol RNA-prep. RNA concentration was determined using a spectrophotometer NanoDrop ND1000. After reverse transcription (RevertAid ™ H Minus First Strand cDNA Synthesis Kit), the resulting single-stranded DNA was used for real time polymerase chain reaction (PCR). Amplification of MHC, beta-1, beta-2 and beta AR-actin (as a housekeeping gene) genes was performed in 10 l of a mixture of SYBR Green PCR Master Mix, using 7500 Fast Real-Time PCR System.

Results: With the development of experimental diabetes glucose concentration in the blood of rats was significantly increased, body and heart weight were significantly decreased.

With help of «Millar» system in the rat II group we found a significant decrease in Stroke volume by 35.65%, Ejection fraction at 29.12%, cardiac output by 36.78%, compared with the I group. We recorded diastolic dysfunction of the heart: a significant increase in End-diastolic pressure (EDP) (2.2-fold), decreased of End-diastolic volume (EDV), which is characterized by increased yocardial stiffness (EDP/EDV) ($P < 0.05$) in diabetic animals. In II group we observed a significant 1.9-fold increase in the maximum stiffness, lower End-systolic volume on 14.7%, reduction in the Maximal power and Preload-adjusted Maximal power on 2 and 1.3-fold respectively ($P < 0.05$) compared with the I group. According to the real-time PCR, the development of diabetes led to decrease in mRNA expression levels of genes β1, β2 adrenoreceptor 2 and 1.3 times respectively, and the increase - β-myosin heavy chain of 1.4.

Conclusions: We have shown that the development of streptozotocin-induced diabetes led to significant changes of cardiohemodynamic and genetic parameters of the heart functioning.

In terms of «Millar» in the rat II group found a significant decrease in stroke volume by 35.65%, ejection fraction at 29.12%, cardiac output by 36.78%, compared with the I. Was recorded diastolic dysfunction of the heart: a significant increase in end-diastolic pressure (EDP) (2.2-fold), decreased end-diastolic volume (EDV), which is characterized by increased myocardial stiffness (KDD / EDV) ($P < 0.05$) in diabetic animals. In group II there was a significant increase in the maximum hardness of 1.9 infarction, lower end-systolic volume of 14.7% reduction in the maximum strength and maximum strength normalized by the preload of 2 and 1.3-fold ($P < 0.05$) compared with the I group. According to the real-time PCR, the development of diabetes was observed decrease in mRNA expression levels of genes β1, β2 adrenoceptor 2 and 1.3 times respectively, and the increase - β-myosin heavy chain of 1.4.

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