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ANTI-COLLAGEN TYPE IV ANTIBODIES AND THE DEVELOPMENT OF MICROVASCULAR COMPLICATIONS IN DIABETIC PATIENTS WITH ARTERIAL HYPERTENSION

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SUMMARY

Background and Aims: Thickening of basement membrane in capillaries and small vessels is a well-known finding and important in the progression of diabetic microangiopathy. Patients with diabetes mellitus and arterial hypertension are at higher risk of vascular disease.

Material and methods: To monitor the metabolism of the basement membrane protein collagen type IV (CIV) in type 2 diabetes mellitus (T2DM), serum levels of antibodies to CIV (ACIV) IgG, IgM and IgA were measured using an ELISA method in 93 patients with type 2 diabetes mellitus and arterial hypertension (AH) (mean age 61,4±11,3 years, diabetes duration 9,88±3,12 years; hypertension duration 9,28±4,98). These values were compared to serum antibodies to CIV in 42 age and sex matched controls. Diabetics were divided in two groups according to presence- Group 1 (n=67) or absence- Group 2 (n=26) of microangiopathy.

Results: Patients with T2DM and AH showed statistically significant higher levels of ACIV IgG in comparison to healthy controls (0.30±0.12 vs. 0.21±0.08) (p=0.0001). Group 1 showed significantly hihger levels of ACIV IgG than Group 2 (0.32±0.13vs. 0.24±0.08) (p=0.009) and healthy controls (0.32±0.13vs. 0.21±0.08) (p=0.0001). ACIV IgG are statistically significant higher in diabetics with retinopathy than this without (0.33±0.10 vs. 0.26±0.13) (p=0.04). ACIV IgG correlates with diabetes duration (r=0.49); (p=0.0004), retinopathy (r=0.20); (p=0.05) and BMI (r=-0.24); (p=0.05). Serum ACIV IgM and IgA levels in patients with T2DM and AH were lower than these in controls, but the differences are not statistically significant.

Conclusion: Our study showed a relationship between elevation of serum levels of ACIV IgG in diabetics and development of microangiopathy.

Key words: Diabetes mellitus, arterial hypertension, anti-collagen type IgG, micrangiopathy

INTRODUCTION

Clinical manifestations of microvascular and macrovascular involvement in diabetes include retinopathy, nephropathy and accelerated atherosclerosis, possible leading to blindness, renal failure, myocardial infarction, stroke and limb amputation. These target organ manifestations show common pathological characteristics underlying all vascular diseases; however, each complication also has some specific features depending on the tissue (s) involved, with important implications for prevention and treatment Mario and Pugliese, 2001 [1]. This diversity is supported by the distinct epidemiological characteristics of vascular complications, which occur with a different prevalence in diabetic subjects Toeller et al. 1999, Laasko 1999 [2]. The incidence of vascular complications also varies with the site involved. Macroangiopathy is sometimes present at the time of diagnosis, particularly in type 2 (non-insulin-dependent) diabetes mellitus [2], whereas microvascular disease usually developed several years after the onset of diabetes Krolewski et al. 1987 [3], Hanefeld et al. 1996 [4]. However, while the incidence of retinopathy increases with diabetes duration, that of nephropathy reaches a peak after about 15 years and declines thereafter. The rate of development and the severity of vascular injury are also dependent on the individual background; as a result, some people show only initial lesions, whereas others progress towards end-stage disease, despite a similar degree of metabolic derangement.

Arterial hypertension and diabetic vascular complications are connected with an elevated degradation of elastic tissue. As a result collagen type IV (CIV) are released in the circulated blood, which are a pathological stimulus for an increased production of antibodies to CIV (ACIV). Because it is very important to find characteristics of pathological activation of collagen turnover in diabetics we studied diabetic patients with arterial hypertension who demonstrated vascular complications.

In diabetes mellitus, thickening of basement membrane in capillaries and small vessels is a well-known finding and important in the progression of diabetic microangiopathy. Collagen type IV is uniquely present in basement membranes and represents their predominant structural element Paulsson 1992 [5], Kuhn 1995 [6]. Metabolic alteration of CIV occurs in micro- or

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RELATIONSHIP BETWEEN ANTI-ELASTIN IgA AND DEVELOPMENT OF MICROVASCULAR COMPLICATIONS: A STUDY IN DIABETIC PATIENTS WITH ARTERIAL HYPERTENSION

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Key words: *diabetes mellitus, arterial hypertension, anti-elastin antibodies (IgG, IgM, IgA), microangiopathy*

SUMMARY

An important factor in the development of vascular wall lesions is degradation of the elastic fiber major protein elastin. Elastin peptides derived from this degradation are present in the circulation and are a stimulus for production of the anti-elastin antibodies (AEAbs) IgM, IgG and IgA. The aim of this study was to investigate the possible association between AEAbs and development of diabetic microvascular complications. Sera of 93 patients with type 2 diabetes mellitus (T2DM) and arterial hypertension were investigated (mean age 61.4±11.3 years, diabetes duration 9.88±3.12 years; hypertension duration 9.28±4.98). These values were compared to serum AEAbs in 42 age- and sex-matched controls. Diabetics were divided into two groups according to the presence (group 1, n=67) or absence (group 2, n=26) of microangiopathy. Patients with T2DM and arterial hypertension showed statistically significantly higher levels of serum AEAbs IgA than healthy controls (0.36±0.03 vs. 0.06±0.01) (p=0.0001). Group 1 patients showed statistically significantly higher levels of AEAbs IgA than healthy controls (0.37±0,03 vs. 0.06±0.01) (p=0.0001). Group 2 patients showed significantly higher levels of AEAbs IgA than controls (0.33±0.02 vs. 0.06±0.01) (p=0.0002).AEAb IgA showed correlation with insulin dose (r=-0.30; p=0.03), systolic blood pressure (r=-0.25; p=0.05), diastolic blood pressure (r=-0.30; p=0.03), total cholesterol (r=-0.28; p=0.04) and triglycerides (r=-0.26; p=0.05). AEAb IgA levels were statistically significantly higher in diabetics with inadequate blood pressure control (≥140/90 mm Hg) than in those with adequate control (130-139/80-85 mm Hg) (p=0.03). Serum levels of AEAbIgG and IgM in patients with T2DM and arterial hypertension were lower than those in controls, but the differences were not statistically significant. Our study showed that elevation of AEAb IgA in diabetics with arterial hypertension may indicate increased elastin degradation and development of microvascular complications.

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confirmed by flow mediated vasodilation and with the intima media thickening measured ac carotid.
Results: Patients in the first and the second groups had significantly higher values of sICAM-1 plasma levels as compared with the control group. Values of sP-selectin were higher in the first group (134,23 ng/ml) compared with the second and the third groups (88,41 ng/ml respectively 68,13ng/ml) with normal values.
sICAM-1 and sP-Selectin have a positive correlation with age but not stronger than the correlation regarding endothelial dysfunction. Inflammatory markers were higher in each group in the smoking subjects ($p<0.001$ comparing each two groups), but the values are better correlated with the endothelial dysfunction.
Regarding blood pressure values, sICAM-1 and sP-selectin are higher in the group with more severe endothelial dysfunction, and there is a positive correlation. The patients who have high values of cholesterol have also high values of sICAM-1.
Groups with endothelial dysfunction have higher values of both sICAM-1 and sP-selectin positive correlated with higher glycemic values.
Conclusion: When functional and structural changes of the endothelial dysfunction are already present these are correlated with a higher inflammation and act as an important risk factor for atherosclerotic lesion development.

EAS-0797.
HUMAN HERPES VIRUS DNA DISTRIBUTION IN PATIENTS WITH ACUTE CORONARY SYNDROME

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Aim: Progression of atherosclerosis of coronary arteries is the main cause of acute coronary syndrome (ACS). Although the association between herpesviruses (HHVs) infection and atherosclerosis has been suggested, these data are still controversial. Here, we investigated HHV DNA distribution in blood and tissue samples of patients with ACS.

Methods: Using quantitative real-time PCR, we evaluated the presence of HHVs DNA in blood samples of 66 patients with ACS and in coronary artery samples of 30 patients, who died from myocardial infarction (MI) or it's complications. Blood samples were obtained at the time of hospitalization while coronary arteries samples were obtained during autopsy.
Results: In blood samplesof patients with ACS, most frequently detected were HHV-4 and HHV-7 DNAs (42,4%and 37,8% of samples, respectively), the DNAs of HHV-3 and HHV-5 were not detected in this group of patients, and other HHV's DNAs were detected between1,5% and 4,5% of samples. In patients died from MI, more than 94% of coronary artery samples contained DNAof at least one HHVs. DNAs of HHV-1&2, HHV-3, HHV-5 were detected in 80% of these samples. DNAs of other HHV's were less frequent and all together were detected in about 50% of the samples.
Conclusions: We detected HHVDNA in blood and in coronary arteries of patients with different forms ofischemic heart disease. HHV DNA was more frequent in arterial walls than inblood. The relation between HHVs and atherosclerosis now can be estimated after assessing viral activity in patients with ACS.

EAS-0966.
FREQUENCY OF CORONARY ARTERY DISEASE IN PATIENTS WITH RHEUMATIC VALVULAR HEART DISEASE: MOROCCAN EXPERIENCE

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The prevalence of coronary artery disease (CAD) in patients with valvular heart disease varies widely between developed and in developing countries because of differences in etiology: rheumatic valvular heart disease (RVHD) is the most important cause of this pathology in Morocco.

Objective: To estimate the prevalence of CAD in RVHD and to evaluate the interest of coronary angiography as a preoperative exploration cause of the constraints of cost, appointments, and risks in our context. Also we studied risk factors prediction of significant CAD in patients with RVHD, and discussed other preoperative exams to explore coronary arteries.
From 01/01/2011 to 31/12/2012, 80 patients underwent coronary angiography at the University Hospital cardiac catheterization laboratory of Casablanca prior to planned RVHD surgery. Data analyses were performed using Epi Info Version 6.04.
Results: The majority of patients were men (58.75% vs. 41.25%). The prevalence of Coronary Artery Disease found was 20%. These patients were all over the age of 55 years. The rate of hypertension was high 62.5% while only 37.5% were current smokers and 75% of the patients had more than one cardiovascular risk factor. Chest pain was found in 12.5%. 38% had mitral valvular disease, 38% had aortic valvular disease and 30% both.
The analysis showed that in our population, age and systemic arterial hypertension (SAH) were the most related to CAD in rheumatic valvular disease.
Conclusion: the prevalence of CAD among RVHD patients is low. Gender, age and SAH were identified as being strongly associated with the presence of CAD in our population.

Diabetes

EAS-0047.
SERUM ANTI-COLLAGEN TYPE IV IGM ANTIBODIES AND DEVELOPMENT OF MICROVASCULAR COMPLICATIONS IN DIABETICS WITH ESSENTIAL HYPERTENSION

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Aims: Arterial hypertension and diabetic vascular complications are connected with an elevated degradation of elastic tissue. As a result collagen type IV derived peptides (CIVDP) are released in the circulated blood, which are a pathological stimulus for an increased production of antibodies to collagen type IV (ACIV Abs).

Material and methods: Serum levels of antibodies to collagen type IV (ACIV) IgG, IgM and IgA were measured using an ELISA method in 93 patients with type 2 diabetes mellitus and arterial hypertension (mean age 61,4±11.3 years, diabetes duration 9,88±3,62 years; hypertension duration 9,28±4,98). These values were compared to serum antibodies to CIV in 42 age and sex matched controls. Diabetics were divided in two groups according to presence: Group 1 (n=67) or absence Group 2 (n=26) of microangiopathy.
Results: Group 1 showed significantly higher levels of ACIV IgM than controls 0,180 (0,136±0,223) vs. 0,143 (0,118±0,173) (KW=5.03; P=0.02). Patients from Group 2 showed statistically significantly higher levels of ACIV IgM than controls 0,176 (0,153±0,202) vs. 0,142 (0,118±0,174) (KW 6.15; p 0.01). ACIV IgM antibodies showed correlation with microalbuminuria ($r=0.21$); ($p=0.04$., BMI ($r=0.19$); ($p=0.04$), creatinine clearance ($r=0.36$); ($p=0.01$) and GFR ($r=0.34$); ($p=0.02$). Serum ACIV IgG levels were higher in patients than in controls, while serum IgA levels were lower than these in controls, but the differences are not statistically significant ($p>0.05$).
Conclusion: Levels of ACIV IgM indicate increased collagen type IV turnover. We suggest that serum ACIV IgM levels can be useful method for identifying a high risk for development of diabetic nephropathy.

EAS-0120.
EFFECTS OF BODY WEIGHT REDUCTION ON PLASMA FIBROBLAST GROWTH FACTOR 21 IN OBESE PATIENTS WITH TYPE 1 DIABETES MELLITUS

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value of LV torsion and to examine effect of aging on LV torsion in healthy young and older.

Methods: LV apical, basal rotation and torsion that was defined as apical rotation relative to base were evaluated by speckle tracking echocardiography. 75 healthy articipants were devided into two group according to age: young <40 older >40 years. Ischemic or valvular disease, arytmi, global or regional wall motion anomaly were excluded.

Results: LV filling pressure;A wave velocity, E/E[1] ratio was higher whereas E wave velocity, E/A ratio was lower in older patients than young.There was increase in apical rotation and decrease in basal rotation in older patients but not significant.With aging torsion was increased insignificantly. Apical rotation and torsion were decreased in older group with increasing degree of LV diastolic dysfunction.

Conclusion: Study showed that torsion was increased slightly with age but this effect reversed in the increased diastolic dysfunction even it normal systolic function.

	Young	Older	p<0.05
Age	29±6	64±12	0.001
Men/women	18/22	14/22	0.596
LVEF(%)	69.2±7	65.9 ±7	0.041
E	76.75±11	52.4±16	0.001
A	57.7±10.6	70.6±13.7	0.001
E/A	1.34	0.75	0.001
E/E'ratio	6.09±1.3	7.7±2.23	0.001
Apical rotation, .	3.3±2.4	4.4±2.9	0.075
Basal rotation, .	-5.2±3.7[illegible]	-4.1±2.7	0.165
Torsion, .	8.53±4.1	8.05±3.3	0.890

	Grade 1 LVDD	Grade 2 LVDD	P<0.05
Apical rotation, .	5.02±3.2	2.4±1.1	0.04
Basal rotation, .	-4.4±-2.86	-4.5±-2.87	0.06[illegible]
Torsion	9.4±3.6	6.9±2.1	0.0[illegible]

EAS-0035.

INTENSIVE VERSUS CONVENTIONAL TREATMENT ON PATIENTS WITH TYPE-2 DIABETES MELLITUS. A COST/EFFECTIVENESS ANALYSIS

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Aims: Evaluate costs and incrementalcost-effectiveness of intensive vs standard treatment in type-2 diabetesmellitus (T2DM).

Methods: From a total group of 650, 37 T2DM arrived in 2010 and werereevaluated during 2011. Retrospective observational study. Follow up: oneyear. Effectiveness. Data: age, sex, weight, height, BMI, years since diabetesdiagnosis, smoking, retinopathy, nephropathy, blood pressure, totalcholesterol, cHDL, cLDL, glucose, A1c, CRPhs. Statistical: mean and SD or n (%); Student's t-tes.

Results: 37 T2DM patients, ages [illegible] y.o. since date of diagnosis. 37.83% smokers, 43.24% renal abnormality and 8.10% retinopathy. Weight 83.48 ±14.59kg, BMI 29.52 ±4.18 kg/m². Total costs: average increase of 30,05±31,43€.Antihypertensives: incremental cost of 5,30±13.43€, yielding decreases ofsystolic pressure (P [illegible] 0.074) and [illegible] 8.70 ±1[illegible] €, resulting, 8.87 ± 34.48 mg/dl reduction ofLDL (P = 0.002) and an average increase of 1.4[illegible] mg/dl of HDL;Antidiabetic incremental cost [illegible]18 ±20.56 €, with average decreases in bloodglucose levels of 13.59 ±49.25 mg/dl (P = 0.049) and in glycated Hb of 0.23 ± 0.97 %, but a 29.70% of T2DM decreases their A1c levels over 0.5% withoutsignificant economic implications.

Conclusions: The most cost-effectiveintervention in the diabetic patient is always the LDL-target one. It would beadvisable to perform an analysis with a larger number of patients, as well as afull economic evaluation which should take into account other costs and thepatients' quality of life.

EAS-0039.

METHYLENE TETRAHYDROFOLATE REDUCTASE GENES MUTATIONS IN RESISTANT HYPERHOMOCYSTEINEMIA

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Aim: Prevalence of MTHFR genesmutations in resistant hyperhomocysteinemia (RH).

Method: 33 patients with moderate-high CVrisk and clinical & biochemical criteria for RH consented to geneticscreening by the use of molecular genetic testing. 24 Males (72.7%): 53.8 ± 17.2 yrs; BMI: 29.1 ± 4.4 Kg/m2; 9 females (27.3%): 62.7 ± 20.3 yrs. BMI: 28.5± 6.5 Kg/m2. Smokers 18.2 %. Hyperglycemia: 48.5%. Hypertension: 66.7%. Clinicalatherosclerosis (including coronary heart disease) in 33.3%; venous thrombosishistory in 9.1%. Subjects with DM1, LADA, folic acid and / or vitamin B12deficiency, and chronic renal failure were excluded. RH defined by: Hcy> 16uM/L (normal values in local laboratory).

Results: N = 20 (60.6%) homozygous, n = 10(30.3%) heterozygous for MTHFR c.677T mutation. 3 subjects (9.1 %) non carriers.29/33 (87.9%) showed at least one CR factor (CVRF) associated. Homozygousprevalence was higher than expected (60.6% vs 15-25 %), whereas heterozygousprevalence was slightly lower than estimated in Caucasian population (30.3 vs 45%). Clinical atherosclerosis (including CHD) is more prevalent than venousthrombosis history (33.3% vs 9.1%).

Conclusions: Our work is the first one to studythe prevalence of mutations in RH and this study emphasizes the relevance ofgenetic testing.

EAS-0048.

ATHEROGENIC INDICES, ELASTIN TURNOVER AND THE DEVELOPMENT OF MICROVASCULAR COMPLICATIONS- STUDY IN DIABETIC PATIENTS WITH ARTERIAL HYPERTENSION

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Aims: Elastin peptides derived from degradation of vascular wall elastic tissue are present in the circulation and are a stimulus for production of anti-elastin antibodies (AEAbs) IgM, IgG and IgA. The aim of this study was to investigate for a possible association between AEAbs, lipid indices and development of microvascular complications.

Material and methods: Sera of 9[illegible] patients with type 2 diabetes mellitus (T2DM) and arterial hypertension (AH) were investigated (mean age [illegible] years; diabetes duration 9.88±1.12 years; hypertension duration [illegible]). [illegible] was used for determination of anti-elastin antibodies. [illegible] were compared to [illegible] AEAbs in 42 age and sex matched controls. Diabetics were divided in two groups according to presence- Group 1 (n [illegible]) or absence- Group 2 (n [illegible]) of microangiopathy. Lipid profile and lipid indices (log TG/HDL, LDL/HDL, TC/HDL and TG/HDL) were [illegible]

Results: Group 1 showed statistically significant higher levels of AEAbs IgA than patients without microangiopathy 0.353 (0,173÷0,471) vs. 0,235 (0,098÷0,377) (KW=3,36; p=0.05) and healthy controls 0,353 (0,173÷0,471) vs 0,006 (0,052÷0,068) (KW 20,37; p<0.0001). Patients from Group 2 showed significantly higher levels of AEAbs IgA than controls 0,235 (0,098÷0,377) vs. 0,006 (0,052÷0,068) (KW 8,54; P 0.003). AEAbs IgA showed correlation with insulin dose (r 0.35); (p 0.01), SBP (r 0.31); (p 0.001), HbA1c (r 0.21); (p 0.04), BMI (r 0.23); (p 0.01). AEAbs IgA correlated with log TG/HDL (r 0.28); (p 0.001), LDL/HDL (r=0.22); (p=0.01) TC/HDL (r=0.22); (p=0.01) and with TG/HDL (r=0.35); (p 0.05).

Conclusion: Our study shows association between elevation of AEAb IgA, lipid indices and development of microvascular complications in diabetic patients with arterial hypertension.

EAS-0134. CLOCK 3111 T/C SNP INTERACTS WITH SLEEP DURATION TO MODIFY BODY MASS INDEX IN A SINGAPOREAN CHINESE POPULATION

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Aim: Circadian genes play an important role in regulating circadian oscillation based on positive/negative transcriptional-translational feedback loops. Sleep duration is known to be inversely associated with weight gain. In this study, we aimed to assess the effects of circadian genes on sleep duration, and the interactions of these variants with sleep duration in body mass index (BMI) among Singaporean Chinese population.

Methods: In a coronary heart disease case-control study nested within the Singapore Chinese Health Study, 2,003 participants (719 cases and 1,284 controls) were genotyped by IlluminaHumanOmniZhongHua-8 Bead Chip. Sleep duration and BMI were measured at baseline. 15 circadian regulation genes were selected based on published papers. Linear regression analyses were assessed separately in cases and controls and subsequently meta-analyzed.

Results: After adjustment for covariates (age and sex) and multiple testing, the C allele at miR-SNP *rs1801260* in the *circadian locomotor output cycles kaput (CLOCK)* gene was associated with shorter sleep duration (Beta=-0.208, P=0.008). The interaction between *rs1801260* and sleep duration on BMI was significant (P=0.046), although there was no main effect of sleep duration on BMI without the interaction term. Stratified linear regression results showed that the C allele at *rs1801260* was associated with higher BMI (Beta=0.621, P=0.024) in non-short sleepers (≥7 hours per night) only.

Conclusions: The present study replicated the previous results that the C allele at *rs1801260 in CLOCK* was associated with shorter sleep duration and showed a novel interaction between *rs1801260* and sleep duration on BMI in the Singaporean Chinese population.

EAS-0210. EZETIMIBE DOES NOT INCREASE FASTING GLUCOSE LEVELS MORE THAN STATINS ALONE IN NON-DIABETIC, HYPERCHOLESTEROLEMIC PATIENTS

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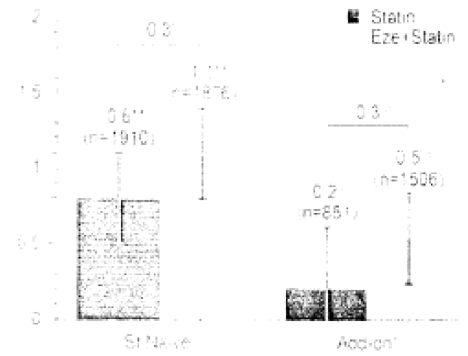
Aim: Statin therapy is associated with a slightly increased risk of diabetes mellitus (DM) and insulin-resistance in nonDM patients. In prior studies, ezetimibe + statins did not increase fasting serum glucose (FSG) more than statins alone in statin-naive, nonDM hypercholesterolemic patients for up to 56 weeks. This analysis assessed the effects of ezetimibe on FSG changes when added to nonDM hypercholesterolemic patients on stable statin therapy.

Methods: Data was pooled from 2 randomized, double-blind, 8-week, add-on studies (ezetimibe [n=1506] vs placebo [n=851] added to stable statin) in nonDM patients at baseline. Mean FSG changes from baseline were estimated for each treatment group (LDA model*) and between-treatment differences calculated. Numbers of patients with FSG ≥126mg/dl and baseline cofactor effects were also assessed.

Results: No significant FSG increases from baseline were observed with statin and ezetimibe+statin in add-on studies; the between-treatment difference was also non-significant (p>0.05; Figure). The lack of an ezetimibe effect on FSG is consistent with prior findings in statin-naive subjects comparing ezetimibe statins vs statins. FSG changes were not related to age, and baseline BMI, HDL-C and TG, nor to changes from baseline in LDL-C, BMI, HDL-C, TG and ApoB. Proportions of patients with FSG ≥126mg/dl during the trial were low, similar for both treatments and highest in those with baseline FSG [illegible] 100-[illegible] mg/dl.

Conclusion: In hypercholesterolemic patients on statin therapy, addition of ezetimibe did not increase FSG levels more than statin therapy, consistent with ezetimibe + statins effects in statin-naive patients.



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EAS-0227. CLINICAL UTILITY OF A CORONARY HEART DISEASE RISK GENE SCORE IN SUBJECTS FROM PAKISTAN

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Increased elastin turnover in diabetic patients with arterial hypertension

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Abstract

Introduction and aims: *Antibodies against products of elastin degradation are found in sera of all people. Presence of anti-elastin antibodies (AEAbs) and relevant antigens in circulation leads to the formation of circulating immune complexes (CIC). The aim of our study is to determine serum levels of anti-elastin antibodies unbound in CIC (free AEAbs).*

Material and methods: *We used a method for detection CIF-ELISA (complement-inhibiting factor-enzyme linked immunosorbent assay) in combination with ELISA to find AEAbs. The levels of free AEAbs IgG were measured in sera of 93 patients with diabetes mellitus and hypertension (mean age 61.4 ±11.3, diabetes duration 9.88 ±5.12; hypertension duration 9.28 ±4.98). These levels were compared to 42 age- and sex-matched controls.*

Results: *Free AEAbs IgG in patients with T2DM and AH are statistically significantly higher than these in healthy controls: 0.421 (0.328-0.572) vs. 0.240 (0.212-0.305), respectively (KW = 19.64; p < 0.0001). Group 1 (patients with microvascular complications) showed a significant increase in free AEAbs IgG in comparison with controls: 0.428 (0.343-0.591) vs. 0.240 (0.212-0.305), respectively (KW = 20.14; p < 0.0001). Group 2 also shows higher levels of free AEAbs IgG than the control group: 0.398 (0.312-0.467) vs. 0.240 (0.212-0.305), respectively (KW = 8.88; p = 0.003). Patients with microvascular complications showed the highest levels of free AEAbs IgG. There were no significant differences between group 1 and group 2.*

Conclusions: *Our results show the association between the activity of elastin turnover and microvascular lesions in diabetic patients with arterial hypertension. We suggest that free AEAbs IgG mark a later "secondary" step of the autoimmunization to elastin.*

Key words: *ELISA, diabetes mellitus, elastin, arterial hypertension, microangiopathy.*

(Cent Eur J Immunol 2013; 38(4): 537-542)

Introduction

Patients with type 2 diabetes mellitus are at a high risk of developing diabetic microvascular complications due to the impaired structure of the vascular protein elastin and collagen type IV. The elastic fibers, responsible for the compliance and elasticity, are organized in elastic lamellae. These structures separate layers of smooth muscle cells and equally distribute the pressure along the entire vascular wall. The degradation or calcification of elastic fibers in many diseases, affecting the small caliber vessels, leads to vascular damages. Our previous studies in patients with type 1 diabetes mellitus found an increased degradation of elastin – the major protein of elastic fibers. As a result, soluble elastin-degradation peptides (EDP) are released in the circulation and act as a pathological stimulus for the formation of anti-elastin antibodies (AEAbs) [2]. In type 2 diabetes mellitus, different types of autoantibodies have been detected: insulin autoantibodies, GAD-antibodies (glutamic acid decarboxylase antibodies), autoantibodies to tyrosine phosphatase IA2, islet antibodies [3], anti-elastin antibodies [2] and collagen type IV autoantibodies. These autoimmune antibodies bind to cognate antigens and thus, form circulating immune complexes (CIC). These CIC have pathogenic properties because they are deposited in the small caliber vessels, accelerating their damage.

Material and methods

In our previous studies, we used a method based on C3-binding glycoprotein: complement-inhibiting factor CIF-enzyme linked immunosorbent assay (CIF-ELISA)

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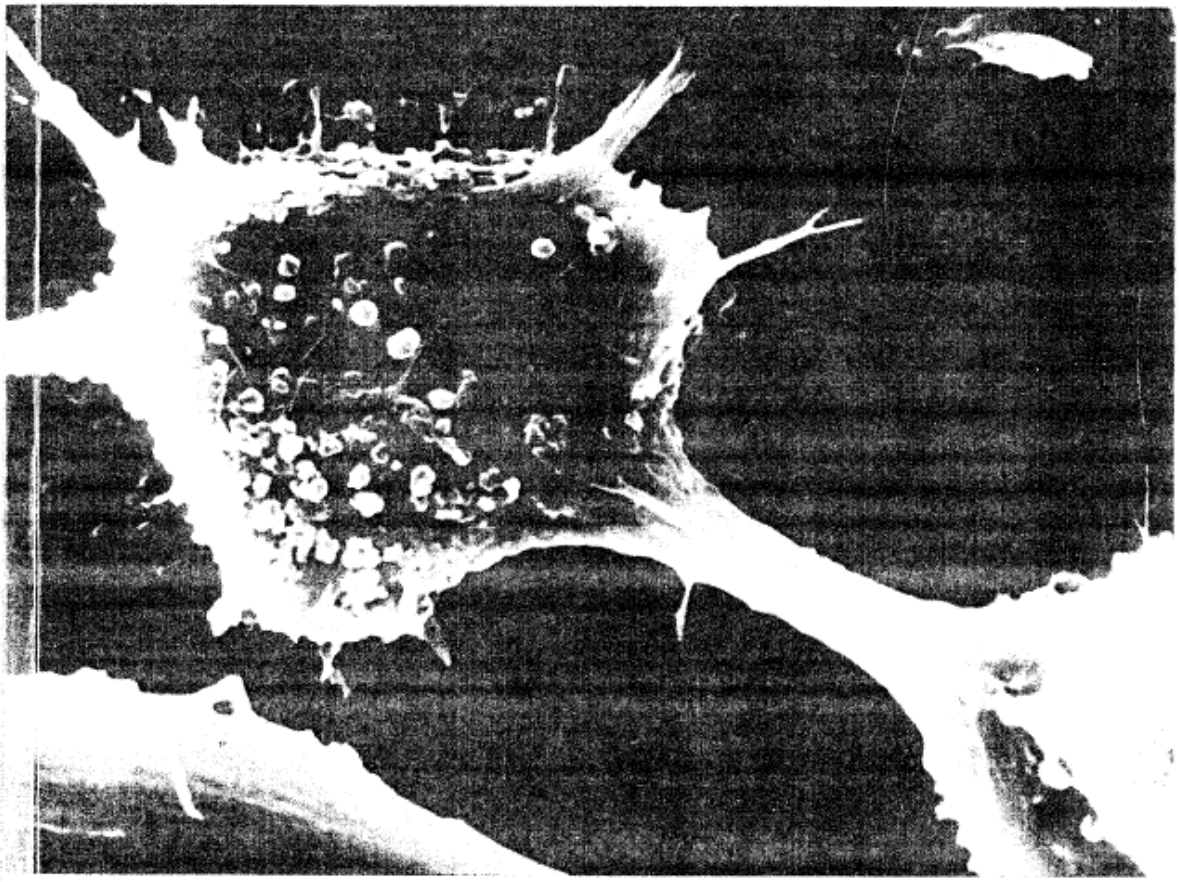

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Abnormal levels of age-elastin derived peptides in sera of diabetic patients with arterial hypertension

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Abstract

Introduction: *An important factor in vascular wall alterations is degradation of elastic fiber major protein – elastin. As a result, elastin derived peptides (EDP) are found in circulation. Advanced glycation might also involve elastin, because it is a protein with slow metabolism. The aim of our study was to measure serum levels of glycated elastin derived peptides (AGE-EDP) of elastin in patients with type 2 diabetes mellitus (T2DM) and arterial hypertension (AH).*

Material and methods: *We adapted an ELISA technique for the determination of AGE-EDP. Sera of 93 patients with T2DM and AH (mean age 61.4 ±11.3 years, diabetes duration 9.88 ±3.12 years; hypertension duration 9.28 ±4.98) were tested. These values were compared to 42 age- and sex-matched controls. Diabetics were divided in two groups according to presence – Group 1 (n = 67) or absence – Group 2 (n = 26) of microangiopathy.*

Results: *Patients with T2DM and AH showed statistically significantly higher levels of AGE-EDP in comparison with healthy controls 0.060 (0.053÷0.065) vs. 0.039 (0.031÷0.044) (KW = 35.2; p < 0.0001). Group 1 showed significantly higher levels of AGE-EDP than the control group 0.069 (0.051÷0.070) vs. 0.039 (0.031÷0.044) (KW = 33.0; p < 0.0001). Group 2 also showed significantly higher levels of AGE-EDP than controls 0.058 (0.049÷0.064) vs. 0.039 (0.031÷0.044) (KW = 22.1; p < 0.0001). AGE-EDP showed a correlation with an insulin dose (r = –0.28; p = 0.05), systolic blood pressure (r = 0.25; p = 0.01), BMI (r = 0.39; p = 0.01) and retinopathy (r = 0.18; p = 0.05).*

Conclusions: *The measurement of non-invasive markers of elastin glycation may be useful in monitoring development of vascular wall alterations and therapeutic interventions.*

Key words: *ELISA, elastin, AGEs, diabetic microvascular complications, arterial hypertension.*

(Centr Eur J Immunol 2014; 39 (3): 345-351)

Introduction

Patients with type 2 diabetes mellitus (T2DM) are at a high risk of development of vascular disease. This risk is increased with existence of arterial hypertension. In diabetic patients, morbidity and mortality are mainly related to the presence of late complications, namely macro-and microangiopathy. Advanced glycation end-products (AGEs) are generated in diabetes mellitus as a result of chronic hyperglycemia and enhanced oxidative stress. These AGEs, via direct and receptor-dependent pathways, promote the development and progression of cardiovascular disease.

Advanced glycation end-products of non-enzyming-glycation/non-enzymatic glycation are a heterogeneous group of chemical components, which are formed through non-enzyminggglycation, i.e. through connection to reduced glucose molecule (also known as glycooxygenation or glycosylation) to proteins, fats and nucleid acids. The term "final product" has been chosen because AGEs are the final product of chain reactions generating some osculant products (for example Schiff bases, Amadori products, Maillard products, deoxyglucosone, methylglyoxal glycolaldehyde). Most important AGEs include carboxymethyl lysine (CML), carboxyethyl lysine (CEL), pentosidine and hydroimidazolone. Carboxymethyl lysine is known as "AGEs-indicator" [1]. Advanced glycation end-products and their receptors, RAGE, can be detected in nearly each body cell and their major role has been discovered in progress of atherosclerosis and particularly in patients with diabetes. In the serum of patients with diabetes type II, significantly higher concentrations of AGEs compared to

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Serum anti-collagen type IV IgM antibodies and development of diabetic nephropathy in diabetics with essential hypertension

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Abstract

Introduction and aims: *Arterial hypertension and diabetic vascular complications are connected with an elevated degradation of elastic tissue. This process leads to an increased production of antibodies to collagen type IV (ACIV Abs). In the present investigation we studied whether the serum levels of antibodies (IgG, IgM and IgA) to collagen are related with microvascular complications.*

Material and methods: *Serum levels of antibodies to collagen type IV (ACIV) IgG, IgM and IgA were measured using an ELISA method in 93 patients with type 2 diabetes mellitus and arterial hypertension (AH) (mean age 61.4 ±11.3 years, diabetes duration 9.88 ±5.12 years; hypertension duration 9.28 ±4.98). These values were compared to serum antibodies to CIV in 42 age and sex matched controls.*

Results: *ACIV IgM antibodies levels in patients with AH and T2DM were statistically significantly higher than controls 0.178 (0.145÷0.220) vs. 0.142 (0.118÷0.173) (KW = 6.31; p = 0.01). Group 1 (patients with microvascular complications) showed significantly higher levels of ACIV IgM than controls 0.180 (0.136÷0.223) vs. 0.142 (0.118÷0.173) (KW = 5.03; p = 0.02). Patients from Group 2 showed statistically significantly higher levels of ACIV IgM than controls 0.176 (0.151÷0.202) vs. 0.142 (0.118÷0.173) (KW = 6.15; p = 0.01). ACIV IgM antibodies showed correlation with microalbuminuria (r = 0.21); (p = 0.04), BMI (r = 0.19); (p = 0.04), creatinine clearance (r = –0.361; (p = 0.01) and GFR (r = –0.34); (p = 0.02).*

Conclusions: *Our study showed an association between elevation of serum levels of ACIV IgM and development of diabetic nephropathy. We suggest that levels of ACIV IgM can be useful method for identifying a high risk for development of diabetic nephropathy.*

Key words: *type 2 diabetes, essential hypertension, anti-collagen type IV IgM antibodies.*

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Introduction

Patients with type 2 diabetes mellitus are at high risk of development of vascular disease. This risk is increased with existence of arterial hypertension. In diabetic patients morbidity and mortality are mainly related to the presence of late complications, namely macro- and microangiopathy. Arterial hypertension is connected with decreased, while type 2 diabetes mellitus is connected with an elevated degradation of connective tissue proteins Laviades *et al.* [1]. Because it is very important to find characteristics of pathological activation of collagen type IV turnover we studied diabetic patients with arterial hypertension with demonstrated vascular complications. In diabetes mellitus, thickening of basement membrane in capillaries and small vessels is a well-known finding and important in the progression of diabetic microangiopathy.

Collagen type IV (CIV) is uniquely present in basement membranes and represents their predominant structural element Klatt *et al.* [2], Coelho *et al.* [3]. Metabolic alteration of CIV occurs in micro- or macrovascular basement membrane of diabetic patients. Collagen type IV constitutes the major component of basement membranes Erben *et al.* [4]. Measurement of serum antibodies to fragments of CIV Nikolov *et al.* [5]; Nicoloff *et al.* [6] is now possible and enables changes to be detected. Investigators Kamie *et al.* [7] measured serum anti-type IV collagen antibody (IgG) in diabetic patients and they found that serum levels of the anti-type IV collagen antibody were significantly higher in diabetics than these in the nondiabetics. However, there was no relationship between the levels of urinary albumin and the serum levels of anti-type IV collagen antibody.

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Патологична обмяна на еластин и колаген тип IV при болните със захарен диабет тип 2 и артериална хипертония

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Хипертонията или високото артериално налягане засяга около 600 млн. хора по целия свят. Артериалната хипертония се среща приблизително два пъти по-често при пациентите със захарен диабет в сравнение с популацията без диабет. Това подкрепя доказателството, че хипертонията, свързана с диабет, представлява рисков фактор за увреждане както на големите, така и на малките. Застъпването на артериалната хипертония със захарен диабет значимо повишава риска за исхемична цереброваскуларна болест, ретинопатия и ренална дисфункция.

Съединителнотъканните протеинни компоненти – еластин и колаген тип IV са основни структурни елементи на артериалната стена и играят важна роля в съдовата функция както в норма, така и при патологични процеси. Съществуват данни, че структурните увреждания на тези елементи на екстрацелуларния матрикс играят важна роля в развитието на артериалните увреждания. Чрез имунологични методи може да се съди за активността на еластиновата и колагеновата обмяна.

Ключови думи: еластин, колаген тип IV, ELISA, захарен диабет тип 2, артериална хипертония, съдови усложнения, съединителна тъкан.

Съдбата на болните от захарен диабет зависи най-вече от тежестта и еволюцията на съдовите усложнения. Захарният диабет (ЗД) е водеща причина за сляпота (70-85% от болните имат диабетна ретинопатия), хронична бъбречна недостатъчност (40% имат диабетна нефропатия), 50% имат диабетна невропатия, а ампутациите на долните крайници са 20-40 пъти повече от лицата без диабет. Тези усложнения определят клиничната картина, терапевтичните възможности и прогнозата при болните от захарен диабет, *(Цинликов, 2012 (1a)*.

Съединителнотъканните протеинни компоненти - еластин и колаген са основни струкурни елементи на артериалната стена и играят важна роля в съдовата функция както в норма, така и при патологични процеси. Съществуват данни, че структурните увреждания на тези елементи на екстрацелуларния матрикс играят важна роля в развитието на артериалните увреждания. Артериалната хипертония е свързана с намаление на съдовия еластицитет, увеличена съдова ригидност и абнормално повишение на отношението колаген/еластин. Това води до променено съдово съдържание на протеините еластин и колаген тип IV. В резултат на тези деградационни процеси, протичащи в екстрацелуларния матрикс, в серума се освобождават разтворими еластинови и колагенови пептиди, които се появяват в циркулацията.

Серумните нива на тези деградационни продукти оказват влияние както върху еластиновия, така и върху колагеновия метаболизъм, защото циркулиращите еластинови и колагенови пептиди имат имуногенни свойства и индуцират продукцията на специфични антитела: антиеластинови и антиколагенови антитела. Тези антитела могат да реагират с антигенните детерминанти на измененените еластинови и колагенни фибри, като по този начин се формират антиген-антитялно комплекси in situ *(G. Nicoloff et al. (16)*.

Известно е, че при пациентите със ЗД са ускорени процесите на еластинова и колагенова тип IV деградация и намалени тези на синтеза, докато при артериална хипертония- колагеновата тип I и III (типични за миокарда) синтеза е ускорена, а разграждането - забавено *Lavindes C. 1998*[2]. Едновременното наличие на ЗДТ2 и АХ значително дисбалансира ЕЦМ обмен и води до по-интензивно и усилено ремоделиране на съдовата стена. Предвид тежестта на усложненията, предизвикани от увреждането на съдовете при пациентите със захарен диабет тип 2 и артериална хипертония, са необходими по-детайлни проучвания върху обмяната на съдовите протеини еластин и колаген тип IV при тази високорискова група пациенти. Чрез имунологични методи може да се съди за активността на еластиновата и колагеновата обмяна, *Nicoloff G., 2006*[3].

Късни продукти на неензимното гликиране (AGES) и развитие на микроангиопатия при болни със захарен диабет тип 2 и артериална хипертония без органни усложнения

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Въведение и цели: Основна цел на настоящата работа е да се проследят възможностите за преценка на съдовите увреждания чрез установяване вероятната корелация между серумните нива на продукти на късната обмяна на неензимното гликране и наличието на микроангиопатия при пациенти със захарен диабет тип 2 и артериална хипертония без органни усложнения.

Материал и методи: В настоящото проучване адаптирахме ELISA метод за определяне на AGE-еластинови-деградационни пептиди (AGE-EDP), като маркер, отразяващ нивото на гликемията за дълъг период от време, и също така изследахме антитела срещу AGEs (anti-AGE antibodies) в серуми на пациенти със ЗДТ2 и АХ и задрави контоли. Изследвани са 93 пациенти със захарен диабет тип 2 и неусложнена артериална хипертония, средна възраст 61,4±11,3 и продължителност на захарния диабет тип 2: 9,88±3,12 и артериална хипертония 9,28±4,98 от региона на Медицински университет гр. Плевен. За контроли са използвани човешки серуми на здрави субекти (n=42), отговарящи по пол и възраст, средна възраст 58,9±7,56. Лицата от основната група са разпределени в две подгрупи, в зависимост от наличието (група 1); (n=67) или отсъствието (група 2); (n=26) на съдови увреждания.

Резултати: Стойностите на анти-AGEs антителата при пациенти със ЗД тип 2 и АХ са достоверно завишени спрямо контролната група (1.390±0.394 vs. 1.184±0.325; F=4.72, P=0.03). Група 1 показа сигнификантно по-високи стойности на анти-AGEs спрямо здравите индивиди (1.399±0.376 vs. 1.184±0.325; F=4,75 P=0.03). Стойностите на анти-AGEs антителата са по-високи при пациентите със съдови увреждания, в сравнение с тези на индивидите без васкуларни поражения (Група 2). Антителата срещу AGEs корелират със систоличното артериално налягане (r=0.17); (p=0.05), BMI (r=0.25); (p=0.01), общия холестерол (r=0.19); (p=0.04).
Установихме статистически значими по-високи стойности на серумни AGE-ЕДП при пациенти със ЗД тип 2 и АХ, в сравнение с контролната група 0,060 (0,053±0,065) vs. 0,039 (0,031±0,044) (KW=35,2; p<0,0001). Група 1 показа сигнификантно повишение на серумни AGE-ЕДП спрямо контролните лица 0,069 (0,051±0,070) vs. 0,039 (0,031±0,044) (KW=33,0; p<0,0001). Пациентите от група 2 са със значимо по-високи стойности на AGE-ЕДП спрямо контролните лица 0,058 (0,049±0,064) vs. 0,039 (0,031±0,044) (KW=22,1; p<0,0001). Най-високи стойности на гликиран еластин се откриват при пациентите с васкуларни увреждания. Серумните AGE-ЕДП корелират с инсулиновата доза (r=-0.28); (p=0.05), систоличното артериално налягане (r=0.25); (p=0.01), BMI (r=0.39); (p=0.01) и ретинопатията (r=0.18); (p=0.05).

Изводи: Изследването на нивата и вероятно динамиката на анти-AGEs антителата могат да направят възможно диагностицирането и прогнозирането на тежестта на късните усложнения на диабета. AGE-ЕДП имат отношение в развитието на микроваскуларни увреждания. Измерването на AGE-ЕДП могат да бъдат полезни за мониториране на развитието и лечението на съдови увреждания при болни със ЗДТ2 и АХ.

Базалните мембрани са главен фокус на научен интерес поради тяхната роля в развитието на различни заболявания. Захарният диабет е едно от тях, поради удебеляването на капилярните мембрани, водещо до микроангиопатични лезии. За да се проучи метаболизмът на крайни продукти на гликирането (AGEs), са тестирани чрез ELISA за наличие на серумни антитела срещу AGEs и гликран еластин AGE-ЕДП пациенти със ЗД тип 2 и некомплицирана АХ.

Хипергликемията индуцира образуването на крайни продукти на гликирането advanced glycation end-products (AGEs), за които се счита, че играят ключова роля в патогенезата на диабетните микро- и макросъдови усложнения Brownlee M 2001[1]. Реакциите на неензимно гликиране между екстрацелуларните протеини и глюкозата са в основата на формирането на AGEs Yui

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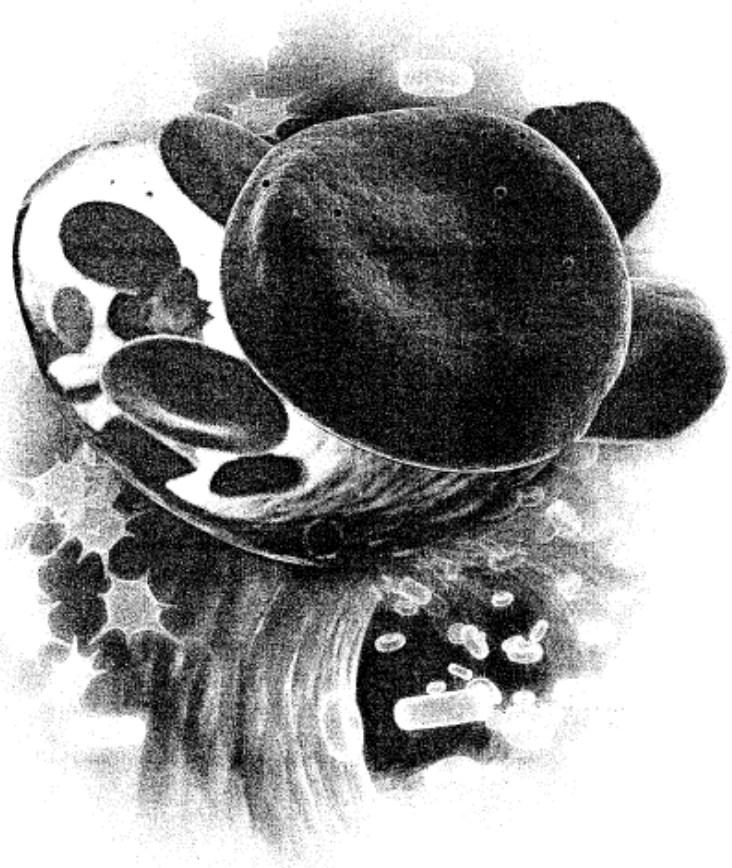

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Серумни антиколагенови тип IV ИгМ антитела и развитие на диабетна нефропатия при болни със захарен диабет тип 2 и артериална хипертония

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Резюме

Въведение и цели: Задебеляването на базалната мембрана на капилярите и малките съдове е добре позната находка и важен компонент в прогресията на диабетната микроангиопатия. Пациентите със захарен диабет (ЗД) и артериална хипертония (АХ) са в по-висок риск за развитие на съдова болест.

Материал и методи: За мониториране на метаболизма на основния базално-мембранен протеин-колаген тип IV (КIV) при пациенти със ЗД тип 2, както и за регистриране на серумните нива на антителата срещу КIV фрагменти от субкласовете Иг1, ИгМ и ИгА, беше използван ELISA методът при 93-ма пациенти със ЗД тип 2 и АХ (средна възраст 61.4±11.3 години; продължителност на диабета 9.88±3.12 г.; продължителност на хипертонията 9.28±4.98 г.). Тези стойности бяха сравнени с тези на 42 възрастово и полово съвпадащи контроли. Диабетиците бяха разделени на две групи според наличието – група 1 (n=67), или отсъствието – група 2 (n=26) на микроангиопатия.

Резултати: Проведените изследвания показват, че серумните нива на анти-КIV ИгМ антитела при пациенти със ЗД тип 2 и АХ са по-високи спрямо контролната група, като тези стойности са сигнификантни 0.178 (0.145÷0.220) *vs.* 0.142 (0.118÷0.173) (KW=6.31; p=0.01). Група 1 (пациенти с микроваскуларни усложнения) показа сигнификантно по-високи стойности на анти-КIV ИгМ в сравнение със здравите контроли 0.180 (0.136÷0.223) *vs.* 0.142 (0.118÷0.173) (KW=5.03; P=0.02). Пациентите от група 2 показаха значимо завишение на изследвания показател спрямо контролите 0.176 (0.151÷0.202) *vs.* 0.142 (0.118÷0.173) (KW=6.15; p=0.01). Най-високи стойности на анти-КIV ИгМ се установиха при пациентите със съдови поражения (група 1).

Серумните анти-КIV ИгМ корелират с микроалбуминурията (r=0.21); (p=0.04), BMI (r=0.19); (p=0.04), креатининовия клирънс (r=-0.36); (p=0.01) и GFR (r=-0.34); (p=0.02).

Серумните анти-КIV Иг нива бяха по-високи при пациентите, отколкото при контролите, докато анти-КIV ИгА нивата бяха по-високи при контролите, но разликите не са значими.

Изводи: Нашето проучване показа връзка между повишените серумни нива на анти-КIV ИгМ и развитието на диабетна нефропатия. Предполагаме, че определянето на серумните анти-КIV ИгМ антитела може да бъде полезен маркер за идентифициране на болни със ЗДТ2 и АХ, които са с висок риск за развитие на съдови увреждания.

Ключови думи: захарен диабет тип 2, артериална хипертония, антиколагенови ИгМ антитела, съдови увреждания, диабетна нефропатия

Определяне на несвързани антиеластинови антитела при пациенти със захарен диабет тип 2 и артериална хипертония

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Антитела срещу продуктите от разграждането на еластина се откриват в серумите на всички хора, корелирайки с нивата на еластиновите пептиди. Присъствието на тези антиеластинови антитела (ЕА) и сродните им антигени в циркулацията води до формирането на циркулиращи имунни комплекси (ЦИК). Целта на настоящето проучване е да определим дали серумните нива на несвързани в ЦИК еластинови антитела (НЕА) корелират с развитието на съдови увреждания при пациенти с тип 2 захарен диабет и артериална хипертония.

Ключови думи: Захарен диабет тип 2, артериална хипертония, комплемент инхибиращ фактор КИФ-ензим свързана имуносорбентна проба, несвързани антиеластинови антитела, съдови увреждания.

Материал и методи

Използвахме метод за детектиране на имунни комплекси (комплемент инхибиращ фактор: КИФ-ензим свързана имуносорбентна проба) в комбинация с ELISA за откриване на ЕА. Нивата на НЕА клас IgG бяха изследвани в серуми на 93 пациенти с тип 2 захарен диабет (Т2ЗД) и артериална хипертония (АХ) (средна възраст - 61.4±11.3, продължителност на диабета - 9.88±3.12; продължителност на хипертонията 9.28±4.98). Тези нива бяха сравнени с тези на 42 контролни лица, съвпадащи по пол и възраст. Диабетиците бяха разделени на две групи в зависимост от наличието (Група 1, n=67) или отсъствието (Група 2, n=26) на микроангиопатия.

Резултати

Несвързаните ЕА пациенти с Т2ЗД и АХ са статистически значимо по-високи в сравнение с контролите (0.42±0.04 vs. 0.24±0.02) (p=0.0009). Група 1 показа сигнификантно завишение на несвързани ЕА спрямо здрави индивиди (0.41±0.02 vs. 0.24±0.02) (p=0.0003). Група 2 също показа завишение на серумни несвързани ЕА спрямо контролната група (0.37±0.04 vs. 0.24±0.02) (p=0.001). Несвързаните еластинови антитела корелират с нивата на HbA1c (r=0.22); (p=0.04), общия холестерол (r=0.33); (p=0.05), триглицеридите (r= 0.38); (p=0.03) и микроалбуминурията (r=0.41); (p=0.002).

Изводи

Тези резултати показват, че повишените серумни нива на НЕА IgG са свързани с развитието на съдови увреждания при диабетици с артериална хипертония. Вероятно НЕА IgG са добър маркер за определяне на съдовите поражения при диабетици с артериална хипертония.

Пациентите с втори тип захарен диабет имат висок риск за развитие на диабетни микроваскуларни усложнения, вследствие на увреждането в структурата на съдовите протеини еластин и колаген тип IV. Еластичните фибри отговарят за комплайънса и еластичността, като са организирани в еластични ламели. Тези структури разделят слоевете от гладкомускулни клетки и разпределят напрежението еднородно по цялата съдова стена. Деградацията на еластичните фибри или калцификацията им при много заболявания, засягащи съдовете с малък калибър, води до васкуларна увреда. Нашите предишни изследвания при пациенти със захарен диабет тип 1 с микроангиопатия[1,2] установиха, че съществува повишена деградация на еластин - главният протеин на еластичните фибри. Вследствие на това, разтворими еластин-деградационни пептиди (ЕДП) се установяват в циркулацията, представлявайки патологичен стимул за образуването на антиеластинови антитела (ЕА)[2]. Различни видове автоантитела са установени при тип 2 захарен диабет: инсулинови автоантитела, GAD-антитела (glutamic acid decarboxylase антитела срещу ензим, декарбоксилиращ глутаминовата киселина), автоантитела срещу тирозинфосфатаза IA2, островни антитела[3], антиеластинови антитела[2] и колаген тип IV автоантитела. Тези автоантитела се свързват със сродни антигени и по този начин формират циркулиращи имунни комплекси (ЦИК). Такива ЦИК имат патогенни свойства поради депозирането им в съдовете с малък калибър, ускорявайки увреждането им.

Колагенов метаболизъм и липидни индекси при болни със захарен диабет тип 2 и артериална хипертония

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Задебеляването на базалната мембрана на капилярите и малките съдове е добре позната находка и важен компонент в прогресията на диабетната микроангиопатия. Пациентите със захарен диабет (ЗД) и артериална хипертония (АХ) са с по-висок риск за развитие на съдова болест.

. За мониториране метаболизма на основния базално-мембранен протеин-колаген тип IV (KIV) при пациенти със ЗД тип 2, както и за регистриране на серумните нива на антителата срещу KIV фрагменти от субкласовете IgГ, IgM и IgA, беше използван ELISA методът при 93-ма пациенти със ЗД тип 2 и АХ (средна възраст 61,4+/-11,3 години; продължителност на диабета 9,88+/-3,12; продължителност на хипертонията - 9,28+/-4,98). Тези стойности бяха сравнени с тези на 42 възрастово и полово съвпадащи контроли. Диабетиците бяха разделени на две групи според наличието - група 1 (n=67), или отсъствието- група 2 (n=26) на микроангиопатия.

Установяват се статистически достоверно по-високи стойности на анти-KIV IgG при пациенти със ЗД тип 2 и АХ, спрямо здрави контроли - 0,298 (0,237÷0,381) vs. 0,210 (0,149÷0,262) (KW=14,01; P<0.0001). Група 1 (пациенти с микроваскуларни усложнения) показа сигнификантно по-високи стойности на анти-KIV IgG, в сравнение с група 2 (без съдови увреди) 0,323 (0,243÷0,391) vs. 0,241 (0,207÷0,291) (KW=7,66; p=0,006), и в сравнение със здравите контроли 0,210 (0,149÷0,262) (KW=17,52; P<0.0001). Най-високи стойности на анти-KIV IgG се установиха при пациентите със съдови поражения (група 1). Серумните анти-KIV IgG корелират с продължителността на диабета (r=0.49); (p=0.01), ретинопатията (r=-0.20); (p=0.04) и BMI (r=-0.24); (p=0.05), систоличното артериално налягане (r=0.16); (p=0.05), общия холестерол (r=0.20); (p=0.03), триглицеридите (r=0.31); (p=0.01).

Анти-KIV IgG показаха корелация с log TG/HDL (r=0.21); (p=0.01), LDL/HDL (r=0.19); (p=0.02) TC/HDL (r=0.16); (p=0.05) и с TG/HDL (r=0.15); (p=0.05).

Нашето проучване показа връзка между повишението на анти-KIV IgG,

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Връзка между серумните нива на анти-еластинови IgA антитела и лечението и контрола на артериалната хипертония при болни със захарен диабет тип 2

Ключови думи:

Цели
Деградацията на главния протеин на еластичните фибри - еластин е важен фактор за развитието на лезии на съдовата стена. Еластинови пептиди (ЕДП), получени след тази деградация, се откриват в циркулацията и са стимул за произвеждането на анти-еластинови анитела (ЕА) IgM, IgG и IgA. Целта на това проучване е да проследи дали съществува връзка между ЕА и: (1) контрола на артериалната хипертония при болни със захарен диабет тип 2; (2) развитие на микроваскуларни увреждания при тези болни.

Материал и методи
Използвахме метод ELISA за откриване на ЕА. Нивата на анти-еластинови анитела (ЕА) IgM, IgG и IgA бяха изследвани в серуми на 93 пациенти с тип 2 захарен диабет (ЗДТ2) и артериална хипертония (АХ) (средна възраст 61,4±11,3, продължителност на диабета 9,88±3,12, продължителност на хипертонията 9,28±4,98). Тези нива бяха сравнени с тези на 42 контролни лица, съвпадащи по пол и възраст. Диабетиците бяха разделени на две групи в зависимост от наличието - група 1 (n=67) или отсъствието - група 2 (n=26) на микроангиопатия.

Резултати
ЕА IgA нива при пациентите със ЗДТ2 и АХ бяха статистически значимо по-високи от тези на здравите контроли 0,338(0,133÷0,452) vs. 0,006(0,052÷0,068) (KW=19,54; P<0.0001). Пациентите с микроваскуларни усложнения (група 1) показаха значимо по-високи нива на ЕА IgA от група 2- 0,353 (0,173÷0,471) vs. 0,235 (0,098÷0,377) (KW=3,36; p=0.05) и контролите 0,353 (0,173÷0,471) vs 0,006 (0,052÷0,068) (KW=20,37; p<0,0001). ЕА IgA показаха корелация с инсулиновата доза (r=-0.35); (p=0.01), систоличното артериално налягане (r=0.31); (p=0.001), HbA1c (r=0.21); (p=0.04); BMI (r=0.22); (p=0.01). Серумните стойности на ЕА IgG бяха по-високи от тези на контролите, а на ЕА IgM - по-ниски, но разликите не бяха статистически значими.
Поради установената силна корелация между серумните нива на ЕА IgA и систоличното артериално налягане, всичките пациенти (n=93) бяха разделени на две подгрупи, в зависимост от контрола на АН: на такива с незадоволителен (n=61) и задоволителен (n=32) контрол според препоръките на Европейското дружество по хипертония (ESH) за прицелни стойности на АН при диабетици. Стойностите на ЕА IgA антитела са статистически значимо повишени при диабетиците с незадоволителен контрол на АН (≥140/90), спрямо тези със задоволителен контрол (130-139/80-85): 0.381 (0,218÷0,480) vs. 0,191 (0,131÷0,344) (KW=4,69; p=0,03).

Заключение
Нашето проучване показва, че повишението на ЕА IgA при диабетици с артериална хипертония може да показва повишена еластинова деградация и развитие на съдови увреждания. Предполагаме, че ЕА IgA са свързани с контрола на артериалната хипертония при болни със захарен диабет тип 2.

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Серумни нива на еластинови деградационни пептиди при болни със стабилна коронарна артериална болест и захарен диабет тип 2

Ключови думи: Стабилна коронарна артериална болест, захарен диабет тип 2, еластинови деградационни пептиди, ELISA

Цели: Еластинът е основен съединителнотъканен протеин на съдовата стена, отговарящ за нейната еластичност. Задебеляването на базалната мембрана на капилярите и малките съдове е добре позната находка и важен компонент в прогресията на микроангиопатията при болните от захарен диабет тип 2 (ЗДТ2). При пациентите със стабилна коронарна артериална болест (С-КАБ) са установени промени в метаболизма на еластина, които са свързани с ускорена деградация и освобождаване в серума на циркулиращи еластинови деградационни пептиди. Целите на настоящето проучване са да се определят серумните нива на еластинови деградационни пептиди (ЕДП): (1) при болни със С-КАБ, (2) при болни със ЗДТ2 и да се сравнят със стойностите при здрави контроли.
Материал и методи: Серумните нива на ЕДП са изследвани при 44 пациенти със С-КАБ и при 20 пациенти със ЗДТ2 (средна възраст - 62,5±12,4 години, продължителност на КАБ-9,88±3,12 години, продължителност на ЗДТ2-8,68±7,26 години). Контролите са представени от четиридесет и двама субекти (средна възраст-58,9±7,56). Ензим свързаната имуносорбентна проба (ELISA) беше използвана за определяне на ЕДП. Диабетиците са разделени на две групи в зависимост от наличието (n=10) - Група 1 или отсъствието (n=10) - Група 2 на съдови увреждания.
Резултати: Пациентите със С-КАБ показаха статистически значими по-високи серумни нива на ЕДП (0,196±0,073) спрямо контролите (0,085±0,033) p<0,001. Група 1 (диабетици със съдови увреждания) също показаха значимо по-високи нива на ЕДП (0,146±0,081) спрямо контролите p<0,01. Пациентите от Група 2 (без съдови усложнения) показаха по-ниски нива на ЕДП (0,064±0,017) от контролите, но разликите не са статистически значими.
Извод: Повишените серумни ЕДП нива показват процес на увреждане на съдовата стена както при болни със С-КАБ, така и при ЗДТ2. Вероятно ЕДП са свързани със съдовата увреда.

Стабилната коронарна артериална болест (С-КАБ) обхваща няколко групи пациенти, включително и стабилизираните, често асимптомни фази на заболяването след ОКС. Стабилната коронарна артериална болест се характеризира най-общо с епизоди на обратимо несъответствие между нуждите и доставката на кислород в миокарда, свързано с исхемия или хипоксия, които обикновено се индуцират от физическо натоварване, емоционален или друг вид стрес. Такива епизоди се свързват с преходен гръден дискомфорт (ангина пекторис). При много пациенти първите прояви на КАБ са ендотелна дисфункция и микроваскуларно заболяване. И двете са свързани с повишен риск от усложнения на КАБ[1].

Захарният диабет е значим рисков фактор за сърдечно-съдови усложнения, увеличава риска от прогресия на коронарната болест и трябва да се лекува внимателно, с добър контрол на гликирания хемоглобин в рамките 7-6,5%. Ускорена деградация на еластин е установена при индивиди с висок риск за развитие на атеросклероза, като в много проучвания ЕДП са маркер за прогресията на артеросклерозата. Известно е, че при пациентите със ЗД са ускорени процесите на еластинова деградация и намалени тези на синтеза Laviades C[2].

Еластинов метаболизъм и атеросклероза

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Еластинът е един от основните структурни компоненти на съдовата стена. Основна негова характеристика е еластичността, която се нарушава при сърдечно-съдовите увреждания. Известно е, че серумните нива на еластиновите деградационни пептиди (ЕДП) оказват влияние върху активността на еластиновия метаболизъм и в частност на търновъра на еластичните структури. В нашето проучване използвахме „сандвич" версия на ELISA (ензим-свързаната имуносорбентна проба) за детекция и количествено измерване на ЕДП в човешки серуми. Изследвахме възрастово свързаните промени в еластиновия метаболизъм при здрави индивиди и при пациенти с атеросклероза на възраст между 50 и 75 години. Най-високи нива на серумни ЕДП бяха установени при пациентите с атеросклероза, а най-ниски - при индивидите на възраст между 18 и 50 години. Според нас нивата на серумните ЕДП, определени чрез „сандвич" версията на ELISA могат да бъдат използвани като параметър за нарушен съдов еластицитет, вследствие на промените в еластиновата обмяна и в частност на еластиновата деградация in vivo.

Ключови думи: Еластинови деградационни пептиди, ELISA, еластин, еластинова обмяна, атеросклероза.

Еластинът е главният протеин на еластичното влакно и допринася за еластичността на някои тъкани като тези на съдовата стена, белите дробове и кожата. В очите той е представен в базалната мембрана (БМ) и хороидалните съдове[1]. Частичната протеолиза на еластина от активираните протеинази води до отделяне на разтворими еластинови деградационни пептиди (ЕДП) в циркулацията. Следователно измерването на ЕДП е индикатор за системната еластинова обмяна[2].

Големи количества ЕДП се продуцират при пациенти със сърдечно-съдови рискови фактори[3,4]. Измерването на ЕДП се предлага като мониторинг на някои болестни процеси като емфизема а така също и за предиктор на експанзията на малки абдоминални аортни аневризми[5]. Повишена еластолиза се наблюдава при пациенти с различни манифестации на атеросклероза[6]. Клинични и епидемиологични изследвания установиха връзка между кардиоваскуларните рискови фактори и маркери при атеросклероза и ВСДМ (възрастово-свързаната дегенерация на макулата)[7]. Вероятно, съдовият матрикс и БМ поделят някои общи промени, включващи деградация на еластина и продуциране на ЕДП в циркулацията.

Поради факта, че циркулиращите ЕДП корелират с увреждането на еластичните влакна[8], цел на настоящето изследване е да се проучи активността на еластиновия метаболизъм при здрави субекти и при пациенти с атеросклероза, използвайки имуноензимен метод ELISA за измерване на цикулиращите ЕДП в серуми на индивиди от различни възрасти и пациенти с атеросклероза. Последните включихме като пример за вече съществуваща активна деструкция на еластичните структури от стената на кръвоносните съдове, за да определим дали с този метод може да се диференцира нормална от патологична деградация на еластина.

До днес все още не е установен параметър, който да е предиктор за клиничното протичане на атеросклерозата. Методите, с които се изследва еластиновата обмяна са твърде малко, а данните за специфичните промени в норма и патология са оскъдни. Вероятно ЕДП биха могли да предоставят необходимата информация относно прогресията на това заболяване и да улеснят идентифицирането на високорисковите групи, на които да се обърне по-голямо клинично внимание.

В настоящото проучване проследихме възможностите за преценка активността на еластиновата обмяна чрез имунологични методи, като разработихме съвременни високочувствителни тестове за определяне на циркулиращи еластинови пептиди в човешки серум.

Материал и методи

Антиген

Материалът за приготвянето на еластина е взет от аортата на 30-годишен здрав човек (загинал в инцидент) без макроскопски увреждания на интимата. Неразтворим еластин е приготвен според метода на *Barnard et al.*[9] и е използван за приготвянето на разтворим алфа-еластин по *Partridge*[10].

ПРОДЪЛЖАВА НА СТР. 54

Диабетна микроангиопатия

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Съдбата на болните от захарен диабет зависи най-вече от тежестта и еволюцията на съдовите усложнения. Захарният диабет е водеща причина за слепота (70-85% от болните имат диабетна ретинопатия), хронична бъбречна недостатъчност (40% имат диабетна нефропатия), 50% имат диабетна невропатия, а ампутациите на долните крайници са 20-40 пъти повече от лицата без диабет. Тези усложнения определят клиничната картина, терапевтичните възможности и прогнозата при болните от захарен диабет.

Ключови думи: захарен диабет, съдови усложнения, късни продукти на гликирането.

Диабетната микроангиопатия (ДМи) представлява специфично, генерализирано поражение на всички съдове от микроциркулаторния отдел на кръвоносната система (артериоли, капиляри и венули). Известно е, че микроциркулацията осигурява доставката в клетките на кислород, енергетични и пластични субстрати, биологично активни вещества (хормони, медиатори, антитела и др.) и освобождава тъканите от въглероден диоксид, крайни продукти на обмяната на веществата и др.

Данните от проведените морфологични и ултраструктурни изследвания доказаха увреждане на асички съдове от микроциркулацията. В ендотелните клетки се установява увеличаване на клетъчните органели, изобилие от микропиноцитозни везикули, микровилозни образувания по луменовата повърхност, считани за морфологичен белег на повишена функционална активност. Ядрата имат диспергиран хроматин и нагъната ядрена мембрана. В периендотелното пространство се установява отлагане на материал, който по структура и електронна плътност наподобява базална мембрана. Този материал се представя като многослойни образувания с неравномерна дебелина, разположени около базалната мембрана. Между тези псевдомембрани се разполагат както хомогенни безструктурни, така и финно грануларни отлагания. Често към тях се прибавят и колагенови фибрили, разположени концентрично, образувайки „маншони" около съдовете. В засегнатите тъкани се наблюдават исхемични зони с рязко нарушена обмяна. Увреждането на съдовете от микроциркулаторния отдел на кръвоносната система затруднява адаптацията им към обичайни и особено към повишени изисквания. ДМи затруднява развитието на колатералното кръвообращение, намалява резултата от провежданото лечение и влошава прогнозата.

Патогенезата на диабетната микроангиопатия не е изяснена напълно. Няколко хипотези (метаболитна, генетична, имунна и др.) дават обяснение на механизмите, водещи до развитие на съдови усложнения. Според метаболитната хипотеза съдовите усложнения са вторични, резултат на инсулинов дефицит и нарушена обмяна. Хипергликемията играе важна роля за развитие на ДМи. Та се свързва с усилена пролиферация на ендотелни клетки, увеличена продукция на патологичен матрикс и тежки дегенеративни изменения.

Няколко основни механизми водят до различни по вид и тежест увреждания на тъканите и до развитие на диабетна микроангиопатия:

Инсулинонезависим път на въглехидратна обмяна (полиолов път)

В условията на инсулинов дефицит нараства делът на сорбитоловия път на обмяната на глюкозата (от 1% при здрави хора до 10% при болните от ЗД). Когато вътреклетъчната глюкозна концентрация нараства се установява активиране на алдозоредуктазата и подтискане на сорбитолдехидрогеназата с последващо увеличение на сорбитола и фруктозата в тъканите. Тази реакция консумира голямо количество НАДФ (отговорен кофактор за възстановяване на редуцирания глутатион). Добре известно е, че глутатионът е важен вътреклетъчен антиоксидант и ако неговата концентрация е понижена, клетките стават много чувствителни към оксидативен стрес.

Неензимно гликиране

То представлява физиологична посттранслационна промяна на протеините. Степента на гликиране зависи от средното ниво на глюкозата, продължителността на взаимодействие и скоростта на обмяна на съответните протеини. Доказано е, че в резултат на гликирането се нарушава структурата (третична и четвъртична), функцията, синтеза-

Анти-колагенови тип IV антитела и развитие на микроваскуларни усложнения при пациенти със захарен диабет тип 2 и артериална хипертония

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Задебеляването на базалната мембрана на капилярите и малките съдове е добре позната находка и важен компонент в прогресията на диабетната микроангиопатия. Пациентите със захарен диабет (ЗД) и артериална хипертония (АХ) са в по-висок риск за развитие на съдова болест.

Ключови думи: Захарен диабет тип 2, артериална хипертония, анти-колагенови ИгГ антитела, съдови увреждания.

Материал и методи: За мониториране метаболизма на основния базално-мембранен протеин - колаген тип IV (KIV) при пациенти със ЗД тип 2, както и за регистриране на серумните нива на антителата срещу KIV фрагменти от субкласовете ИгГ, ИгМ и ИгА, беше използван ELISA методът при 93[м/ж] пациенти със ЗД тип 2 и АХ (средна възраст 61.4+/-11.3 год.; продължителност на диабета - 9.88+/-3.12; продължителност на хипертонията - 9.28+/-4.98). Тези стойности бяха сравнени с тези на 42 възрастово и полово съвпадащи контроли. Диабетиците бяха разделени на две групи според наличието на микроангиопатия - Група 1 (n=67) или отсъствието - Група 2 (n=26).

Резултати: Пациентите със ЗД тип 2 и АХ показаха значимо по-високи нива на анти-KIV ИгГ, в сравнение със здравите контроли (0.30+/-0.12 срещу 0.21+/-0.08); (p=0.0001). Група 1 показа значимо по-високи нива на анти-KIV ИгГ, отколкото Група 2 (0.32+/-0.13 срещу 0.24+/-0.08); (p=0.009) и здравите контроли (0.32+/-0.13 срещу 0.21+/-0.08); (p=0.0001). Нивата на анти-KIV ИгГ са значимо по-високи при диабетиците с ретинопатия, отколкото при тези без (0.33+/-0.10 срещу 0.26+/-0.13) (p=0.04). Анти-KIV ИгГ корелира с продължителността на диабета (r=0.49); (p=0.0004), ретинопатията (r=0.20); (p=0.05) и BMI (r=0.24); (p=0.05). Серумните нива на анти-KIV ИгМ и ИгА при пациенти със ЗД тип 2 и АХ бяха по-ниски, отколкото при контролите, но тези разлики не са статистически значими.

Изводи: Нашето проучване показа връзка между повишените серумни нива на анти-KIV ИгГ при диабетици и развитието на микроангиопатия.

Клиничните манифестации на микро- и макроваскуларно увреждане при захарен диабет (ЗД) включват ретинопатия, нефропатия и бързо развиваща се атеросклероза. Възможните последици от горните са слепота, бъбречна дисфункция, миокарден инфаркт, инсулт, ампутация на крайници. Тези манифестации в таргетните органи показват общи патологични характеристики, които са в основата на всички съдови заболявания. Въпреки това, всяко усложнение има свои отличителни черти, в зависимост от замесената тъкан, както и специфично насочени превенция и лечение[1]. Това разнообразие е подкрепено от ясните епидемиологични характеристики на съдовите усложнения, които са различно проявени при диабетно болните[2]. Разпространението на съдовите усложнения също варира, в зависимост от ангажираното място. Макроангиопатията е понякога представена по време на поставяне на диагнозата, особено при ЗД тип 2[2], докато микроваскуларните усложнения обикновено се развиват няколко години след началото на диабета[3,4].

От друга страна, докато развитието на ретинопатията се увеличава с продължителността на диабета, тази на нефропатията достига връх след около 15 г., след което намалява. Отношението на развитието и тежестта на съдово заболяване са също зависими от индивидуалните характеристики на индивида. Някои пациенти развиват само начални лезии, докато други прогресират до крайните стадии на заболяването, дори и да са на сходно метаболитно ниво.

Артериалната хипертония и диабетните съдови усложнения са свързани с повишени нива на разграждане на еластичните фибри. В резултат на това, колагенови тип IV (KIV) фрагменти са освобождавани в кръвообращението, което е патологичен стимул за повишена продукция на автоантитела срещу епи-

ПРОДЪЛЖАВА НА СТР. 34

Липидни индекси и еластинов метаболизъм при болни със захарен диабет тип 2 и артериална хипертония

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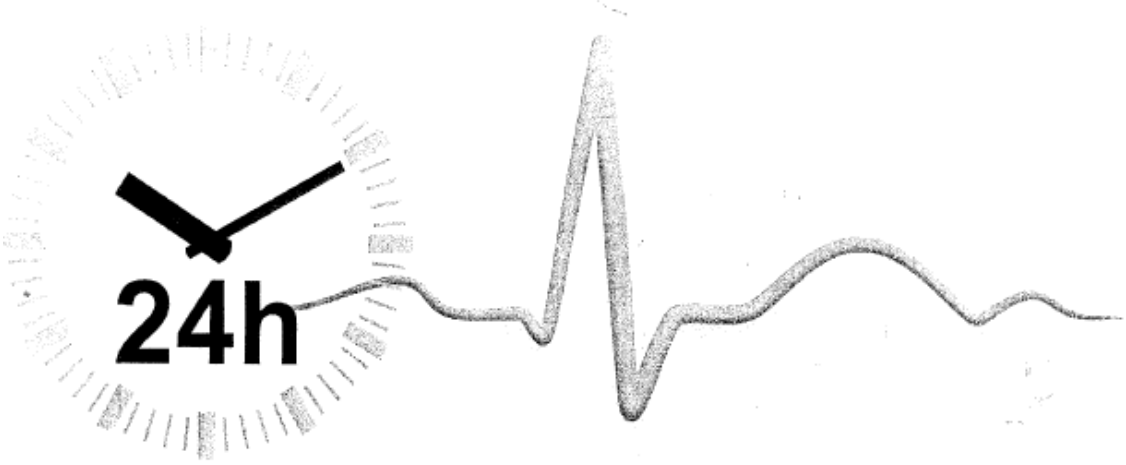

Цел

Деградацията на главният протеин на еластичните фибри-еластин е важен фактор за развитието на лезии на съдовата стена. Еластинови пептиди (ЕП), получени след тази деградация, се откриват в циркулацията и са стимул за произвеждането на анти-еластинови антитела (АЕА) IgM, IgG и IgA. Целта на това проучване е да проследи дали съществува връзка между АЕА, липидните индекси и развитието на микроваскуларни увреждания при диабетици с артериална хипертония.

Материал и методи

Използвахме метод ELISA за откриване на АЕА. Нивата на анти-еластинови антитела (АЕА) IgM, IgG и IgA бяха изследвани в серуми на 93 пациенти с тип 2 захарен диабет (Т2ЗД) и артериална хипертония (АХ) (средна възраст 61,4±11,3, продължителност на диабета 9,88±3,12; продължителност на хипертонията 9,28±4,98). Тези нива бяха сравнени с тези на 42 контролни лица съвпадащи по пол и възраст. Диабетиците бяха разделени на две групи в зависимост от наличието - група 1 (n=67) или отсъствието - група 2 (n=26) на микроангиопатия.

Резултати

Установихме, че серумните АЕА IgA антитела при пациенти със ЗД тип 2 и АХ са статистически значимо по-високи в сравнение с контролната група 0,338 (0,133÷0,452) vs. 0,006 (0,052÷0,068) (KW=19,54; P<0.0001). Пациентите, които имаха данни за микроваскуларни увреждания (група 1) показаха сигнификантно по-високи стойности на АЕА IgA спрямо тези без 0,353 (0,173÷0,471) vs. 0,235 (0,098÷0,377) (KW=3,36; p=0.05) и спрямо контролите 0,353 (0,173÷0,471) vs 0,006 (0,052÷0,068) (KW=20,37; p<0,0001). Субектите без съдова увреда имаха също значимо по-високи нива на АЕА IgA спрямо контролите 0,235 (0,098÷0,377) vs. 0,006 (0,052÷0,068) (KW=8,54; P=0.003) Най-високите стойности на АЕА IgA се откриват при група 1 (пациенти с васкуларни поражения). АЕА IgA корелират с log TG/HDL (r=0.28); (p=0.001), LDL/HDL (r=0.22); (p=0.01), TC/HDL (r=0.22); (p=0.01) и TG/HDL (r=0.15); (p=0.05).

Извод

Нашето проучване показа връзка между повишението на АЕА, високите липидни индекси и развитието на микроваскуларни увреждания при болни със ЗДТ2 и АХ.

Пациентите с втори тип захарен диабет имат висок риск за развитие на диабетни микроваскуларни усложнения вследствие на увреждането в структурата на съдовите протеини еластин и колаген тип IV. Еластичните фибри отговарят за къмплайанса и еластичността, като са организирани в еластични ламели. Тези структури разделят слоевете от гладкомускулни клетки и разпределят напрежението

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Serum fibrillin–antifibrillin immune complexes among diabetic children

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Abstract

The fibrillins are large glycoproteins components of 10-nm microfibrils found in the extracellular matrix of most tissues. Microfibrils play a role in elastic fiber assembly and serve to link cells to elastic fibers in the extracellular matrix. Fibrillin-1 (FBN-1) and -2 (FBN-2) are large, secreted glycoproteins known to be components of extracellular matrix microfibrils located in the vasculature, basement membrane, and various connective tissues and are often associated with a superstructure known as the elastic fiber. Anti-fibrillin antibodies found in some autoimmune diseases could form circulating immune complexes (CIC) with corresponding antigens. Type 1 (insulin-dependent) diabetes mellitus is an autoimmune disease leading to formation of different types of autoantibodies. To determine the possible presence of FBN-anti-FBN CIC (IgG and IgM) were studied by modified version of ELISA 35 children with Type 1 diabetes mellitus (mean age—12.37±3.77 years, diabetes duration 4±3.5 years). Eight of the diabetics had vascular complications. Twenty healthy children (mean age—11.58±2.89 years) were used as controls. Diabetics showed statistically significant higher levels of FBN-anti-FBN-2 CIC — IgG (0.303±0.076 vs. 0.252±0.029; $p=0.029$) and IgM (0.415±0.085 vs. 0.348±0.069; $p=0.018$) compared to the control group. FBN-anti-FBN-1 CIC IgM correlate with diabetes duration ($r=0.52$; $p=0.0015$) and BMI ($r=0.33$, $p=0.053$) while FBN-anti-FBN-1 CIC IgG correlate with serum Zinc ($r=0.49$, $p=0.006$). FBN-anti-FBN-2 CIC IgG correlate with microalbuminuria ($r=0.65$, $p=0.0046$) and retinopathy ($r=0.61$, $p=0.0001$). This study suggests that there may be a relationship of levels of FBN-anti-FBN-2 CIC IgG with the development of diabetic microangiopathy. Of course the number of the tested patients is limited for definitive conclusions. Although the meaning of these results is still being determined, the measurement of FBN-anti-FBN CIC may represent immunologic markers of FBN metabolism.

Keywords: Diabetes mellitus; Diabetic microangiopathy; Fibrillin–antifibrillin circulating immune complexes; Autoantibodies

1. Introduction

Fibrillin (FBN) was identified in 1986 in the extracellular matrix of skin, lungs, cartilage, and vascular tissue among other major tissues (Sakai et al., 1986). FBN-1 and FBN-2 constitute the backbone of extracellular filaments, called microfibrils. FBN assembly involves complex multistep mechanisms to result in a periodical head-to-tail alignment in microfibrils (Lin et al., 2002). Impaired assembly potentially plays a role in the molecular pathogenesis of genetic disorders caused by mutations in FBN-1 (Marfan syndrome — Dietz and Pyritz, 1995) and FBN-2 (congenital contractural arachnodactyly — Lee et al., 1991). It is possible that these mutations alter the ability of FBN to bind major microfibril-associated glycoprotein-1 (MAGP-1), which may contribute to the severity of the disease (Werneck et al., 2004). FBN-1 is the major structural glycoprotein of connective tissue microfibrils, which are important components of elastic fibers widely distributed throughout the body (Reinhardt et al., 1996). The exact role of FBN within the extracellular connective tissue is unknown mainly due to the lack of information on the actual mechanical role of microfibrils. However, it is known that it is a major protein construction block for this ever important tissue with its capacity for elasticism and its

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Serum AGE-elastin derived peptides among diabetic children

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Abstract

The purpose of the study was to measure advanced glycated end products (AGE) of elastin in human serum. In the present study, we adapted an ELISA technique for the determination of AGE-elastin-derived peptides (AGE-EDP) in human sera of healthy and diabetic subjects. This test makes use of human aortic elastin hydrolyzed by a chemical procedure (α-elastin) and AGE-Hemocyanin. Polyclonal sera from rabbit against AGE-Hemocyanin and from sheep against α-elastin were obtained and their specificity was tested via direct and competitive ELISA. Sera of 60 Type 1 (insulin-dependent) diabetic children and 28 healthy subjects were tested. The patients with vascular complications showed significant higher levels of age, diabetes duration, systolic blood pressure (SBP), diastolic blood pressure (DBP), dose, EDP and AGE-EDP than those without vascular complications. AGE-EDP concentrations of all diabetics correlated with triglycerides ($r=0.19$; $p=0.04$). The correlation was found between AGE-EDP and DBP in the subgroup of patients with microalbuminuria+retinopathy ($r=0.94$; $p=0.0006$). The subgroup of patients with microalbuminuria ($n=19$) showed correlation with age ($r=0.24$; $p=0.008$), AGE-EDP ($r=0.65$; $p=0.0001$), EDP ($r=0.51$; $p=0.0001$) and SBP ($r=0.33$; $p=0.0003$). Further studies are necessary to elucidate the relationship between the serum level of AGE-elastin degradation products and diabetic vascular complications. The measurement of non-invasive markers of elastin synthesis and degradation may be useful in monitoring development and therapeutic intervention in diabetic vascular complications.

Keywords: Diabetes mellitus; AGE-elastin; Diabetic vascular complications

1. Introduction

An increase in the amount of advanced glycation end products (AGE) is seen in the blood of patients with diabetes mellitus (Hayase et al., 1989; Makita et al., 1992). This increase is believed to play a causal role in diabetic neuropathy (Brownlee et al., 1988), nephropathy (Hayase et al., 1989; Makino et al., 1995) and retinopathy (Brownlee, 1994; Hammes et al., 1996; Vlassara et al., 1994; Murata et al., 1997). Glucose reacts non-enzymatically with proteins to form Schiff base and Amadori products, which are early stage products. Further incubation of early stage products leads to the formation of AGE (Horiuchi et al., 1991).

The connective tissue protein elastin is largely responsible for maintaining of the elasticity of vascular wall and lung tissue. The degradation of elastin was shown to occur in several diseases such as emphysema (Bignon and Robert, 1978), atherosclerosis (Robert and Robert, 1980; Robert et al., 1984; Hornebeck et al., 1984) and a variety of skin diseases (Hornebeck et al., 1984; Frances and Robert, 1984). Soluble elastin-derived peptides (EDP) are then released and can reach the circulating blood. EDP were shown to posses several important biological properties such as chemotactic activity to monocytes and fibroblasts (Senior et al., 1980) activation of ion fluxes (Jacob et al., 1987) and induction of anti-EDP antibodies (Bako et al., 1987). The degradation of elastin was shown to occur during aging, the development of atherosclerosis and some skin diseases (Robert and Robert, 1980; Robert et al., 1984; Frances and Robert, 1984). Therefore, the determination of EDP concentration in the sera might be interesting in the detection and monitoring of age-dependent diseases and especially pulmonary and vascular diseases.

The aim of the present study was to try to measure serum AGE-EDP concentrations in the sera of healthy and diabetic children. For the purpose were studied 60 diabetic children.

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Original Research Article

Serum Cobalt in Children With Essential Hypertension

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ABSTRACT The effect of cobalt on the cardiovascular system is one of many aspects of cobalt metabolism in humans. Elastin and collagen are the main proteins of the vascular wall. The aims of this study were: 1) to determine serum cobalt concentrations in children with hypertension; and 2) to study the correlation between serum cobalt and some biological markers of the extracellular matrix of the vascular wall, i.e., anti-elastin and anti-collagen type IV antibodies. Patients showed statistically significant higher levels of systolic and diastolic blood pressure, and significantly lower serum cobalt concentrations, than controls. Children with hypertension showed significantly higher levels of total cholesterol ($P = 0.0003$) and collagen type IV IgM ($P = 0.04$). Collagen type IV IgG levels ($P = 0.027$) were lower than in controls. Serum cobalt in patients showed a correlation with systolic blood pressure ($r = -0.44$, $P = 0.05$), elastin IgM ($r = 0.60$, $P = 0.007$), and collagen type IV IgG ($r = -0.46$, $P = 0.04$). Our data suggest the existence of a correlation between changes in levels of serum cobalt, total cholesterol, anti-collagen type IV antibodies, and essential hypertension in children. This is the first study of serum cobalt in children with essential hypertension. Am. J. Hum. Biol. 18:798–805, 2006.

Changes in concentrations of cobalt in biological liquids and tissues are observed in different diseases and conditions, yet many aspects of the metabolism of cobalt in the organism are unclear (Tsalev, 1995; World Health Organization, 1996). Cobalt is one of the microelements that exercise an influence on the vascular system. Cobalt dilates the vessels and has a hypotensive effect (Dugin et al., 1991; Cavun and Millington, 2001). It has a positive effect on cholesterol level, and normalizes lipoproteins (Kliorin, 1981; Schuster and Caughman, 2004). The effect of cobalt in experimentally induced atherosclerosis is considered to be a factor in hastening a reversal of the condition (Dzhuraev and Nasriddinova, 1992). The effect of cobalt on the cardiovascular system is one of many aspects of cobalt metabolism in the human organism which has not been investigated exhaustively.

Elastin and collagen are the main proteins of the vascular wall. An important factor in the development of vascular wall alterations is degradation of the elastic fiber major protein, elastin (Rosenbloom et al., 1993). Basement membranes regulate the functions of many cells and mediate the interactions between different tissues (Paulsson, 1992; Kuhn, 1994). Collagen type IV (CIV) constitutes the major component of basement membranes (Schuppan and Riecken, 1990). Measurement of serum antibodies to fragments of elastin (Fulop et al., 1990; Gminski et al., 1991; Daskalova et al., 1997; Nicoloff et al., 2005a) and CIV (Balashova et al., 2000; Nicoloff et al., 2002) is now possible, and enables changes to be detected.

Bako et al. (1987) reported that in group of patients with hypertension, 60% of sera were positive for anti-elastin antibodies (AEAbs) of the IgG type, independent of age. In obliterative arteriosclerosis of the legs and in type IIb hyperlipoproteinemia, elastin-derived peptides levels (EDP) showed a marked increase, while in hypertension, the increase was moderate (Fulop et al., 1990).

There are data for the detection of serum CIV in animals or humans with arterial hy-

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Detection of free elastin-derived peptides among diabetic children

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Abstract

Elastin breakdown products are found in the serum of all human subjects. The presence of these elastin-derived peptides (EDP) and the corresponding antibodies in circulation leads to formation of circulating immune complexes (CIC). The aim of this study was to determine if serum level of free-EDP (unbound in CIC) correlate with the development of microvascular complications in children with Type 1 (insulin-dependent) diabetes mellitus. To this end we used a method for detecting immune complexes (CIF-ELISA) in combination with an ELISA for detection of EDP. The levels of free EDP were studied in sera of 81 diabetic children (mean age 13.46 ± 3.51 years, diabetes duration 5.17 ± 4.21 years). Forty-two of the children had vascular complications (group 1) and 39 were without vascular complications (group 2). Twenty-one healthy children (mean age 12.6 ± 2.47 years) were used as controls. Diabetics showed significantly higher levels of free EDP (68.1 ± 25 ng/ml versus 51 ± 12.5 ng/ml; $p = 0.003$) compared to the control group. In group 1, free EDP showed significantly higher levels than controls (78.9 ± 25.6 ng/ml versus 51 ± 12.5 ng/ml; $p = 0.0001$). About 38 of 81 (47%) patients were positive for free EDP (30/42 – 71% in group 1 and 8/39 – 21% in group 2). Free EDP levels in all diabetics showed a correlation with insulin dose ($r = 0.23$; $p = 0.041$), and microalbuminuria ($r = 0.57$; $p = 0.0001$). Patients who had vascular pathology showed a correlation of free EDP with microalbuminuria ($r = 0.41$; $p = 0.0081$), retinopathy ($r = 0.32$; $p = 0.041$), insulin dose ($r = 0.37$; $p = 0.02$), HbA1c ($r = 0.35$; $p = 0.03$), systolic blood pressure ($r = 0.30$; $p = 0.045$) and total cholesterol ($r = 0.36$; $p = 0.02$). These findings suggest that elevated levels of free EDP are associated with the development of diabetic vascular complications in children.

Keywords: Diabetes mellitus; CIF-ELISA; Free elastin-derived peptides; Microalbuminuria; Retinopathy

1. Introduction

Patients with juvenile onset of Type 1 (insulin-dependent) diabetes mellitus are at high risk of diabetic microvascular complications due to alteration in the structure of the vascular proteins.

Elastin is one of the major structural matrix proteins of the arterial wall [1–3]. Mature elastin is composed of soluble elastin subunits, which are intermolecularly cross-linked into a fibrous network (desmosine and isodesmosine formation) and thus construct a highly polymerized insoluble protein. Degradation of arterial wall elastin is a characteristic feature in atherogenesis. Serum concentration of elastin-derived peptides (EDP) is elevated in atherosclerotic patients and reflects elastin turnover [4]. Increased serum concentration of EDP is a potential indicator of advanced atherosclerosis such as plaque instability and is also a predictor of rupture in atherosclerotic aortic aneurysms [5].

Our previous studies have documented an increased degradation of elastin and production of antielastin antibodies (AEAbs) in diabetic children with microangiopathy [6,7]. These autoantibodies bind to their cognate antigen and thus form circulating immune complexes (CIC). Such CIC may have pathogenic potential since they can give rise to microangiopathy following deposition in small blood vessels. CIC containing LDL or elastin–antielastin has been identi-

Abbreviations: EDP, elastin-derived peptides; AEAbs, antielastin antibodies; CIF, complement inhibition factor

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ORIGINAL INVESTIGATION

Abnormal Levels of Serum Antielastin Antibodies in Children with Diabetes Mellitus Type 1

George Nicoloff, Antony S. Weiss, Violeta Iotova, Valentina Tzaneva, Chayka Petrova, Nadja Donnuschieva, Asparuh Nikolov, Plamen Tzvetanov, and Petkana Christova

Antibodies to α-elastin (elastin breakdown product) and elastin sequences devoid of cross-linked regions (linear elastin) are found in the serum of all human subjects and correlate with their respective serum peptide levels. The aim of this study was to determine if the serum level of antielastin antibodies (AEAbs) differs between type 1 diabetic children and nondiabetic children. Enzyme-linked immunosorbent assay was used to measure the levels of immunoglobulin (Ig)G and IgM AEAbs in the sera of 45 diabetic children (mean age 12.8 ± 3.2 years, diabetes duration 5.3 ± 3.6 years). Twenty-two children presented with vascular complications (group 1), whereas 23 displayed no vascular complications (group 2). The controls were 18 healthy children (mean age 11.9 ± 2.3 years). Diabetic patients showed statistically significant higher levels of IgM α-AEAbs (0.82 ± 0.26 vs 0.61 ± 0.14, $p = .0013$) than the control group. In group 1, α-AEAbs showed statistically significant higher level than controls: IgG (0.86 ± 0.42 vs 0.59 ± 0.12; $p = .0109$) and IgM (0.88 ± 0.24 vs 0.61 ± 0.14; $p = .0001$). IgM antilinear elastin antibodies (ALEAbs) in group 1 were significantly lower than in controls (0.462 ± 0.191 vs 0.652 ± 0.127; $p = .0009$). IgG α-AEAbs showed correlation with microalbuminuria ($r = -.26$; $p = .05$) and IgM ALEAbs correlated with microalbuminuria ($r = -.32$; $p = .035$). IgG α-AEAbs correlated with neuropathy ($r = -.32$; $p = .035$). Group 1 patients displayed a correlation between IgG ALEAbs and retinopathy ($r = -.48$; $p = .023$) and IgM ALEAbs and microalbuminuria ($r = .52$; $p = .014$). Levels of AEAbs and ALEAbs can serve as immunologic markers of the extent of elastin degradation. These markers may provide a tool to study elastin metabolism and a potential clinical role for AEAbs in the pathogenesis and development of vascular complications in diabetic children.

Key words: diabetes mellitus, antielastin antibodies, microalbuminuria, retinopathy

Elastin fibers, which are composed primarily of elastin, endow loose connective tissue with resilience that complements the tensile strength of collagenous fibers. Elastin is the main component of the extracellular matrix of arteries, where it additionally performs a regulatory function during arterial development by controlling proliferation of smooth muscle and stabilizing arterial structure.[1] Elastin is composed largely of glycine, valine, proline, and other hydrophobic residues that contribute to uncross-linked elastic regions within the molecule. Elastin also contains multiple lysine residues in alanine-rich environments that contribute to lysine-derived cross-links, such as desmosines, which link the individual polypeptide chain into an elastic network.[2] During aging, the elasticity of connective tissue becomes reduced, mainly owing to a combination of molecular modification[3] and elastolysis.

Humans normally have measurable serum levels of immunoglobulin (Ig)G antielastin antibodies (AEAbs), as well as IgA, IgM, and IgD.[4] AEAbs of different Ig

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DETECTION OF SERUM COLLAGEN TYPE IV AND ELASTIN DERIVED PEPTIDES IN PATIENTS WITH BREAST CANCER

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Key words: breast cancer, elastin-derived peptides, collagen type IV derived peptides, ELISA

SUMMARY

Breakdown of basement membrane is believed to be an essential step for tumor invasion and metastasis. The interaction between tumor cells and extracellular matrix can also result in the induction of basement membrane and elastin synthesis by tumor and stromal cells. The aim of our study was to detect serum concentrations of collagen type IV and elastin in patients with breast cancer, and to test the possible relationship of elastin-derived peptides (EDP) and collagen type IV derived peptides (CIVDP) with breast cancer. Serum levels of CIVDP and EDP were measured by ELISA in 39 breast cancer patients. These values were compared with serum levels in 25 age- and sex-matched controls. In patient group, EDP levels were independently associated with age ($r=0.36$; $P=0.003$) and tumor size ($r=0.48$; $P=0.034$), while CIVDP correlated with breast cancer stage ($r=0.35$; $P=0.04$). Our data suggested the possible correlation between changes in serum levels of EDP and CIVDP and breast cancer. Higher concentrations of EDP and CIVDP correlated with tumor pathology in breast cancer. Prospective and longer studies of larger populations are needed to identify the role of EDP and CIVDP as potential markers in breast cancer pathology.

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INTRODUCTION

Breast cancer is an important disease because of its high frequency, which is continuously growing, its high death rate and the fact that this type of cancer more often affects women under 45. In 2003, the breast cancer morbidity and death rates in Bulgaria were 87.4 /100000 and 28.3 /100000, respectively (1). This morbidity rate is comparable with that of industrially developed countries. The higher mortality rate is a consequence of disease detection only in advanced stages.

Elastin is one of the major structural matrix proteins of the arterial wall (2-4). Mature elastin is composed of soluble elastin subunits, which are intermolecularly cross-linked (desmosine and isodesmosine formation) into a fibrous network that results in a highly polymerized insoluble protein. Elastin is composed largely of glycine, valine, proline and other hydrophobic residues that cluster in distinct domains that

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Smoking And Thiocyanates In High School Students, University Students And Children With Hypertension

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SUMMARY: *To objectify smoking and its connection with various diseases and conditions are used analytical markers. The aim of our study was to estimate smoking and its intensity by determination of thiocyanates in blood serum and or urine at high school students, university students and children with essential hypertension (PAH). In the group of children with high blood pressure (BP) were also determined lipid parameters. Thiocyanates are determined in the urine of 86 students aged 15-18 years, and 10-15 year olds 41 - hypertensive. 84 medical students - 18-22 years old were studied serum and urine thiocyanate. We found that 44.49% of students and 50 % of students are smokers , and 47.4% of smokers and 50 %, respectively smoke more than 10 cigarettes a day .The differences in thiocyanates levels in serum and urine in the groups of non - smokers , smoking 10 cigarettes a day and smoking more than 10 cigarettes a day students are statistically significant. Children with hypertension smokers are 31.02%. They have statistically higher levels of thiocyanates in urine, higher values of cholesterol and triglycerides and lower HDL-cholesterol, compared to non - smokers with hypertension.The results supported by published data shows the relationship between smoking, high BP and lipid profile in infancy. Given that smoking not only affects the cardiovascular system and overall development of the child's body , it is necessary to introduce health programs and strategies for family life improvement, for prevention of smoking at school age and to provide support to those who want to quit smoking.*

KEY WORDS: *smoking, thiocyanate, hypertension, children.*

I. INTRODUCTION

Information for statistical evaluation of smoking is often gathered by surveys. Their results depend on many factors and are not always reliable. To objectify smoking assessment quantitative analytical criteria are used to distinguish smokers from non-smokers, determine the intensity of smoking or are used in the process of treatment.The markers that are most commonly used are carbon monoxide (CO , COHb), nicotine (in plasma or serum, saliva , urine, hair, nails) , cotinine (plasma, saliva , urine, hair) , thiocyanates (plasma, saliva , urine) (1-3).Practically suitable are the methods based on defining thiocyanates , which are metabolites of cyanide from tobacco smoke. Thiocyanates have - long half-life - 14 days which excludes false negative results in case of smoking interruption for over two days (3). Thiocyanates are also received endogenously with certain foods, so for their determination it is necessary to have a control group of non-smokers. Smoking damages the body of both active smokers and passive smokers. Unfortunately, smoking among adolescents and children becomes more and more frequent. The peak of early smoking is shifting from 18 years to 14-16 years of age, and smoking attempts were observed in the first decade of life for some of the children. Smoking in adults leads to cardiovascular disease (CVD), cerebrovascular, and respiratory diseases. Smoking affects the neuro-psychical functions by reducing the protective functions of the immune system (3-7). Smoking in adolescence sets the risk of developing these diseases in adulthood.Many of the traditional risk factors for CVD, such as high blood pressure, dyslipidemia, tobacco use, unhealthy diet and obesity begin in childhood. Prophylactic determination of these risk factors could prevent CVD (8). It is considered that smoking affects the increasing spread of the GCC and increases the risk of death by 20% (9). Studies, most often in adult populations show a relationship between smoking and arterial endothelial dysfunction, lipid parameters and onset of arterial hypertension and atherosclerosis. (5, 8).Therefore, the aim of our survey was to study smoking and its intensity by the usage of thiocyanate markers in blood serum and or urine in school children, students and children with hypertension - one of the risk factors for CVD. In the group of children with elevated blood pressure (BP) lipid parameters were also identified.

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СТАТУС НА ТЮТЮНОПУШЕНЕТО ПРИ ПАСИВНИ ПУШАЧИ

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SMOKING STATUS IN PASSIVE SMOKERS

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Резюме. *Пушенето не е регламентирано на обществени места в България, но ограниченията или не се прилагат напълно, или свързаните с опасност за здравето последици не се признават от голяма част от българското население. Чрез обективен маркер за установяване на статуса на тютюнопушене и неговата интензивност – тиоцианати в серум и урина, това изследване има за цел да посочи, че рисковете за здравето на пасивните пушачи са еднакви – дори по-големи, в сравнение с тези при активно пушещите.* **Методи:** *Спектрофотометрично количествено определяне на биомаркера тиоцианати в серум и урина. Статистическата обработка е направена по Statgraphics Plus for Windows.* **Резултати:** *От 187 лица, работещи в среда с тютюнопушене, 31 (17%) са пасивни пушачи. Изследвани бяха тиоцианатите при 18 пасивни пушачи и за сравнение – при 84 студенти пушачи и непушачи. Тиоцианатите в серум и урина при пасивните пушачи са близки до нивата на активно пушещите над 10 цигари дневно.* **Заключения:** *Получените резултати показват висока интензивност на пасивното и на активното тютюнопушене. Като един от рисковите фактори за различни заболявания и смърт, тютюнопушенето следва да бъде забранено на обществени места. Необходима е ефективно контролирана законова уредба за забраната му, както и програми за предотвратяване на пушенето и за подкрепа на отказващите се от тютюнопушене.*

Ключови думи: *пасивно пушене, тютюнопушене, биомаркер тиоцианати*

Summary. Introduction: *Smoking in public places is not permitted in Bulgaria, but the restrictions are either not fully applied or the related adverse health effects are not recognized by the majority of Bulgarian population.* **Objective**: *Using an objective marker to identify the status of the tobacco smoking and its intensity – thiocyanate in serum and urine, this study is intended to demonstrate that the risks to health of passive smoking are the same and even greater than those of the active smoking.* **Methods**: *Spectrophotometric quantitative determination of the biomarker – thiocyanates in serum and urine. Statistical processing is done by Statgraphics Plus for Windows.* **Results**: *Of 187 persons working in an environment of smoking, 31 (17%) were passive smokers. Thiocyanates in 18 passive smokers were tested and compared to 84 students – smokers and nonsmokers. Thiocyanates in serum and urine in passive smokers are close to the levels of active smoking of more than 10 cigarettes per day.* **Conclusions**: *The results indicate the high intensity of passive and active smoking. Being one of the risk factors for various diseases and death, smoking should be banned in public places. Effectively controlled legal regulations of its ban as well as programs to prevent smoking and to support smoking withdrawal are required.*

Key words: *passive smoking, tobacco smoking, biomarker, thiocyanate*

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Review

DISEASES AND CONDITIONS ASSOCIATED WITH ZINC DEFICIENCY. SERUM ZINC IN PREGNANT WOMEN WITH REPRODUCTIVE FAILURES AND SERUM ZINC IN CHILDREN WITH TYPE I DIABETES

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ABSTRACT

Apart from severe zinc deficiency in akrodermatitis enteropatika, clinical effects of more moderate zinc deficiency are diarrhea, pneumonia, behavioral problems, impaired memory, learning disability and neuronal atrophy, alopecia, growth retardation, gonadal hypofunction, abnormal pregnancy, susceptibility to infections, delayed wound healing, impaired glucose tolerance, and many others. These effects are obtained in clinical studies that give a positive response to zinc supplement therapy. In this aspect, our study is a brief overview of diseases and conditions where zinc deficiency is observed.

The second part of the study presents our results on the levels of serum zinc in women with reproductive failures and in children with type I diabetes. The results showed that serum zinc was in deficient levels. We recommend proper diet, including foods and fortifitsirani fortified multivitamin preparations with zinc.

In conclusion we consider that the addition of zinc to the diet could improve the current status of patients with zinc deficiency and could even lead to survival of children with various diseases and conditions.

Due to varied results for concentrations of zinc and other trace elements in blood serum as indicators of micronutrient status it is necessary to carry out more detailed studies to identify the reasons and mechanisms of the micronutrient deficiency in different disorders.

Key words: zinc deficiency, pregnancy - reproductive failures, Type I Diabetes Mellitus

CONSEQUENCES OF ZINC DEFICIENCY

In the first part of this article we present a brief review on common diseases and conditions where zinc deficiency is found, while in the second part we present our own studies on patients in relations with zinc deficiency.

Due to many biological functions of zinc and its distribution in almost all human tissues, there is a wide range of physiological signs of zinc deficiency. These signs vary depending on the severity of the deficiency. Clinical signs of apparent zinc deficiency are seen in acrodermatitis enteropathica, which is a rare autosomal recessive genetic disease with zinc malabsorption (1). Clinical manifestations of zinc deficiency may vary in different ages. In early childhood, a common symptom is diarrhea. Furthermore, zinc deficiency leads to behavioral problems, impaired memory, learning disability and neuronal atrophy (2, 3).

Dermatic problems are becoming more common as the child grows. Alopecia, growth retardation and recurrent infections are common in school-aged children. Chronic skin ulcers and recurrent infections are common among older people.

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Conclusion: This findings showed that SCF may reflect early atherosclerotic changes in the microvasculature of the coronary arteries.

PP.11.445 LEVELS OF ELASTIN-DERIVED PEPTIDES IN SERA OF CHILDREN WITH OBESITY AND ESSENTIAL HYPERTENSION

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Objective: Elastin and collagen are the main proteins of vascular wall. An important factor in the development of vascular wall alterations is degradation of elastin. Arterial hypertension (AH) is connected with the loss of arterial wall's elasticity and an abnormal increase in the collagen/elastin ratio. The aim of our study was to: (1) Measure levels of elastin-derived peptides (EDP) in sera of obese children with essential hypertension; (2) Compare them with EDP levels in obese children without essential hypertension and healthy controls.

Design and Method: The study population consisted of 113 children divided into three groups as follows: obese children with AH (n = 43), mean age 12.1 ± 2.2 years (Group 1); obese children without AH (n = 32), mean age 11.3 ± 3.1 years (Group 2); and control group of healthy children (n = 38), mean age 11.8 ± 2.8 years (Group 3). Serum total cholesterol, triglycerides and HDL-C were determined enzymatically. The sandwich version of an enzyme-linked immunosorbent assay (ELISA) for detection of EDP was used.

Results: Children from Group 1showed statistically significantly higher levels of serum EDP (102 ± 18 ng/ml) in comparison with Group 2 (75 ± 31 ng/ml) and controls (60 ± 22 ng/ml) ($p < 0,05$). There were non-significant differences in serum EDP levels (75 ± 31 vs. 60 ± 22 ng/ml) between Group 2 and healthy controls ($p > 0,05$). Twenty-three percent of children from Group 1 were positive for EDP. The concentrations of total cholesterol and LDL were significantly higher in both groups of obese children in comparison with the control group ($p < 0.01$). The results indicated both the obese boys and girls with AH to have increased mean levels of total cholesterol (7,2 ± 1,3 and 7,9 ± 1,5 mmol/l) in comparison with the obese boys and girls without AH (6,4 ± 1,5 and 6,9 ± 1,5 mmol/l; $p < 0,01$).

Conclusions: Our data suggest the existence of an association between changes in levels of serum EDP, obesity and essential hypertension in children. Determination of serum EDP levels may be a useful method for monitoring of development of arterial hypertension in obese children.

PP.11.446 COMPARATIVE STUDY OF PERINDOPRIL/IVABRADINE AND PERINDOPRIL/METOPROLOL COMBINATIONS EFFECT ON MICROCIRCULATORY BLOOD FLOW IN HYPERTENSIVE PATIENTS WITH CORONARY HEART DISEASE

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Objective: The study was designed to evaluate the microcirculatory effect of clinically isoeffective perindopril/ivabradine and perindopril/metoprolol combinations in hypertensive patients with coronary heart disease.

Design and Methods: 77 male and female patients (mean age 60,0 ± 6,0 years) with mild to moderate arterial hypertension and concomitant angina pectoris class 2 were randomized into 2 groups. The 1st group (n = 40) received perindopril 4–8 mg + ivabradine 7,5–15 mg daily. The 2d group was administered the same dose of perindopril + metoprolol tartrate 50–100 mg/day. Both groups were treated and followed up for 24 weeks. Microcirculatory blood flow was measured before the administration of both drug combinations and after 12 and 24 weeks of treatment by laser Doppler flowmetry with LAKK-02 analyzer.

Results: Both combinations had equal effect on blood pressure profile and ST depression episodes number and duration exerting equipotent statistically significant bradycardic action. In contrast with perindopril/metoprolol tartrate combination treatment we observed statistically significant 19,2% increase in microcirculatory blood flow in the dorsal hand skin after 24 weeks of treatment with perindopril/ivabradine. The latter combination was particularly effective in patients with initially diminished level of microcirculation.

Conclusions: Ivabradine has more favorable effect on microcirculatory blood flow than metoprolol tartrate being co administered with perindopril in clinically isoeffective doses to hypertensive patients with angina pectoris.

individuals (β=-1.45, Ptrend =0.02).**Conclusions:** BMI is positively associated with inflammatory and cardiometabolic markers and inversely associated with vitamin D in Canadian adults. These results emphasize the inflammatory state of obesity that may increase cardiometabolic disease risk, and highlight the potential to modulate risk by improving vitamin D status.

Conflict of Interest: None Disclosed

Funding: Public Health Agency of Canada

616 accepted poster

ATHEROGENIC INDEXES AND LIPID STATUS IN CHILDREN WITH OBESITY AND ESSENTIAL HYPERTENSION

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Abstract Text: Introduction:Obesity is one of the major characteristics of the population with essential hypertension and a key risk factor underlying pathogenesis of atherosclerosis. During the last years, atherosclerosis has become one of the main causes of high mortality in younger population. That is why it is necessary to try to find reasons for early atherosclerosis in childhood and to prevent development of atherosclerosis by screening of the high risk children and searching predictorsof cardiovascular risk. The aim of our study was to: 1. Determine lipid status (LS) and calculate atherogenic indexes (AI) in obese children with essential hypertension;2. To compare LS and AI of obese children with essential hypertension with LS and AI in obese children without essential hypertension and healthy controlsMethods:The study population consisted of 113 children divided into three groups as follows: obese children with elevated blood pressure (n=43), mean age 12.1±2.2 years (Group 1); obese children with normal blood pressure (n=32), mean age 11.3±3.1 years (Group 2); and control group of healthy children (n=38), mean age 11.8±2.8 years (Group 3).Serum total cholesterol (TCL), triglycerides (TGL) and high density lipoprotein cholesterol (HDL-C) were determined enzymatically. LDL-C was calculated according to the formula of Friedewald. Main lipid indexes (TCL index, TGL index, HDL index, LDL index and percent difference between indexes from obese controls) were calculated.Results:The results indicated both the obese boys and girls with AH to have increased mean levels of TCL (7.2±1.3 and 7.9±1.5 mmol/l, respectively) in comparison with the obese boys and girls without AH (6.4±1.5 and 6.9±1.5 mmol/l, respectively; p<0.01). However, the mean levels recorded in the obese children without AH were relatively higher in comparison with the healthy controls (p<0.01). Interestingly enough, the obese girls from group 1 showed a lower mean value of HDL-C (0.92±0.24 mmol/l) than either the obese boys from the same group or obese controls (p<0.05). Atherogenic indexes were high in both groups of obese children, with a higher percent recorded in the girls. In the group 1 girls, TCL index was 7.58 and 35.35%. In the boys with high BMI and AH, TCL index was 5.40, but the percent was very low, i.e. 8.28%. Therefore, the girls with high BMI and AH were at a higher risk of the development vascular changes than the boys from the same group. In the group 1 boys and girls, HDL index was 6.63 with a very low percent and 8.94 with a percent of 59.54%, respectively. TGL index was within the normal range in all study groups. LDL index was 5.94 and 11.93% in the boys, and was higher in the girls, i.e. 8.13 and 32.19%. Conclusions:The high lipid indexes (TCL, HDL and LDL/HDL) in girls indicated a higher probability of the development of vascular changes in these children, particularly in those from group 1. Our data suggest the existence of an association between changes in lipid status, atherogenic indexes, obesity and essential hypertension in children. Monitoring of lipid status and atherogenic indexes could be a useful method for identifying a high atherosclerotic risk in children with obesity and essential hypertensoin.

Conflict of Interest:

Funding:

617 accepted poster

BODY MASS INDEX IS THE COMMONEST DEPENDENT PREDICTOR OF C3, ADIPONECTIN AND C-REACTIVE PROTEIN CONCENTRATIONS IN APPARENTLY HEALTHY YOUNG ADULTS

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Abstract Text: **Introduction:** The inflammatory process can be the link between obesity and associated cardiometabolic disturbances. Therefore, several inflammatory biomarkers have been proposed to investigate this relationship, among these is complement C3 (C3), adiponectin and C-reactive protein (CRP). **Methods:** 157 individuals aged between 18 and 35 years were evaluated for BMI, waist circumference (WC), systolic (SBP) and diastolic blood pressure (DBP). Serum C3, CRP, glucose, triacylglycerols and HDL-c were determined by colorimetric kits, followed reading by automatic analyzer. Normality of distribution was assessed by the Shapiro-Wilk test. The Spearman correlation coefficients and the multivariate linear regression model were used to investigate the association between concentrations of the biomarkers (dependent variables) and other variables (cardiometabolic syndrome components and BMI). The software SAS version 9.0 was used. It was considered the significance level of 5% probability. **Results:** The C3 (r= 0.38435) and CRP concentrations (r=0.39545) were associated with triacylglycerols and the adiponectin concentrations were associated with SBP (r=-0.20279) and HDL-c (r=0.53289). The CRP concentrations were indirectly associated with glucose (r=-0.20877). WC were associated with C3 (r=0.21266), adiponectin (r=-0.21199) and CRP (r=0.16487). BMI were associated with C3 (r= 0.23417), adiponectin (r=-0.17810) and CRP (r=0.16147). In a multivariate linear regression models, triacylglycerols and BMI (r^2=0.1664) were predictors of C3. HDL-c and BMI (r^2=0.2837) were predictors of adiponectin. Triacylglycerols, glucose and BMI (r^2=0.0989) were predictors of CRP.**Conclusions:** C3, adiponectin and CRP concentrations were correlated with cardiometabolic syndrome components, and BMI represented the commonest association and prediction. Finally, the BMI seems to exert a dependent role in inflammation.

Conflict of Interest: None Disclosed

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618 accepted poster

CD36 MODULATES LONG-CHAIN FATTY ACID-TRIGGERED CALCIUM SIGNALING AND MAY INFLUENCE PRODUCTION OF PROINFLAMMATORY EICOSANOIDS.

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Abstract Text: **Introduction:** FAT/CD36, a scavenger receptor linked to inflammation, exhibits high affinity for long-chain fatty acids (LCFA). Recently, a new role of CD36 in calcium-dependent arachidonic acid release from membrane phospholipids by phospholipase A2 was discovered. We examined whether FAT/CD36-phospholipase A2 pathway may be triggered also by CD36 ligands, namely by LCFA.**Methods:** Chinese hamster ovary cells (CHO) expressing human CD36, or murine macrophage cell line RAW 246.7, were loaded with FURA2AM calcium dye and exposed to the SERCA2 inhibitor thapsigargin, which prevents sequestration of calcium by the endoplasmic reticulum, or to LCFA complexed with bovine serum albumin. Specificity of various fatty acids to induce calcium transients at concentrations 12.5-50 μM was tested, in reference to thapsigargin used as a positive control, using microscopy. The same experimental design was used to explore changes in MAPK and phospholipase A2 activation using Western blots. **Results:** Both CHO cells and RAW 246.7 macrophages responded to high concentrations of LCFA, while specificity to linoleic, arachidonic and docosahexaenoic acid was found at low concentrations. Involvement of CD36 was confirmed using CD36 siRNA and SSO, an inhibitor of CD36, when the cells had impaired calcium signaling pathways possibly leading to changes in eicosanoid release.**Conclusion:** CD36, an important modulator of arachidonic acid release, may trigger calcium signaling based on its interaction with specific fatty acids, thereby providing a potential link between dietary fatty acid composition and some CD36 effects in inflammation.

Conflict of Interest:

Funding:

causes EC hypertrophy, remodeling, leading to microvessel lumen deformation, narrowing and obstruction of them, causing CMC hypoperfusion. Long-term hibernation, caused by HT, leads to EC and CMC apoptosis causing HF. Onset of AMI in patients with hypertensive cardiomyopathy except necrosis leads to the progression of long-term hibernation and development of short-term hibernation of CMC and vascular endothelium. The latter occurs mainly due to PO and CS triggering cellular apoptosis or secondary necrosis. Stunned cardiomyocytes often transform in to hibernating cells. Accumulation of glycogen granules in CMC and EC was the most sensitive marker of cellular hibernation and dysfunction.

Conclusion: Hypertension causes CMC and vascular endothelium hypertrophy, their structural and functional heterogeneity, hibernation and apoptosis leading to the development of HF. Development of AMI except necrosis of CMC cause progressive myocardial hibernation, activates CMC and EC apoptosis and exacerbate HF. Appropriate pharmacotherapy of HT may partly prevent CMC and EC remodeling, hibernation and HF, while invasive treatment is vital in saving of hibernated myocardium in AMI.

PP.41.388 RETINOPATHY IN DIFFERENT HYPERTENSION PHENOTYPES, ANOTHER EXAMPLE OF TARGET ORGAN DAMAGE IN MASKED HYPERTENSIVES

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Objective: Longitudinal epidemiological studies have shown that hypertensive patients with retinal arteriolar alterations are at increased risk for cardiovascular events. However, the extent of retinal microvascular changes in naïve, never-treated patients with recent appearance of hypertension has been substantially understudied. In addition, the lack of relevant data regarding other hypertension phenotypes, masked (MHT) and white-coat hypertensives (WCH) is notable, and constitutes the aim of our study.

Design and Method: Ambulatory blood pressure was measured using the oscillometric Spacelabs 90,207 device. Retinal vascular calibers were estimated using a computer-based program for retinal photographs taken with a non-mydriatic digital fundus camera (NIDEK AFC-230/210). Central retinal artery (CRAE) and vein (CRVE) equivalents, as well as arterio-venous ratio (AVR) were calculated to estimate retinal abnormalities.

Results: We studied 99 newly diagnosed hypertensive patients, (71 with hypertension (HT), mean age 43.9 ± 11.1, 16 with MHT, mean age 40.1 ± 11.5 and 12 with WCH, mean age 49.2 ± 13.4) and 30 normotensive individuals (mean age 43.5 ± 11.5), without other comorbidities. Comparison of the retinal vascular parameters is depicted in table 1. Patients with HT as well as MHT had both lower CRAE and AVR, indicating narrower retinal vessels. CRAE and AVR were strongly and negatively associated with mean, systolic and diastolic daytime, nighttime, and 24-h blood pressure, even after adjustment for other factor in multivariate analysis.

Conclusion: Subtle retinal microvascular alterations are observed in patients with HT and also MHT, in contrast to patients with WCH, who have retinal findings resembling normotensive subjects. These changes, easily assessed by retinal photography, may be indicative of or mediating the differences in cardiovascular mortality in those groups.

Table 1. Central retinal arteriolar (CRAE) and venular (CRVE) caliber equivalents and arteriovenous ratio (AVR) according to blood pressure status groups

	CRAE	CRVE	AVR
HT ($n = 71$)	87.1 ± 10.4**	119.7 ± 15.0	0.734 ± 0.099**
MHT ($n = 16$)	87.3 ± 9.5*	126.3 ± 11.4	0.694 ± 0.072***
WCH ($n = 12$)	94.4 ± 8.8	121.0 ± 15.9	0.790 ± 0.117
NORMOTENSIVES ($n = 30$)	95.5 ± 10.3*,**	117.7 ± 14.3	0.816 ± 0.087**,***
p value	0.001	0.297	<0.001

*$p < 0.05$, ** $p = 0.001$, ***$p < 0.001$.

PP.41.389 LEVELS OF COLLAGEN TYPE IV DERIVED PEPTIDES IN SERA OF CHILDREN WITH OBESITY AND ESSENTIAL HYPERTENSION

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Objective: Elastin and collagen are main proteins of vascular wall connective tissue. An important factor in development of vascular wall alterations is degradation of basement membrane's major protein – collagen type IV. The aims of our study were to: (1) Measure levels of collagen type IV derived peptides (CIVDP) in sera of obese children with essential hypertension; (2) To compare serum CIVDP levels of obese children with essential hypertension with CIVDP levels in obese children without essential hypertension and healthy controls.

Design and Method: The study population consisted of 113 children divided into three groups as follows: obese children with elevated blood pressure ($n = 43$) (Group 1); obese children with normal blood pressure ($n = 32$) (Group 2); and control group of healthy children ($n = 38$) (Group 3). Sandwich version of an enzyme-linked immunosorbent assay (ELISA) for detection of CIVDP was used.

Results: Children with obesity and AH (Group 1) showed statistically significantly higher levels of CIVDP (380 ± 16 ng/ml) in comparison with Group 2 (290 ± 58 ng/ml) and controls (270 ± 39 ng/ml) ($p < 0.05$). There were nonsignificant differences in serum CIVDP levels (290 ± 58 vs. 270 ± 39 ng/ml) between obese children without AH and healthy controls ($p > 0.05$). Twenty percent of children from Group 1 were positive for CIVDP. The results indicated both the obese boys and girls with AH to have increased mean levels of total cholesterol (7.2 ± 1.3 and 7.9 ± 1.5 mmol/l) in comparison with the obese boys and girls without AH (6.4 ± 1.5 and 6.9 ± 1.5 mmol/l; $p < 0.01$). Mean levels recorded in obese children without AH were relatively higher in comparison with healthy controls ($p < 0.01$). Interestingly, obese girls from Group 1 showed lower mean value of HDL-C (0.92 ± 0.24 mmol/l) than either obese boys from the same group (1.12 ± 0.18) or controls (1.31 ± 0.10) ($p < 0.05$).

Conclusion: Our data suggest existence of an association between changes in levels of serum CIVDP, obesity and essential hypertension in children. Determination of serum CIVDP levels may be a useful method for monitoring of development of arterial hypertension in obese children.

PP.41.390 FRAME COUNT RESERVE AND SLOW CORONARY FLOW FOR THE EVALUATION OF MICROVASCULAR ANGINA

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Objective: Previous studies suggested that the degree of frame count reserve (FCR) and slow coronary flow (SCF) were related with microvascular dysfunction. We investigated the clinical implication of FCR and SCF for the evaluation of microvascular angina.

Methods: We included consecutive 77 patients with the complaint of chest pain showed normal coronary angiography. Basal TIMI frame count (TFC) was obtained from left anterior descending artery. Intracoronary nitroprusside (15 μg) was infused to induce hyperemia, and repeated angiogram was performed after 30 s. FCR were calculated by dividing basal TFC by hyperemic TFC. SCF was defined as being present when TFC was more than 28. All patients underwent a treadmill test without medication after angiography.

Results: After the treadmill test, patients were divided into a microvascular angina group (40 patients) and a control group (37 patients). Hyperemic TFC was significantly higher in the microvascular angina group (10.9 ± 4.7) than in the control group (9.0 ± 3.5, $p < 0.05$). FCR were similar in both groups (2.0 ± 1.0 and 2.1 ± 0.9, microvascular angina and control group, respectively). Patients with SCF had a significantly higher incidence of microvascular angina (78.5%) than patients with a normal coronary flow (46.0%, $p < 0.05$). We defined a positive nitroprusside stress test result as the presence of SCF or an FCR of <1.7, and patients with a positive result had more microvascular angina (26/38 patients) than patients with negative result (14/39 patients, $p < 0.01$).

Conclusion: The presence of SCF or FCR <1.7 was found to have a diagnostic value for microvascular angina.

T6:PO.027

Effect of abdominal obesity on postprandial lipoprotein concentrations by linear electrophoresis

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Introduction: The effects of visceral fat accumulation on postprandial lipoprotein concentrations have not yet been studied in details. We therefore focused on the postprandial lipoprotein profile in otherwise healthy men and women with abdominal obesity and their comparison with the control group of volunteers with normal waist circumference

Methods: The concentration of lipoprotein classes and subclasses was measured before and 4 hours after a standard meal by linear polyacrylamide gel electrophoresis.7

Results: A statistically significant postprandial rise in triacylglycerol (TAG) concentration occurred in all cohorts. Highest rise was in the cohort of obese men. VLDL increased 4 hours after meal in all cohorts except the women with normal waist circumference. The concentration of large IDL particles increased in both non-obese men and women. In women with abdominal obesity, however, it decreased, while in obese men there was no statistically significant change. The concentration of small and medium-sized IDL particles decreased in all cohorts. Analyzing subclasses changes of large, medium-sized and small LDL particles we saw no significant shift in their concentrations, except the subclass of large LDL particles, which decreased in men. Concentrations of medium and small HDL particles decreased postprandially in cohorts of volunteers with normal waist circumference. However, they remained unchanged in cohorts of subjects with abdominal obesity.

Conclusion: We observed significant postprandial changes of the lipoprotein profile, but the nature and extent of these changes depended on gender and presence of abdominal obesity.

T6:PO.028

Evaluation of cardio metabolic control in obese patients with metabolic syndrome

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Introduction: Metabolic syndrome /MS/ starts to become epidemic during the last few decades associated with growing cardiovascular morbidity and mortality despite progress of therapeutical strategies. The arterial hypertension /AH/ and dyslipidaemia /DLP/ in MS are leading important known risk factors with the major frequency. Their relationships with insulin resistance and impaired glucose metabolism start to become more and more clarified.

Methods: The aim of the study is to identify the frequency of optimal control of AH and DLP according gender, ages and global risk in obese patients with MS according ESC 2009 and ESC/EAS 2011 guidelines and the most frequently used classes and molecules of antihypertensive and lipid lowering medications. Retrospectively a group of 152 hospitalized obese patients with MS, 64 male and 88 female aged from 20 to 84 years old was analyzed and ambulatory measured blood pressure, laboratory measured lipid profile and ESC risk score were registered. The global risk according additional risk factors was stratified and current AN and DLP therapy intervention including class and molecule of medications was analyzed.

Results: In 126 patients with AH 17,46% were without pharmacological treatment, in 30,16% of treated pharmacologically was achieved target levels of blood pressure and in 69,84% was identified unsatisfactory control of blood pressure. Among all the patients was identified DLP but only 23,03% were pharmacologically treated and 14, 47% were achieved target lipid levels.

Conclusion: Among predominant part of obese patients with MS was necessary to optimize pharmacological treatment in order to achieve better cardio metabolic control.

T6:PO.029

Levels of circulating Elastin-Antielastin Immune Complexes and Elastin derived Peptides in sera of Patients with obesity and essential hypertension

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Introduction: Elastin and collagen are the main proteins of vascular wall. An important factor in the development of vascular wall alterations is degradation of the elastic fiber major protein – elastin. The aim of our study was to: (1) Measure levels of elastin-derived peptides (EDP) and elastin-antielastin circulating immune complexes (EA CIC) in sera of obese patients with essential hypertension and (2) to compare their levels in obese patients with essential hypertension and in obese patients without essential hypertension and healthy controls.

Methods: The study population consisted of 135 patients divided into three groups as follows: obese patients with elevated blood pressure (n = 47), mean age 62.5 ± 12.58 years (Group 1); obese patients with normal blood pressure (n = 46), mean age 60.4 ± 8.4 years (Group 2); and control group of healthy subjects (n = 42), mean age 58.9 ± 7.56 years (Group 3).

An elastin-specific ELISA for detection of EDP was used. EA CIC were investigated by new method for immune complexes detection by means of ELISA-type techniques (CIF-ELISA).

Results: Patients with obesity and AH (Group 1) showed statistically significantly higher levels of EDP (0.261 ± 0.027) in comparison with Group 2 (0.218 ± 0.030) and healthy controls (0.199 ± 0.004) ($p < 0,05$). There were non-significant differences in serum EDP levels between obese patients without AH and healthy controls ($p > 0,05$). Group 1 showed statistically significantly higher levels of EA CIC (0.204 ± 0.045) than patients from Group 2 (0.152 ± 0.014) and healthy controls (0.089 ± 0.008).

Conclusion: Determination of serum EDP and EA CIC levels may be a useful method for monitoring of development of arterial hypertension in obese patients.

T6:PO.030

Comparison of Obesity Indices for detecting metabolic impairments in lebanese adults

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Introduction: This study examines three obesity indices: body mass index (BMI), waist circumference (WC), and waist-to-height ratio (WHtR), to define the index that has the best discriminatory power against metabolic and cardiovascular outcomes.

Methods: We used 2148 records generated from a multifactoral cardiovascular assessment service including fasting blood sugar, blood pressure, self-reported history of diabetes, hypertension, dyslipidemia and CVD. Receiver-operating characteristic curve analyses were used to define the optimal cutoff points of the three obesity indices against a cardiovascular outcome measure defined as the presence of two metabolic impairments and/or history of CVD. The predictive characteristics of the three obesity indices were compared through by comparing of the Areas Under the Curve between each of the obesity indices and each of the outcome variables, and Odds ratio obtained from a logistic models adjusted for

25 - Vascular biology of the arterial wall: Miscellaneous

EAS-0259.
PATHOGENESIS OF INTERMEDIATE LESION OF HUMAN CORONARY ATHEROSCLEROSIS: LIPID POOL FORMATION WITHOUT NECROSIS AND DISPERSION OF INTIMAL SMOOTH MUSCLE CELLS

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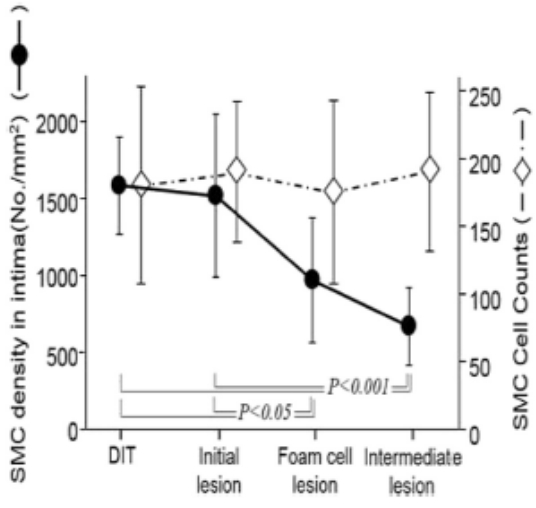
Objectives: Proliferation of smooth muscle cells (SMCs) and deposition of lipids by death of macrophage foam cells are key events in atherosclerosis in animal models. However, different processes occur in human atherosclerosis. The purpose of this study is to clarify the pathogenesis of intermediated lesion (preatheroma) of human atherosclerosis, focusing on intimal SMCs and extracellular lipids.

Methods: Step and serial frozen sections of the right coronary artery were obtained from 43 Japanese autopsied subjects (from 15 to 49 years of age) with no or earlier atherosclerotic lesions. The lesions were classified into 4 categories according to the grade of atherosclerosis; diffuse intimal thickening (DIT), initial lesion, foam cell lesion and intermediate lesion.
Results: DIT, a physiological intimal thickening, contained plenty of SMCs and no lipid deposition in the intima. Initial lesions and foam cell lesions exhibited mild deposition of extracellular lipids and accumulation of macrophage foam cells in the SMC-rich intima, respectively. Intermediate lesions consisted of lipid pools with abundant extracellular lipids in the thickened intima, in addition to many SMCs and macrophage foam cells. No necrosis or lytic changes were observed in the lipid pools, and the extracellular lipids colocalized with ApoB and fibrinogen, suggesting that the penetration of plasma lipoproteins played an important role in lipid pool formation. The density of intimal SMCs was significantly decreased in the foam cell lesion and the intermediate lesion, but the number of cells showed no significant change (Figure). No MIB-1-positive cells or TUNEL-positive cells were observed, and only a few SMCs showed positive immunostain for BAX, LC3B and NLRP3, suggesting that SMCs were spread out in the intima as the lesion progressed without undergoing excessive proliferation or death.



Conclusion: Intermediate lesion of human atherosclerosis develops primarily by infiltration of plasma lipoproteins and lipid pool formation, and dispersion of pre-existing intimal SMCs.

25 - Vascular biology of the arterial wall: Miscellaneous

EAS-0029.
FREE ANTI-ELASTIN IGG ANTIBODIES ARE ASSOCIATED WITH HIGH RISK OF ATHEROSCLEROSIS IN DIABETIC PATIENTS WITH ESSENTIAL HYPERTENSION

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Objectives: The aims of our study were to determine if serum levels of anti-elastin antibodies unbound in CIC (free AEAbs) correlate with: (1) development of microvascular lesions and (2) high risk of atherosclerosis in patients with type 2 diabetes mellitus (T2DM) and arterial hypertension (AH).

Methods: We used a method for detection CIF–ELISA (complement-inhibiting factor– enzyme linked immunosorbent assay) in combination with ELISA to find AEAbs. Levels of free AEAbs IgG were measured in sera of 93 patients with T2DM and AH (mean age 61,4±11,3, diabetes duration 9,88±3,12; hypertension duration 9,28±4,98). These levels were compared to 42 age and sex matched controls. Diabetic patients were divided into two groups– Group 1 (n=67) with microangiopathy and Group 2 (n=26) without.
Results: Group 1 (patients with microvascular complications) showed significant increase in free AEAbs IgG in comparison with controls 0,428 (0,343÷0,591) vs. 0,240 (0,212÷0,305) (KW=20,14; p<0,0001). Group 2 also shows higher levels of free AEAbs IgG than control group 0,398 (0,312÷0,467) vs. 0,240 (0,212÷0,305) (KW=8,88; p=0,003). Free AEAbs showed correlation with HbA1c (r=0.22); (p=0.04), duration of diabetes (r=0.18); (p=0.05), systolic blood pressure (r=0.15); (p=0.05), total cholesterol (r=0.20); (p=0.03), tryglicerides (r=0.21); (p=0.02).
Conclusion: The elevation of free AEAbs levels can be related with later clinical manifestation of atherosclerosis. We suggest that free AEAbs can be useful method for identifying a high atherosclerotic risk in diabetic patients.

25 - Vascular biology of the arterial wall: Miscellaneous

EAS-0030.
ANTI-COLLAGEN TYPE IV IGG ANTIBODIES AND RISK FOR DEVELOPMENT OF ATHEROSCLEROSIS IN DIABETICS WITH ESSENTIAL HYPERTENSION

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Objectives: Thickening of basement membrane in small vessels is an important factor in progression of diabetic microangiopathy. Patients with diabetes mellitus and arterial hypertension are at higher risk for development of atherosclerosis.

Methods: Serum levels of antibodies to collagen type IV (ACIV) IgG, IgM and IgA were measured using an ELISA in 93 patients with type 2 diabetes mellitus and arterial hypertension (AH) (mean age 61,4±11,3 years, diabetes duration 9,88±3,12 years; hypertension duration 9,28±4,98). These values were compared to serum antibodies to CIV in 42 age and sex matched controls. Diabetics were divided in two groups according to presence- Group 1 (n=67) or absence- Group 2 (n=26) of microangiopathy.
Results: Group 1 (patients with microvascular complications) showed significantly higher levels of ACIV IgG in comparison with Group 2 0,323 (0,243÷0,391) vs. 0,241 (0,207÷0,291) (KW=7,66; p=0,006) and control group 0,210 (0,149÷0,262) (KW=17,52; P<0.0001). Patients from Group 2,

were with higher ACIV IgG levels than controls 0,176 (0,151–0,202) vs. 0,142 (0,118–0,173) (KW=6,15; p=0,01). ACIV IgG showed correlation duration of diabetes (r=0.49); (p=0.01), retinopathy (r=–0.20); (p=0.04), BMI (r=–0.24); (p=0.05), systolic blood pressure (r=0.16); (p=0.05), total cholesterol (r=0.20); (p=0.03), tryglicerides (r=0.31); (p=0.01).
Conclusion: Our study showed a relationship between elevation of serum levels of ACIV IgG in diabetics and development of vascular changes. The elevation of ACIV IgG can be related with later clinical manifestation of atherosclerosis. We suggest that ACIV IgG can be useful method for identifying a high atherosclerotic risk in diabetic patients.

25 - Vascular biology of the arterial wall: Miscellaneous

EAS-1109.
SERUM ACYLCARNITINES AND RISK OF ACUTE MYOCARDIAL INFARCTION AND CARDIOVASCULAR DEATH IN PATIENTS WITH STABLE ANGINA PECTORIS

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Objectives: Carnitine is an essential metabolite for mitochondrial transport and metabolism of fatty acids (FAs). FAs are transferred to carnitine by carnitine acyltransferases, producing acylcarnitines with a wide range of different acyl chain-lengths. Partially metabolized acylcarnitine intermediates can be exported out of the mitochondria and tissues for use at other destinations or for urinary excretion. An excess of serum acylcarnitines have been associated with metabolic diseases like type 2 diabetes and preeclampsia. We aimed to evaluate a possible association between serum acylcarnitines and risk of acute myocardial infarction (AMI) and cardiovascular death in patients referred to coronary angiography for suspected stable angina pectoris (SAP).

Methods: This prospective cohort study was based on the Western Norway B-Vitamin Intervention Trial and the Bergen Coronary Angiography Cohort, and included a total of 4,164 patients. Baseline serum acylcarnitines were measured using liquid chromatography/tandem mass spectrometry. Risk was evaluated by Cox regression using a simple model adjusted for age and gender and a multivariate model containing relevant established risk factors. The upper versus lower quartile of serum acetyl-, octanoyl-, palmitoyl-, propionyl-, and (iso)valerylcarnitine were compared.
Results: Participants (72% males, mean age 62 years) were followed for a mean 4.5 years. We observed significant although modest increased risk for AMI in patients with high levels of octanoyl-, palmitoyl-, and (iso) valerylcarnitine, with octanoylcarnitine showing the strongest risk estimate (multivariate model: HR, 1.73; 95% CI, 1.19, 2.51). Furthermore, high levels of both octanoyl- and palmitoylcarnitine was significantly associated with increased risk of cardiovascular death (HR (95% CI): 2.90 (1.45, 5.80) and 2.11 (1.27, 3.51), respectively).
Conclusion: Elevated serum acylcarnitines, particularly octanoylcarnitine, were associated with a modest increased risk of AMI, while high octanoylcarnitine was also associated with a profound increased risk of cardiovascular death among patients with SAP. These associations were independent of established risk factors.

25 - Vascular biology of the arterial wall: Miscellaneous

EAS-0415.
A NEW ROLE FOR MMP-10 IN PATIENTS WITH PERIPHERAL ARTERY DISEASE AND EXPERIMENTAL ARTERIAL ISCHEMIA

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Objectives: Matrix metalloproteinases (MMPs) contribute extensively to tissue remodeling in a variety of normal and disease processes, including atherothrombotic and ischemic disorders such as peripheral artery disease (PAD). High gelatinolytic activity is necessary for tissue remodeling in response to arterial occlusion in experimental ischemia, however, the contribution of other MMPs has not yet been investigated. MMP-10 has been suggested to play a role in diseases associated to tissue remodeling and inflammation, thus representing a novel therapeutic target in different pathologies. Objetives i) to analyze the circulating levels of MMP-10 in PAD patients and ii) to determine the role of MMP-10 in wound repair after experimental femoral artery ligation.

Methods: Circulating MMP-10 levels were measured by ELISA in patients. we used a model of severe hindlimb ischemia in wild type (WT) and MMP-10 deficient (*Mmp10*$^{-/-}$) mice in the experimental study.
Results: Circulating MMP-10 levels were increased (P<0.001) in PAD patients (946±473, n=187) compared to healthy controls (702±326, n=200) suggesting its role as a biomarker in PAD. To study the role of MMP-10 in tissue repair, we used a model of severe hindlimb ischemia in WT and *Mmp10*$^{-/-}$ mice. At the degenerative phase, MMP-10 deficiency reduced tissue perfusion and increased necrosis and inflammation. At the regenerative phase, MMP-10 deficiency resulted in reduced tissue regeneration. The injection of recombinant human MMP-10 (rhMMP10) in *Mmp10*$^{-/-}$ mice rescued the observed phenotype.
Conclusions: Our results suggest a possible role of MMP-10 as a biomarker in a clinical setting of chronic ischemia or PAD, while the experimental study demonstrates that MMP-10 is crucial for proper muscle repair during degenerative and regenerative phases of limb ischemia, and open new pathways for specific manipulation of MMP-10 in ischemic conditions.

25 - Vascular biology of the arterial wall: Miscellaneous

EAS-0987.
VEGFR2 BLOCKADE IN MURINE VEIN GRAFT RESULTS IN REDUCED INTRAPLAQUE HEMORRHAGE AND STABLE ATHEROSCLEROTIC LESIONS

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Objectives: Immature plaque neovessels contribute to atherosclerotic plaque instability and intraplaque hemorrhage by leaking erythrocytes and leukocytes in the plaque. Vascular Endothelial Growth Factor Receptor 2 (VEGFR2), together with the angiopoietin (Ang)-Tie2 system, regulates the maturation of growing neovessels. We have previously shown that murine vein graft lesions exhibit massive plaque neovascularization and that leaky vessels and intraplaque hemorrhage contribute to lesion growth. We hypothesized that blockade of VEGFR2 results in more mature plaque microvessels and less intraplaque hemorrhage.

Methods: Donor caval veins were engrafted in carotid arteries of recipient hypercholesterolemic ApoE3*Leiden mice (n=14/group). Mice were treated at day 14, 17, 21 and 25 with VEGFR2 blocking antibodies (DC101) or control IgG antibodies (10 mg/kg). At day 28 mice were sacrificed for histological analysis of the vein grafts.
Results: Morphometric analysis revealed a striking 50% decrease in vein graft segments that expressed intraplaque haemorrhage in the form of leaky vessels in the DC101 treated group. This was accompanied by a significant 25-fold decrease in extravasated erythrocytes. Furthermore, lesions that exhibit intraplaque hemorrhage showed a strong increase in Ang-2, indicative for immature neovessels. VEGFR2 blockade however, did not affect the neovessel density in the lesions (control 52±19 neovessels/section; DC101 63±25 neovessels/section). Interestingly, the vein graft lesion area in the DC101 group was significantly reduced with 32% compared to the control group. Moreover, plaque stability was clearly increased in DC101 treated mice, determined by a 25% reduction in macrophage content, a 50% increase in collagen content and a 120% increase in SMC content.

PP.13.09 ASSOCIATION BETWEEN INCREASED COLLAGEN TYPE IV TURNOVER AND LEFT VENTRICULAR HYPERTROPHY IN HYPERTONIC PATIENTS WITH TYPE 2 DIABETES MELLITUS

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Objective: Left ventricular hypertrophy (LVH) and myocardial remodelling are signs of cardiac damage in arterial hypertension (AH). Elastin and collagen are the main proteins of the vascular wall. Arterial hypertension and diabetic vascular complications are connected with an elevated degradation of elastic tissue, increasing rigidity of the arterial wall and an abnormal increase in elastin/collagen ratio. As a result collagen type IV derived peptides (CIVDP) are released in the circulated blood, which are a pathological stimulus for an increased production of antibodies to collagen type IV (ACIV Abs). In the present investigation we studied whether the serum levels of antibodies (IgG, IgM and IgA) to collagen are related with left ventricular hypertrophy.

Design and method: To monitor the metabolism of the basement membrane protein collagen in hypertonic patients with type 2 diabetes mellitus (T2DM), serum levels of antibodies to collagen ACIV Abs IgG, IgM and IgA were measured using an ELISA method in 93 patients with arterial hypertension (AH) and diabetes mellitus (mean age 61,4±11,3 years, diabetes duration 9,88±3,12 years; hypertension duration 9,28±4,98). These values were compared to serum antibodies to collagen type IV in 42 age and sex matched controls. The Sokolow-Lyon index criteria was used to diagnose LVH via electrocardiography: S in V1 + R in V5 or V6 (whichever is larger) >= 35 mm (>= 7 large squares); R in aVL >= 11 mm.

Results: Patients showed statistically significant higher levels of ACIV IgG incomparison to healthy controls (0.30±0.12 vs. 0.21±0.08); (p=0.0001). Serum AEAbs IgM and IgA levels in hypertonic patients with T2DM were lower than these in controls, but the differences are not statistically significant. ACIV IgG correlated with electrocardiography estimated left ventricular hypertrophy (r=0.24; P=0.03).

Conclusions: We suggest that there is association between biological markers of extracellular-matrix: ACIV IgG and clinically estimated left ventricular hypertrophy. Serum markers of collagen metabolism (ACIV IgG antibodies) are elevated and might be valuable markers for progression of LV hypertrophy in hypertonic patients with T2DM.

PP.13.10 LEVELS OF CIRCULATING ELASTIN-ANTIELASTIN IMMUNE COMPLEXES AND ANTI-ELASTIN ANTIBODIES IN SERA OF PATIENTS WITH OBESITY AND ESSENTIAL HYPERTENSION

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Objective: Antibodies to α-elastin (elastin breakdown product) and elastin sequences devoid of cross-linked regions (tropoelastin) are found in the serum of all human subjects and correlate with their respective serum peptide levels. The aim of our study was to: (1) Measure levels of elastin-antielastin antibodies (AEAbs) and elastin-antielastin circulating immune complexes (EA CIC) in sera of obese patients with essential hypertension and (2) to compare serum AEAbs and EA CIC levels of obese patients with essential hypertension with AEAbs and EA CIC in obese patients without essential hypertension and healthy controls.

Design and method: The study population consisted of 135 patients divided into three groups as follows: obese patients with elevated blood pressure (n=47), mean age 62.5±12.58 years (Group 1); obese patients with normal blood pressure (n=46), mean age 60.4±8.4 years (Group 2); and control group of healthy subjects (n=42), mean age 58.9±7.56 years (Group 3). Blood pressure (BP) was measured with a random zero sphygmomanometer in the sitting position after at least 5 min rest. Serum total cholesterol, triglycerides and HDL-C were determined enzymatically. ELISA was used to measure the levels of IgG, IgA and IgM AEAbs. EA CIC were investigated by new method for immune complexes detection by means of ELISA-type techniques (CIF-ELISA).

Results: Patients with obesity and AH (Group 1) showed statistically significantly higher levels of elastin-antielastin CIC (0.161±0.020) in comparison with Group 2 (0.118±0.030) and healthy controls (0.069±0.008) (p<0,05). Patients with obesity and AH showed statistically significantly lower levels of AEAbs-IgG (0.406±0.060), IgM (0.430±0.080) and IgD (0.130±0.031) than healthy controls (0.635±0.080), (0.509±0.108), (0.179±0.056) and higher levels of IgA (0.192±0.030) vs. (0.106±0.026) p<0.05. There were non-significant differences in serum AEAbs levels between obese patients without AH and healthy controls (p>0,05).

Conclusions: Our data suggest the existence of an association between changes in levels of serum AEAbs IgA, EA CIC obesity and essential hypertension in patients. Determination of serum AEAbs IgA and EA CIC levels may be a useful method for monitoring of development of arterial hypertension in obese patients.

PP.13.11 NORMAL-HIGH BLOOD PRESSURE OBESE SUBJECTS SHOW FIRST CAPILLARY RAREFACTION BEFORE ELEVATED ARTERIAL STIFFNESS

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Objective: The significant increase of arterial stiffness, as pulse wave velocity (PWV>12m/sec), and the capillary rarefaction are common findings in hypertensives. Aim of the study was to highlight the relationship between these markers of preclinical vascular damage in patients at risk for hypertension such as obese adult males with normal –high blood pressure (ONHBP).

Tertile/Var	age	SBP/DBP	BMI	HOMA	PWV	INT	CVC
1st PWV	51±12	132±4/86±6	30.4±6.9	2.56±1.73	8.9±.6	7±.2	61.4±8.6
2nd PWV	53±12	133±4/86±4	29.1±3.7	2.74±1.81	10.1±.4***	8±.1	55.4±9.7***
3rd PWV	51±13	133±5/84±4	30.1±4.3	2.99±1.48	12.1±.6******	8±.2	51.0±6.9***

Design and method: 87 first-diagnosed ONHBP, confirmed by ABPM, with similar metabolic assessment and insulin resistance (HOMA) underwent echodoppler, to determine carotid intima-media thickness (IMT), and videocapillaroscopy of the medial and distal phalanx of the 2nd, 3rd and 4th finger of the non-dominant hand, to determine the structural capillary density by venous congestion (CVC). Patients were divided based on PWV (Arteriograph) values (27, 32 and 28 as 1st/3 2nd/3 and 3rd/3 tertile, respectively).

Results: The findings are presented as mean±s.d in the table (*:p<0.05; **:p<0.01; ***:p<0.001 vs 1st/3 and (°:p<0.05; °°:p<0.01; °°°:p<0.001 vs 2nd/3. CVC was early reduced in the 2nd/3.
Pearson test, adjusted for age and BP, showed a significant association between HOMA and PWV (-.355**) and CVC (-.297*).

Conclusions: The findings show that in ONHBP the structural microvascular damage tend to increase with insulin resistance, is manifest prior the onset of macrovascular preclinical damage at borderline values and suggest a precocious therapeutic approach.

PP.13.12 AGE, WAIST CIRCUMFERENCE AND BLOOD PRESSURE ARE ASSOCIATED WITH SKIN MICROVASCULAR FLOWMOTION: THE MAASTRICHT STUDY

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Objective: Skin microvascular flowmotion (SMF) – blood flow fluctuation attributed to the rhythmic contraction and dilation of arterioles – is thought to play an important role in ensuring optimal delivery of nutrients and oxygen to tissue and also in maintaining low peripheral resistance. It is unclear however, which determinants influence SMF. Therefore, we investigated which cardiovascular risk factors are associated with SMF.

Design and method: We measured SMF in 506 participants without a prior cardiovascular event. Of these, we selected a healthy subpopulation of 193 participants with normal glucose metabolism, normotension, BMI<30 kg/m2, and without use of cardiovascular medication for additional analysis. SMF was investigated using Fourier transform analysis of skin laser Doppler flowmetry at rest. The associations of the cardiovascular determinants age, sex, waist circumference, 24-h systolic blood pressure (SBP), total-to-HDL cholesterol, fasting plasma glucose (FPG), and cigarette smoking with SMF were analyzed by use of multiple linear regression analysis.

Results: The mean age of the study population (n=506) was 58.8 ± 8.5 years,

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POSTER SESSION 2

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P452

Antibodies to advanced glycation end products and development of vascular injury in diabetics with essential hypertension

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Purpose: The tissue accumulation of advanced glycation end products (AGEs) alters the structure and function of long-lived proteins. A number of studies have shown that tissues accumulation of AGEs correlates with the severity of diabetic complications. Proteins containing AGEs are highly immunogenic and anti-AGEs antibodies were found in sera of diabetic rats and human.

Methods: Considering the potential use of anti-AGE antibodies as a marker of AGEs deposition during diabetes, we have investigated, by competitive ELISA, the presence of anti-AGEs antibodies in sera of 93 patients with Type 2 diabetes mellitus (T2DM) and arterial hypertension (AH) (mean age 61,4 ± 11,3 years, diabetes duration 9,88 ± 3,12 years; hypertension duration 9,28 ± 4,98). These values were compared to serum antibodies to AGEs in 42 age and sex matched controls. Diabetics were divided in two groups according to presence- Group 1 (n=67) or absence- Group 2 (n=26) of microangiopathy.

Results: Serum anti-AGEs antibodies levels in patients with T2DM and AH were statistically significantly higher that these in control group (1.390 ± 0.394 vs. 1.184 ± 0.325) F=4.72, P=0.03. Group 1 showed significantly higher levels of anti-AGEs antibodies than healthy controls (1.399 ± 0.376 vs. 1.184 ± 0.325) F=4,75 P=0.03. Anti-AGEs antibodies levels are highest in patients with vascular complications than these in all other groups. Antibodies against AGEs correlate with systolic blood pressure (r=0.17); (p=0.05), BMI (r=0.25); (p=0.01), total cholesterol (r=0.19); (p=0.04).

In our study we found higher precentage of positive patients for anti-AGEs antibodies (mean+ 2SD) in patients from Group 1 than Group 2. Six patients from 43 (14%) with microalbuminuria were positive for anti-AGEs antibodies, compared to 3 from 26 (10%) of patients without complications. Five patients from 20 (25%) with retinopathy were positive for AGE-antibodies ,while 4 from 26 (15%) in Group 2 were positive.

Conclusions: In conclusion, our study showed that investigation of the levels of anti-AGEs antibodies might be associated with higher risk for development of vascular wall damage and severity of diabetic late complications.

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P460

Anti-collagen type IV IgM serum antibodies levels are associated with development of microangiopathy in diabetic patients with uncomplicated essential hypertension

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Purpose: Thickening of basement membrane in capillaries and small vessels is a well-known finding and important in the progression of diabetic microangiopathy. Patients with diabetes mellitus and arterial hypertension are at higher risk of vascular disease.

Methods: To monitor the metabolism of the basement membrane protein collagen type IV (CIV) in type2 diabetes mellitus (T2DM), serum levels of antibodies to CIV (ACIV) IgG, IgM and IgA were measured using an ELISA method in 93 patients with type2 diabetes mellitus and arterial hypertension (AH) (mean age 61,4 ± 11,3 years, diabetes duration 9,88 ± 3,12 years; hypertension duration 9,28 ± 4,98). These values were compared to serum antibodies to CIV in 42 age and sex matched controls. Diabetics were divided in two groups according to presence- Group 1 (*n*=67) or absence- Group 2 (*n*=26) of microangiopathy.

Results: Patients with T2DM and AH showed statistically significantly higher ACIV IgM antibodies than healthy controls 0,178 (0,145→0,220) vs. 0,142 (0,118→0,173) (KW=6,31; p=0,01). Group 1 (patients with microvascular complications) showed significantly higher levels of ACIV IgM in comparison with control group 0,180 (0,136→0,223) vs. 0, 142 (0,118→0, 173) (KW=5,03; P=0.02). Patients from Group 2, were with higher ACIV IgM levels than controls 0,176 (0,151→0,202) vs. 0,142 (0,118→0,173) (KW=6,15; p=0,01). Group 1 showed the highest values of ACIV IgM. ACIV IgM showed correlation with microalbuminuria (*r*=0.18); (p=0.05), and BMI (*r*=0.19); (p=0.04). Serum ACIV IgG and IgA levels in patients with T2DM and AH were lower than these in controls, but the differences are not statistically significant.

Conclusions: Our study showed a relationship between elevation of serum levels of ACIV IgM in diabetics and development of microangiopathy.

We-P11:5 POSTPRANDIAL LIPEMIA AND INSULIN RESISTANCE IN INDIVIDUALS WITH AND WITHOUT TYPE 2 DIABETES

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Objective: The aim of this study was to evaluate if insulin resistance influences the postprandial lipemia in type 2 diabetic obese patients and non diabetic obese controls.

Methods: Thirteen type 2 diabetic patients with HbA1c < 8%, treated with diet or diet plus oral hypoglycemics agents, but not with lipid-lowerin drugs, and fasting TG < 250 mg/dl, were selected. Ten non-diabetic individuals with same sex, age, BMI and ApoE genotypes were included as controls. Postprandial lipemia was analyzed for 8 hours after a breakfast containing 50g of lipids and 40g of carbohydrates. Total area under curve for triglycerides, sampling each 2 hours, was calculated as well as fasting glucose and insulin levels to obtain the HOMA-IR index. Anthropometric parameters were also recorded.

Results: Diabetic patients tended to show higher fasting TG (141 ± 55 vs 121 ± 50 mg/dL) and higher total area under curve for TG (1452 ± 539 vs 1200 ± 528) than control subjects. The correlation study showed a significant correlation between HOMA-IR index and total area under curve for TG (Rho = 0.648; p = 0.043) in control subjects but not in diabetics. In addition, regression analysis showed that waist circunference is an independent predictor for total area under curve for TG (B=11.34;95%IC 0.005-22.68).

Conclusions: Insulin resistance, measured as HOMA-IR, is related to postprandial lipemia in control subjects but not in type 2 diabetics, being waist cincunference an independent predictor of postprandial TG response.

We-P11:6 ANTI-ELASTIN IGG SUBCLASSES AND MICROVASCULAR COMPLICATIONS

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Background and Aims: IgG is deposited in the walls of small blood vessels in diabetes. The IgG subclass might preferentially produced in response to different antigens and pathological conditions. An important factor in the development of vascular wall lesions is degradation of the elastic fiber protein, elastin. Elastin peptides derived from this degradation are present in the circulation and are a stimulus for production of elastin antibodies. Examination of the distribution pattern of anti-elastin IgG (AE IgG) subclasses in diabetes mellitus may provide insight into the immunological process involved and may assist in the early diagnosis of diabetic vascular complications. The aim of the study was to assess the relationship between AE IgG subclasses and diabetic vascular complications.

Materials and Methods: Levels of AE IgG subclasses were determined by ELISA in sera of 28 children with Type 1 (insulin-dependent) diabetes mellitus (mean age 13.2± 3.4 years, diabetes duration - 5.9± 2.9 years). Sixteen patients had microalbuminuria, 10 - retinopathy, and 2 - both retinopathy and microalbuminuria. As controls were used 24 healthy children of similar age and sex.

Results: Sixty four percent (18/28) of the patients were positive for AE IgG subclasses. Among positive patients 89% were positive for IgG1, 6% for IgG2 and 50% for IgG3. AE IgG1 were associated with retinopathy (r=0.41, p=0.001), HbA1c (r=0.51, p=0.001), and AE IgG3 with the duration of the diabetes (r=0.44, p=0.03).

Conclusion: The identification of a subset of patients who are immunologically more susceptible for development of diabetic vascular complications will enable us to target these patients for prevention of such complications.

We-P11:7 SERUM FIBRILLIN-ANTIFIBRILLIN IMMUNE COMPLEXES AMONG DIABETIC CHILDREN

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Background and Aims: The fibrillins are large glycoproteins components of 10-nm microfibrils found in the extracellular matrix of most tissues. Microfibrils play a role in elastic fiber assembly and serve to link cells to elastic fibers in the extracellular matrix. Fibrillin-1 (FBN-1) and -2 (FBN-2) are large, secreted glycoproteins known to be components of extracellular matrix microfibrils located in the vasculature, basement membrane, and various connective tissues and are often associated with a superstructure known as the elastic fiber. Anti-fibrillin antibodies found in some autoimmune diseases could form circulating immune complexes (CIC) with corresponding antigens. Type 1 (insulin-dependent) diabetes mellitus is an autoimmune disease leading to formation of different types of autoantibodies.

Materials and Methods: To determine the possible presence of FBN-anti-FBN CIC (IgG and IgM) were studied by modified version of ELISA 35 children with Type 1 diabetes mellitus (mean age-12.37±3.77 years, diabetes duration 4±3.5 years). Eight of the diabetics had vascular complications. Twenty healthy children (mean age-11.58±2.89 years) were used as controls.

Results: Diabetics showed statistically significant higher levels of FBN-anti-FBN-2 CIC - IgG (0.303±0.076 vs. 0.252±0.029; p=0.029) and IgM (0.415±0.085 vs. 0.348±0.069; p=0.018) compared to the control group. FBN-anti-FBN-1 CIC IgM correlate with diabetes duration (r=0.52; p=0.0015) and BMI (r=0.33, p=0.053) while FBN-anti-FBN-1 CIC IgG correlate with serum Zinc (r=0.49, p=0.006). FBN-anti-FBN-2 CIC IgG correlate with microalbuminuria (r=0.65, p=0.0046) and retinopathy (r=0.61, p=0.0001).

Conclusion: We suggested that elevated levels of FBN-anti-FBN-2 CIC IgG are associated with the development of early diabetic microangiopathy.

We-P11:8 ABILITY OF HDL TO RECEIVE LIPIDS FROM AN ARTIFICIAL LIPOPROTEIN MODEL IN DIABETIC PATIENTS WITH OR WITHOUT CORONARY ARTERY DISEASE

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Objectives: Low HDL cholesterol is a common feature of Type II diabetes mellitus (DM) and may contribute to the increased risk of developing coronary artery disease (CAD) in DM. We studied the ability of HDL to simultaneously receive cholesterol (FC) colesteryl esters (CE), phospholipids (PL) and triglycerides (TG) from an artificial nanoemulsion model of LDL (LDE). HDL particle diameter and Paraoxonase 1 (PON1) activity in DM patients with or without CAD to verify whether the HDL fraction bear functional alterations that might be related to CAD development.

Methods: 24 DM patients with and 13 DM without CAD in use of Simvastatin (20 mg/day) were studied. LDE labeled with ^{3}H-TG and ^{14}C-FC or ^{3}H-CE and ^{14}C-PL was incubated with plasma. After chemical precipitation the supernatant containing HDL was counted for radioactivity. HDL diameter was measured by laser light scattering.

Results: HDL cholesterol was smaller in DM with CAD than in DM without CAD, but total and LDL cholesterol and triglycerides were not different. There were no differences in lipid transfer rates to HDL, in HDL particle diameter and in PON1 activity in DM with or without CAD. Lipid transfer is given in % of total incubated radioactivity. HDL size in nm and PON1 activity in nmol.ml -1.min-1. With CAD: CE (0.6±0.4), CL (1.5±0.7), TG (1.0±0.7), PL (5.1±2.1), HDL Size (9.3±1.0) and PON1 (68.9±50.2). Without CAD: CE (0.6±0.4), CL (1.9±1.7), TG (1.0±0.9), PL (6.2±5.1), HDL Size (9.4±1.0) and PON1 (68.0±50.0).

Conclusion: Among the determined parameters, HDL cholesterol only was predictive of CAD in DM patients.

We-P11:9 BLOOD PRESSURE VARIATION AND ANTIHYPERTENSIVE TREATMENT MODIFICATION IN TYPE 2 DIABETES MELLITUS

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The aim of this study was to assess 24-hour blood pressure variation before and after a modification of antihyperten-sive medication in type 2 diabetes patients.

Materials and Methods: 118 hypertensive type 2 diabetes patients in antihypertensive treatment was subject to single modification in effort to achieve optimal blood pressure control. ABPM was performed twice in each patient: before and 7-10 days after the medication change was made.

Results: Mean systolic and diastolic blood pressure values as well as systolic and diastolic night time falls were similar before and after the medication change: 121.2±16.9 vs 11.8±18.7 mmHg, 72.9±9.9 and 73.1±11.8 mmHg, 5.8±7.8 and 5.3±8.9%, 5.7±8.2 and 6.7±8.6%. Mean relative change in systolic blood pressure was 0.38%,diastolic 1.1% Non-dipping was found in 90 patients in the first ABPM, and sixteen out of them converted to dipping in the second ABPM. In addition, six out of 28 'dippers' changed into 'non-dippers', 'Converters' were significantly younger than 'non-converters':

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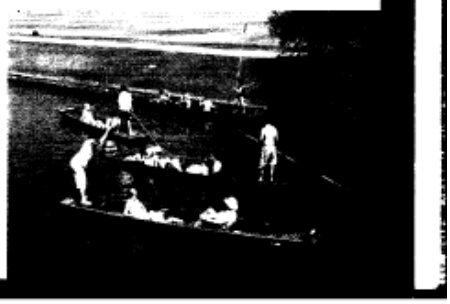

to their cultural background for optimal success. Obesity is on the rise in Oman due to the conveniences of modern day society and the sedentary lifestyle so many Omanis are having. Diet and physical activity together played a role in decreasing Obesity among the Omani population. On-going education of the population is important in changing the rise in Obesity.

Nisak Mohd Yusof

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It has been postulated that low glycemic index (GI) diets may result in greater weight loss compared to conventional weight reduction diets. This randomised controlled trial was conducted to compare the effect of a low GI against carbohydrate exchange (CE) diets on glycemic control and anthropometric measurements in overweight and obese patients with type 2 diabetes over a 3-month period. Patients with type 2 diabetes whose BMI > 25kgm-2 (n=61) were randomly assigned to receive a low GI or CE diets for a 3-month period. At week 4, the GI had significantly lower fructosamine level than the CE group ($p< 0.05$; ΔGI= -16.3 + 3.4; ΔCE= -5.9 + 3.1 umol/L). HbA1c did not differ significantly between groups but the magnitude of reduction within the GI (Δ:-0.45% + 0.1%; p= 0.001) was significantly greater than the CE group (Δ: 0.25 + 0.2%; p= 0.10). Although there was no significant difference between the two groups in terms of weight loss, the reduction in waist circumference was significantly greater in the GI than the CE group at week 4 (ΔGI=-2.2+0.60; ΔCE=-0.40+0.4 cm, $p<0.01$) and week 12 (Δ GI= -3.2 + 0.6; ΔCE = -0.9+0.46 cm, $p< 0.05$). Despite the absence of significant glycaemic improvement and weight loss, a 3-month intervention with low GI diet in overweight and obese type 2 diabetes patients resulted in a significant reduction in waist circumference.

Tirang Neyestani

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Introduction
Extra fat mass is usually accompanied by metabolic as well as clinical derangements including systemic inflammation and high blood pressure. This study aimed to determine the actual predictors of hsCRP and blood pressure in overweight/obese non-diabetic women in Tehran.

Methods
A total of 200 women with body mass index (BMI)≥25 kg/m² were enrolled in a cross-sectional study. Dietary intake, anthropometric as well as laboratory evaluations including fasting plasma glucose (FPG), lipid profile, serum insulin, high sensitivity C-reactive protein (hsCRP) and percent of body fat mass (FM) were performed for all the subjects. Pearson (r) and Spearman (rs) correlation coefficients and multivariate linear regression analysis were used to establish a model to predict hsCRP and systolic blood pressure (SBP) variations.

Results
Though serum hsCRP directly correlated with levels of FPG, triglycerides (TG), total cholesterol, BMI and waist circumference (WC), its strongest association was found with FM (r_s=0.326, $p<0.001$). Also, SBP directly correlated with FPG, TG, and FM but it was more strongly correlated with BMI (r=0.343, $p<0.001$) and WC (r_s=0.350, $p<0.001$). No association was found between blood or anthropometric variables and dietary data. In different regression models WC and FM were the predictors of hsCRP but BMI was the significant predictor of SBP.

Conclusion
Adiposity in Iranian middle-aged women can affect both inflammatory biomarkers and systolic blood pressure thus predisposing for MeS and further morbidities. We identified FM and WC as the predictors of serum hsCRP levels and BMI as the predictor of SBP in our population.

Conflict of interest: none.
Funding: This project was funded by National Nutrition and Food Technology Research Institute (NNFTRI).

Asparuh Nikolov

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Introduction
Elastin and collagen are the main proteins of vascular wall. An important factor in the development of vascular wall alterations is degradation of the elastic fiber major protein – elastin. Arterial hypertension (AH) is connected with the loss of arterial wall's elasticity and an abnormal increase in the collagen/elastin ratio.
The aim of our study was to:
1. Measure levels of elastin-derived peptides (EDP) in sera of obese children with essential hypertension;
2. To compare serum EDP levels of obese children with essential hypertension with EDP levels in obese children without essential hypertension and healthy controls

Methods
The study population consisted of 113 children divided into three groups as follows:
obese children with elevated blood pressure (n=43), mean age 12.1±2.2 years (Group 1);

obese children with normal blood pressure (n=32), mean age 11.3±3.1 years (Group 2); and control group of healthy children (n=38), mean age 11.8±2.8 years (Group 3).
Blood pressure (BP) was measured with a random zero sphygmomanometer in the sitting position after at least 5 min rest. Serum total cholesterol, triglycerides and HDL-C were determined enzymatically. The sandwich version of an enzyme-linked immunosorbent assay (ELISA) for detection of EDP was used.

Results

Children with obesity and AH (Group 1) showed statistically significantly higher levels of EDP (102±18 ng/ml) in comparison with Group 2 (75±31 ng/ml) and controls (60±22 ng/ml) ($p<0,05$). There were non-significant differences in serum EDP levels (75±31 vs. 60±22 ng/ml) between obese children without AH and healthy controls ($p>0,05$). Twenty-three percent of children from Group 1 were positive for EDP. The concentrations of total cholesterol and LDL were significantly higher in both groups of obese children in comparison with the control group ($p<0.01$).
The results indicated both the obese boys and girls with AH to have increased mean levels of total cholesterol (7,2±1,3 and 7,9±1,5 mmol/l, respectively) in comparison with the obese boys and girls without AH (6,4±1,5 and 6,9±1,5 mmol/l, respectively; $p<0,01$). The mean levels recorded in obese children without AH were relatively higher in comparison with healthy controls ($p<0,01$). Interestingly, obese girls from Group 1 showed lower mean value of HDL-C (0,92±0,24 mmol/l) than either obese boys from the same group (1,12±0,18) or controls (1,31±0,10) ($p<0,05$).

Conclusion

Our data suggest the existence of an association between changes in levels of serum EDP, obesity and essential hypertension in children. Determination of serum EDP levels may be a useful method for monitoring of development of arterial hypertension in obese children.

Nicolae Panduru

Panduru, N

Introduction

Diabetes is the epidemic of our times. Diabetic nephropathy (DN) is one of the most important diabetes complications due to high mortality rate and increased care costs. The pathogenesis of diabetic nephropathy is not fully understood. Abdominal obesity and the subsequent insulin resistance is typically described for type 2 diabetes mellitus, but seems to exist also in type 1 diabetes. The aim of the study is to evaluate if insulin resistance defined by eGDR can be used to predict DN and which is the cut off value that can predict the appearance of nephropathy in type 1 diabetes.

Material and Methods

We studied 88 type 1 diabetic patients. The diagnostic of type 1 diabetes was confirmed by measuring the C-peptide value (<0.3 nmol / l). They were divided into two groups: A – 50 patients with DN and B – 38 patients without microalbuminuria and more than 20 years diabetes duration. All patients were investigated for: creatinin, estimated GFR, microalbuminuria, HbA1C, blood pressure, anthropometric measurements, eGDR. The statistical analysis was performed with S-plus software. We estimated the ROC curve for eGDR and measured sensibility, specificity, positive predictivity and negative predictivity of eGDR for diabetic nephropathy.

Results

The first part of the ROC curve is much closed to the first bisector, for levels of eGDR smaller then 3.5. Aria under curve or the C statistic=0.6785. The optimum threshold is toptim=5.6. At this level sensitivity=64.7%, specificity=67.5%, positive predictivity=73.3% and negative predictivity=58.1%.

Discussions

Even if the study is performed on a relatively small number of patients, the result are encouraging. A level of sensitivity and sensibility of 64.7%, respectively 67.5% are very close to an accepted level. We would like to draw attention about the threshold of 5.6 (below 8.7 which is predictive for metabolic syndrome), which means that is possible to have insulin resistance in type 1 diabetes. In the same time further studies are necessary to evaluate this promising results and clarify the role of abdominal obesity and insulin resistance in pathogenesis of diabetic nephropathy in type 1 diabetes.

Acknowledgements

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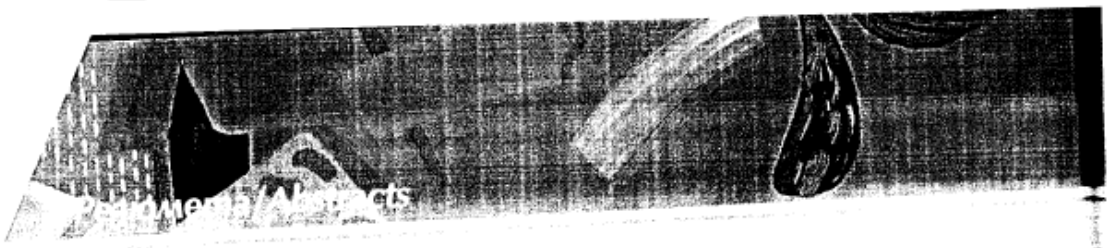
Background

Obesity is a multi-factorial disease with excess of fat storage and leads to ailments like hypertension, diabetes, stroke and cancer. Diet & exercise alone cannot help in reduction of adiposity in problematic areas like hips, thighs & abdomen. Various non – invasive procedures like High Focalized Intensity Ultrasound (HIFU), Endermology, Mesotherapy and laser are thus used for lipolysis and lipo-mobilization.

Design

Randomized, controlled, multicenter, multiracial study comparing effects of lipolysis with lymphatic drainage of fat, on fat percentage and waist circumference was carried out in men and women of different ethnicities with BMI of 28 to 30.



а също така и от вида на антидиабетното лечение.

Карциномните клетки са с много големи възможности да усвояват глюкозата и да се мул-типлицират, благодарение на механизми в техните инсулинови рецептори и на особености в техния клетъчен растеж, който не е свързан с остаряване на карциномните клетки, а напро-тив – с тяхното постоянно подмладяване и перекъснато размножаване, което задушава и превзема периферията на нормалните клетки на организма.

Видът на антидиабетното лечение също играе роля за развитие на карциноми. Една част от антидиабетните медикаменти стимулират карциномната инвазия, друга част от тях са индиферентни по отношение на карциномната пролиферация, а трета група от тях има ан-тиканцерогенно действие. Антидиабетното лечение трябва да се съобразява с риска от раз-витие на карцином при болни с преканцерозни състояния, фамилна обремененост с карциноми или при вече появил се карцином, така че той да забавя, а не да ускорява своето развитие.

Метформинът е общопризнатият медикамент с антиканцерогенен ефект. Това е устано-новено при лабораторни условия, при експериментални проучвания и в клиничната практика. Той предотвратява трансформирането на нормалните клетки в преканцерозни, а по-късно и в канцерозни клетки. При вече възникнал карцином, препятства неговото развитие и поява на метастази. На клетъчно ниво той блокира редица етапи в превръщането на нормалната клетка в ракова клетка. При вече появила се ракова клетка той блокира вътреклетъчните ме-ханизми за нейния непрекъснат растеж и неконтролирано развитие. Ето защо, наред с общопри-знатия ефект на метформина за намаляване на сърдечносъдовия риск при болните с диа-бет, следва да се прибави и неговия антиканцерогенен ефект.

Серумни анти-колагенови тип IVIgM антитела и развитие на диабетна нефропатия при болни със захарен диабет тип 2 и артериална хипертония

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Въведение и цели: Задебеляването на базалната мембрана на капилярите и малките съдове е добре позната находка и важен компонент в прогресията на диабетната микроангиопатия. Пациентите със захарен диабет (ЗД) и артериална хипертония (АХ) са в по-висок риск за развитие на съдова болест.

Материал и методи: За мониториране метаболизма на основния базално мембранен протеин-колаген тип IV (KIV) при пациенти със ЗД тип 2, както и за регистриране на серумните нива на антителата срещу KIV фрагменти от субкласовете IgG, IgM и IgA, беше използван ELISA методът при 93-ма пациенти със ЗД тип 2 и АХ (средна възраст 61,4+/-11,3 години; продължителност на диабета 9,88+ -3,12; продължителност на хипертонията 9,28+ - 4,98). Тези стойности бяха сравнени спрямо 42 възрастово и полово съвпадащи контроли. Диабетиците бяха разделени на две групи според наличието – Група 1 (n=67), или отсъствието - Група 2 (n=26) на микроангиопатия.

Резултати: Проведените изследвания показаха, че серумните нива на Анти-KIV IgM антитела при пациенти със ЗД тип 2 и АХ са по-високи спрямо контролната група, като тези стойности са сигнификантни 0,178 (0,145–0,220) vs. 0,142 (0,118–0,173) (KW=6,31; p=0,01). Група 1 (пациенти със микроваскуларни усложнения) показа сигнификантно по-високи

стойности на Анти-KIV IgM в сравнение със здравите контроли 0,180 (0,136÷0,223) vs. 0,142 (0,118÷0,173) (KW=5,03; P=0,02). Пациентите от Група 2, показаха значимо завишение на изследвания показател спрямо контролите 0,176 (0,151÷0,202) vs. 0,142 (0,118÷0,173) (KW=6,15; p=0,01).Най-високи стойности на Анти-KIV IgM се установиха при пациентите със съдови поражения (Група 1).

Серумните Анти-KIV IgM корелират с микроалбуминурията (r=0,21); (p=0,04), BMI (r=0,19); (p=0,04), с креатининовият клирънс (r=-0,36); (p=0,01) и GFR (r=-0,34); (p=0,02). Серумните Анти-KIV IgG нива бяха по-високи при пациентите отколкото при контролите, докато Анти-KIV IgA нивата бяха по-високи при контролите, но разликите не са значими.

Изводи: Нашето проучване показа връзка между повишените серумни нива на анти-KIV IgM и развитието на диабетна нефропатия. Предполагаме, че определянето на серумните анти-KIV IgM антитела може да бъде полезен маркер за идентифициране на болни със ЗДТ2 и АХ, които са с висок риск за развитие на съдови увреждания.

Serum anti-collagentype IV IgM antibodies and development of diabetic nephropathy in diabetics with essential hypertension

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Background and aims: Elastin and collagen are the main proteins of the vascular wall. Arterial hypertension and diabetic vascular complications are connected with an elevated degradation ofelastic tissue. As a result collagen type IV derived peptides (CIVDP) are releasedin the circulated blood, which are a pathological stimulus foran increased production of antibodies to collagen type IV (ACIV Abs). In the present investigation we studied whether theserum levels of antibodies (IgG, IgM and IgA) to collagen are related with microvascular complications.

Material and methods: Serum levels of antibodies to collagen type IV (ACIV) IgG, IgM and IgA were measured using an ELISA method in 93 patients with type 2 diabetes mellitus and arterial hypertension (AH) (mean age 61,4±11,3 years, diabetes duration 9,88±3,12 years; hypertension duration 9,28±4,98). These values were compared to serum antibodies to CIV in 42 age and sex matched controls. Diabetics were divided in two groups according to presence- Group 1 (n=67) or absence- Group 2 (n=26) of microangiopathy.

Results: ACIV IgM antibodies levels in patients with AH and T2DM were statisticaly significantly higher than controls 0,178 (0,145÷0,220) vs. 0,142 (0,118÷0,173) (KW=6,31; p=0,01). Group 1 (patients with microvascular complications) showed significantly higher levels of ACIV IgM than controls 0,180 (0,136 ÷0,224) vs. 0,142 (0,118÷0,173) (KW=5,03; P=0,02). Patients from Group 2 showed statistically significantly higher levels of ACIV IgM than controls 0,176 (0,151÷0,202) vs. 0,142 (0,118÷0,173) (KW=6,15; p=0,01).

ACIV IgM antibodies showed correlation with microalbuminuria (r=0,21); (p=0,04), BMI (r=0,19); (p=0,04), creatinine clearance (r=-0,36); (p=0,01) and GFR (r=-0,34); (p=0,02). Serum ACIV IgG levels were higher in patients than in controls, while serum ACIV IgA levels were lower than these in controls, but the differences are not statistically significant.

Conclusion: Our study showed an association between elevation of serum levels of ACIV IgM and development of diabetic nephropathy. Elevation of ACIV IgM can be related withlater clinical manifestation of nephropathy. We suggest that levels of ACIV IgM can be useful method for identfying a high risk for development of diabetic nephropathy.

ДЕСЕТА НАЦИОНАЛНА КОНФЕРЕНЦИЯ
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ОПРЕДЕЛЯНЕ НА СВОБОДНИ АНТИЕЛАСТИНОВИ АНТИТЕЛА ОТ КЛАС IgG ПРИ ПАЦИЕНТИ СЪС ЗАХАРЕН ДИАБЕТ ТИП 2 И АРТЕРИАЛНА ХИПЕРТОНИЯ

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Въведение и цели: Антитела срещу продуктите от разграждането на еластин са открити в серума на всички хора. Наличието на анти-еластинови антитела (AEAbs) и съответните антигени в кръвобращението води до образуването на циркулиращи имунни комплекси (CIC). Целта на проучването е да се определят серумните нива на несвързаните в комплекси анти-еластинови антитела от клас IgG(свободни AEAbs).

Материали и методи: За определянето на свободните AEAbs използвахме метод за изолирането на имунни комплекси чрез CIF (комплемент инхибиращ фактор), последван от ELISA за откриване на AEAbs. Нивата на свободен AEAbs IgG бяха измерени в серума на 93 пациенти със захарен диабет и хипертония (средна възраст 61,4 ± 11,3, диабетна продължителност 9,88 ± 3,12; продължителност на хипертонията 9,28 ± 4,98). Тези нива са сравнени с контролни лица (n= 42), съвпадащи по пол и възраст.

Резултати: Свободни AEAbs IgG при пациенти със захарен диабет тип 2 и артериална хипертония са статистически значително по-високи от тези при здрави контроли 0,421 (0,328-0,572) спрямо 0,240 (0,212-0,305) (KW = 19,64; p <0,0001). Група 1 (пациенти с микросъдови усложнения) показва значително увеличение на свободните AEAbs IgG в сравнение с контролите 0,428(0,343-0,591) спрямо 0,240 (0,212-0,305) (KW = 20,14; p <0,0001). Група 2 (пациенти без микросъдови усложнения) също показва по-високи нива на свободни AEAbs IgG от контролната група 0,398 (0,312-0,467) спрямо 0,240 (0,212-0,305) (KW = 8,88, p = 0,003). Пациентите от група 1 показат най-високите нива на свободен AEAbs IgG. Няма значими разлики между група 1 и група 2.

Заключение: Резултатите показват връзка между еластиновия обмен и микросъдовите лезии при пациенти с диабет и артериална хипертония. Предполагаме, че свободните AEAbs IgG са определящи на по-късен етап за автоимунизацията към еластина.

Ключови думи: захарен диабет тип 2; артериална хипертония; свободни антиеластинови антитела; ELISA; CIF.

XI
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DIABETES MELLITUS AND ITS LATE COMPLICATIONS

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ICMS 2012 / PP 08 Therapy

Abstract

Background and Aims: Type 2 Diabetes mellitus (T2DM) is a chronic disease, with an impact on connective tissue metabolism. It is well known that the prognosis of T2DM and patients' life duration correlate with the presence of vascular complications. Our aim is to illustrate the late complications of T2DM and to underline the importance of early diagnosis and treatment, intensive control and multidisciplinary approach to this disease. We present the case of a 58-year-old white male patient with a history of longstanding T2DM with bad metabolič control of blood glucose levels, despite insulin therapy, uncontrolled arterial hypertension and chronic kidney failure with high levels of blood urea nitrogens (BUN) and abnormal diuresis. Materials and Methods: History of the disease, Physical examination, Laboratory tests- blood and urine samples, Ultrasound Doppler, consultations with an endocrinologist, neurologist, nephrologist and ophtalmologist Results: History of the disease revealed T2DM for 17 years with retinopathy manifestations with trials for laser therapy, diabetic polyneuropathy complaints and chronical kidney disease I-II grade. Physical examination showed poor general condition with facies of Bright, bilateral ankle oedema, blood pressure- 170/90 mmHg. Laboratory tests (blood and urine) gave an evidence for high blood glucose levels- 15 mmol/l, very high serum creatinine levels- 422 μmol/l, creatinine clearance- 10.54 ml/min (a creatinine clearance value of approximately 10ml/min is an indication that dialysis may be necessary), microalbuminuria- 201 mg/ml of protein in 24 hour urine sample, BUN- 23.1 mmol/l. USG of the abdominal viscera showed bilateral diffuse structure impairment of the kidneys because of diabetic glomerulopathy, hepatic steatosis, hepatosplenomegaly, adenoma glandulae prostate, cystitis. USG Doppler- bilateral thrombosis of the tibial artery. Neurological examination- loss of feeling in the toes, feet, legs pain. Ophtalmological examination- haemophtalmus of right eye, angiosclerotic changes in both eyes, pale, fatty deposits on retina- signs of leaking blood vessels, severe diabetic rethinopathy. Cardiological findings- ischaemic heart disease, congestive heart failure. Discussion: The following late complications of T2DM were determined: Diabetic neuropathy, Diabetic retinopathy, Diabetic nephropathy with secondary anaemia, Arterial hypertension, Peripheral vascular disease (PVD). The initiated therapy included: Insulin NovoRapid 100 Units/ml solution (Insulin Aspart, fast acting insulun) for injection s.c. according blood glusose levels; Insulin Levemir (long acting insulin)- 28U/24h; Furosemide (loop diuretic); Clonidine (central sympathicolityc); Metoprolol (selective ?-blocker); Telmisartan (angiotensin receptor blocker); Thoigamma (alpha-lipoic acid). The patient was discharged with improved and stable physical condition. He was prescribed an insulin analogue, loop diuretic, antihyprtensive, antistenocardic and antianaemic drugs. Earlier and controlled personalized treatment would help to prevent serious levels of damage, especially microvascular complications of T2DM.

Keywords: diabetes mellitus, nephropathy, retinopathy, neuropathy, arterial hypertension

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ANTI-ELASTIN IGG SUBCLASSES AND MICROVASCULAR COMPLICATIONS OF DIABETES MELLITUS

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ICMS 2012 / OP 14 Therapy

Abstract

Background and aims: The IgG subclass can be preferentially produced in response to different antigens and pathological conditions. In a patient with diabetes mellitus IgG is deposited in the walls of small blood vessels. An important factor in the development of vascular wall lesions is the degradation of the elastic fiber protein, elastin. Elastin peptides derived from this degradation are present in the circulation and are a stimulus for the production of elastin antibodies. Examination of the distribution pattern of anti-elastin IgG (AE IgG) subclasses in diabetes mellitus may provide an insight into the immunological process involved and may assist in the early diagnosis of diabetic vascular complications. The aim of our study was to assess the relation between AE IgG subclasses and diabetic vascular complications. Materials and methods: Levels of AE IgG subclasses were determined by ELISA in sera of 28 children with Type 1 (insulin-dependent) diabetes mellitus (mean age 13.2± 3.4 years, diabetes duration - 5.9± 2.9 years). Sixteen patients had microalbuminuria, 10 - retinopathy, and 2 - both retinopathy and microalbuminuria. Twenty-four healthy children of similar age and sex were used as a control group. Results: Sixty four percent (18/28) of the patients were positive for AE IgG subclasses. Among positive patients 89% were positive for IgG1, 6% for IgG2 and 50% for IgG3. AE IgG1 were associated with retinopathy (r=0.41, p=0.001), HbA1c (r=0.51, p=0.001), and AE IgG3 with the duration of the diabetes (r=0.44, p=0.03). Conclusion: The identification of a subset of patients who are immunologically more susceptible to diabetic vascular complications will enable us to prevent the patients from developing such complications and serious levels of damage.

Keywords: diabetes mellitus, anti-elastin IgG subclasses, diabetic vascular complications

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БЪЛГАРСКА КАРДИОЛОГИЯ

ИЗДАНИЕ НА ДРУЖЕСТВОТО НА КАРДИОЛОЗИТЕ В БЪЛГАРИЯ

Проследени са 32-ма пациенти – 10 мъже (31.2 %) и 22 жени (68.8 %). Средната възраст при представянето е 45 години. Според етиологията се отличават идиопатична (65.6%) и асоциирана (34.4%) БАХ. При първоначалната презентация един пациент [illegible] ФК, 4 [illegible] ФК, 25 (78.1%) в III ФК и двама (6.3%) в IV ФК, като 22 (68.8%) от пациентите бяха без специфична терапия.

Резултати. Периодът на проследяване е средно 544 дни. Регистрирахме [illegible] (18.8%). При 12 (37.5%) от пациентите [illegible] хоспитализации [illegible]

Заключение. [illegible]

П-7.7. СЕРУМНИ КОНЦЕНТРАЦИИ НА ЕНДОТЕЛИН-1 И С-РЕАКТИВЕН ПРОТЕИН ПРИ ПАЦИЕНТИ С АРТЕРИАЛНА ХИПЕРТЕНЗИЯ СЪС И БЕЗ ЗАХАРЕН ДИАБЕТ ТИП 2

К. Костов[1], А. Димитрова[1], С. Тишина[2], К. Господинова[2], А. Блажев[3], М. Атанасова[1], А. Русева[1], И. Цанкова[1] и А. Николов[1]

[illegible]

Цел. Ендотелин-1 (ЕТ-1) е един от най-силните вазоконстриктори. [illegible]

на съдовите промени при артериална хипертензия и диабет. С-реактивният протеин (CRP) е острофазов белтък, който се синтезира от хепатоцитите под въздействието на интерлевкини (IL-6) при възпаление. Има данни, че нивата на CRP могат да бъдат увеличени при пациенти с артериална хипертензия и диабет, както и бъдат предвестници на сърдечно-съдови инциденти. Целта на проучването беше да се установи дали съществуват сигнификантни разлики между серумните концентрации на ЕТ-1 и CRP [illegible] захарен диабет тип 2 (ЗД2) [illegible]

Материал и методи. Формирани бяха 3 групи: Г1 – [illegible] артериална хипертензия без диабет (мъже – [illegible], жени – [illegible]; САН = 155.4 ± 4.6 mm Hg, ДАН = 87.15 ± 2.5 mm Hg), средна възраст 65.3 ± [illegible] години; Г2 – [illegible] пациенти с артериална хипертензия с ЗД2 [illegible] ДАН = 82 [illegible] mm Hg, средна възраст 63.5 ± 11.0 години; Г3 – 20 нормотензивни лица без диабет и без сърдечно-съдови заболявания, контролна група (мъже – 13, жени – 22; САН = 124 [illegible] mm Hg, ДАН = 82.2 ± 4.1 mm Hg, средна възраст 47.92 ± 11.3 години). ЕТ-1 е определен чрез ELISA [illegible] CRP – чрез имунотурбидиметричен метод [illegible] статистическа програма [illegible]

Резултати. Установиха се статистически значими разлики на серумните концентрации на ЕТ-1 [illegible]

Заключение. Серумните концентрации на ЕТ-1 и CRP са значително повишени при пациентите с артериална хипертензия със ЗД2, което потвърждава тяхната връзка с патогенезата на заболяването. Ролята им в [illegible] за възникването на съдовите възпаления [illegible] при ЗД2.

П-7.8. КОЛХИЦИН В ЛЕЧЕНИЕТО НА ПЕРИКАРДИТА – ПРОМЕНИЛА ЛИ СЕ Е ЧЕСТОТАТА НА ПРИЛОЖЕНИЕТО МУ ЗА ПОСЛЕДНИТЕ ПЕТ ГОДИНИ?

А. [illegible], [illegible] и И. Иотов

[illegible]

[illegible]

Целта на настоящото проучване е да се сравни лечението на перикардита в два периода – 2004-2005 и 2013-2014 [illegible]

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poisonings.
Key words: professional exposure, pesticides, chronic intoxications

LEVELS OF ANTI-COLLAGEN TYPE IV IgG ANTIBODIES ARE ASSOCIATED WITH HIGH RISK OF ATHEROSCLEROSIS IN DIABETICS WITH ESSENTIAL HYPERTENSION

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Summary
Background and Aims: Thickening of basement membrane in capillaries and small vessels is a well-known finding and important in the progression of diabetic microangiopathy. Patients with diabetes mellitus and arterial hypertension are at higher risk for development of atherosclerosis. Material and methods: Serum levels of antibodies to collagen type IV (ACIV) IgG, IgM and IgA were measured using an ELISA method in 93 patients with type 2 diabetes mellitus and arterial hypertension (AH) (mean age 61,4±11,3 years, diabetes duration 9,88±3,12 years; hypertension duration 9,28±4,98). These values were compared to serum antibodies to CIV in 42 age and sex matched controls. Diabetics were divided in two groups according to presence- Group 1 (n=67) or absence- Group 2 (n=26) of microangiopathy. Results: Group 1 (patients with microvascular complications) showed significantly higher levels of ACIV IgG in comparison with Group 2 0,323 (0,2430,391) vs. 0.241 (0,2070,291) (KW=7,66; p=0,006) and control group 0.210 (0,1490,262) (KW=17,52; P<0.0001). Patients from Group 2, were with higher ACIV IgG levels than controls 0,176 (0,1510,202) vs. 0.142 (0,1180,173) (KW=6,15; p=0,01). ACIV IgG showed correlation duration of diabetes (r=0.49); (p=0.01), retinopathy (r=-0.20); (p=0.04), BMI (r=-0.24); (p=0.05), systolic blood pressure (r=0.16); (p=0.05), total cholesterol (r=0.20); (p=0.03), tryglicerides (r=0.31); (p=0.01). Serum ACIV IgM and IgA levels in patients with T2DM and AH were lower than these in controls, but the differences are not statistically significant. Conclusion: Our study showed a relationship between elevation of serum levels of ACIV IgG in diabetics and development of vascular changes. The elevation of ACIV IgG can be related with later clinical manifestation of atherosclerosis. We suggest that ACIV IgG can be useful method for identfying a high atherosclerotic risk in diabetic patients.
Key words: collagen type IV, arterial hypertension, diabetes mellitus

POSTERS

FATAL OUTCOMES WITH DATA OF METHADONE ABUSE IN SOFIA FOR THE PERIOD 2012-2013

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Summary
Methadone is a synthetic opioid commonly used as medication in the therapy of heroin addiction. It also is used as an illegal drug by addicts. Aim: To establish the consequences of illegal use of methadone. Material and methods: Forensic medical examination of cadavers of drug addicts for the period 2012-2013, establishing the cause

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DIABETES MELLITUS AND ITS LATE COMPLICATIONS

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Objectives: Type 2 Diabetes mellitus (T2DM) is a chronic disease, with an impact on connective tissue metabolism. It is well known that the prognosis of T2DM and patients' life duration correlate with the presence of vascular complications. Our aim is to illustrate the late complications of T2DM and to underline the importance of early diagnosis and treatment, intensive control and multidisciplinary approach to this disease. We present the case of a 58-year-old white male patient with a history of longstanding T2DM with bad metabolic control of blood glucose levels, despite insulin therapy, uncontrolled arterial hypertension and chronic kidney failure with high levels of blood urea nitrogens (BUN) and abnormal diuresis.

Material & Methods: History of the disease, Physical examination, Laboratory tests- blood and urine samples, Ultrasound Doppler, consultations with an endocrinologist, neurologist, nephrologist and ophtalmologist

Results: History of the disease revealed T2DM for 17 years with retinopathy manifestations with trials for laser therapy, diabetic polyneuropathy complants and chronical kidney disease I-II grade. Physical examination showed poor general condition with facies of Bright, bilateral ankle oedema, blood pressure- 170/90 mmHg. Laboratory tests (blood and urine) gave an evidence for high blood glucose levels- 15 mmol/l, very high serum creatinine levels- 422 μmol/l, creatinine clearance- 10.54 ml/min (a creatinine clearance value of approximately 10ml/min is an indication that dialysis may be necessary), microalbuminuria- 201 mg/ml of protein in 24 hour urine sample, BUN- 23.1 mmol/l. USG of the abdominal viscera showed bilateral diffuse structure impairment of the kidneys because of diabetic glomerulopathy, hepatic steatosis, hepatosplenomegaly, adenoma glandulae prostate, cystitis. USG Doppler- bilateral thrombosis of the tibial artery. Neurological examination- loss of feeling in the toes, feet, legs pain. Ophtalmological examination- haemophtalmus of right eye, angiosclerotic changes in both eyes, pale, fatty deposits on retina- signs of leaking blood vessels, severe diabetic rethinopathy. Cardiological findings- ischaemic heart disease, congestive heart failure.

Conclusion: The following late complications of T2DM were determined: Diabetic neuropathy, Diabetic retinopathy, Diabetic nephropathy with secondary anaemia, Arterial hypertension, Peripheral vascular disease (PVD). The initiated therapy included: Insulin NovoRapid 100 Units/ml solution (Insulin Aspart, fast acting insulun) for injection s.c. according blood glusose levels; Insulin Levemir (long acting insulin)- 28U/24h; Furosemide (loop diuretic); Clonidine (central sympathicolityc); Metoprolol (selective β-blocker); Telmisartan (angiotensin receptor blocker);

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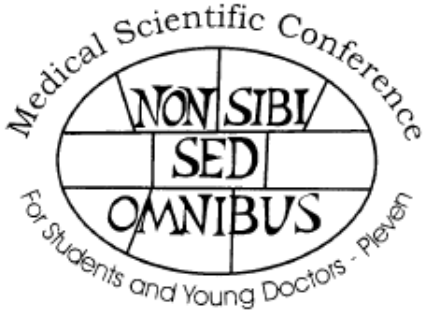

ABSTRACT BOOK

AND PROGRAM

Under the auspices of the Rector of Medical University - Pleven, Bulgaria
Prof. G. Gorchev, M.D.PhD

P. 4

LEVELS OF ELASTIN DEGRADATION PEPTIDES AND DEVELOPMENT OF MICROVASCULAR COMPLICATIONS IN PATIENTS WITH TYPE 2 DIABETES MELLITUS

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AIMS/OBJECTIVES
Type 2 Diabetes mellitus (T2DM) is a chronic disease, with generall impact of connective tissue metabolism. It is well known that the prognosis of T2DM and patients' life duration correlate with presence of vascular complications.
Elastin is one of the main proteins of the vascular wall. Elastin degradation is accerelated in patients with diabetes mellitus. Elastin peptides derived from the degradation are present in the circulating blood and they are a stimulus for pathologically increased production of elastin antibodies. The aim of our study was to investigate if elastin degradation peptides (EDP) can be used as early marker for vascular damage.

METHODS
We investigated 60 patients with T2DM and 30 controls. Patients were divided in two groups: Group 1- diabetic patients without vascular complications, Group 2- diabetic patients with vascular complications and Group 3- healthy controls. The sandwich version of enzyme linked immunosorbent assay (ELISA) was used for determination of EDP.

RESULTS
There were no statistically significant differeces between levels of EDP in sera of patients from Group 3 (64±25 ng/ml) and patients from Group 1 (68±30ng/ml) ($p>0.05$). Diabetics from Group 2 (148±38 ng/ml) showed statistically significan higher levels of EDP than both patients from Group 1 (68±30ng/ml) and Group 3 (64±25 ng/ml): ($p<0.05$).
EDP showed correlation with retinopathy and nephropathy, diabetes duration, HbA1c and triglycerides.

CONCLUSION
Patients with T2DM have accelerated elastin tissue degradation. We suggest that levels of EDP can be used as marker for early development of microvascular complications in patients with diabetes mellitus.

KEY WORDS: type 2 diabetes mellitus, elastin, ELISA, microvascular complications

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ABSTRACT BOOK

Under the auspices of the Rector of Medical University – Pleven, Bulgaria
Prof. Sl. Tomov, MD, PhD, DSc

P.29. SERUM ANTI-COLLAGEN TYPE IV IgM ANTIBODIES AND DEVELOPMENT OF MICROVASCULAR COMPLICATIONS IN DIABETICS WITH ESSENTIAL HYPERTENSION

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AIMS

Elastin and collagen are the main proteins of the vascular wall. Arterial hypertension and diabetic vascular complications are connected withan elevated degradation of elastic tissue. As a result collagen type IV derived peptides (CIVDP) are released in the circulated blood, which are a pathological stimulus for an increased production of antibodies to collagen type IV (ACIV Abs). In the present investigation we studied whether the serum levels of antibodies (IgG,IgM and IgA) to collagen are related with microvascular complications.

METHODS

Serum levels of antibodies to collagen type IV (ACIV) IgG, IgM and IgA were measured using an ELISA method in 93 patients with type 2 diabetes mellitus and arterial hypertension (AH) (mean age 61,4±11.3 years, diabetes duration 9,88±3,12 years; hypertension duration 9.28±4,98). These values were compared to serum antibodies to CIV in 42 age and sex matched controls. Diabetics were divided in two groups according to presence - Group 1 (n=67) or absence - Group 2 (n=26) of microangiopathy.

RESULTS

ACIV IgM antibodies levels in patients with AH and T2DM were statisticaly significantly higher than controls 0.178(0.145ø0.220) vs. 0.142(0.118ø0.173)(KW=6.31; p=0,01). Group 1 (patients with microvascular complications) showed significantly higher levels of ACIV IgM than controls 0.180 (0.136ø0.223) vs. 0.142 (0.118ø0.173) (KW=5.03; P=0.02). Patients from Group 2 showed statistically significantly higher levels of ACIV IgM than controls 0.176 (0.151ø0.202) vs. 0.142 (0.118ø0.173) (KW=6.15; p=0,01).

ACIV IgM antibodies showed correlation with microalbuminuria (r=0.21); (p=0.04), BMI (r=0.19); (p=0.04), creatinine clearance (r=-0.36); (p=0.01) and GFR (r=-0.34); (p=0.02). Serum ACIV IgG levels were higher in patients than in controls, while serum

ACIV IgA levels were lower than these in controls, but the differences are not statistically significant.

CONCLUSION

Our study showed an association between elevation of serum levels of ACIV IgM and development of diabetic nephropathy. Elevation of ACIV IgM can be related with later clinical manifestation of nephropathy. We suggest that levels of ACIV IgM can be useful method for identfying a high risk for development of diabetic nephropathy.

KEY WORDS:collagen type IV, ELISA, diabetic nephropathy, arterial hypertension

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