CETP-deficiency manifests a unique plasma lipoprotein profile without other apparent symptoms. It is highly common in East Asia, while rare anywhere else. An environmental screening factor(s) should be conceived for this eccentric distribution, such as a region-specific infectious disease. Blood flukes use the host plasma lipoproteins as nutrient sources through the lipoprotein receptor-like systems and its Asian-specific species, Schistosoma (S) japonicum has been endemic in East Asia. The adults and eggs of S. japonicum take up cholesteryl ester (CE) from HDL for the egg embryonation to miracidia, a critical step of the hepatic pathogenesis of this parasite and this reaction was retarded with the HDL of CETP-deficiency. CD36-related protein (CD36RP) was cloned from the adults and the eggs of S. japonicum, with 1880-bp encoding 506 amino-acid residues exhibiting the CD36 domains and two transmembrane regions. Its extracellular domain selectively bound human HDL but neither LDL nor CETP-deficiency HDL, and the antibody against the extracellular domain suppressed the selective HDL-CE uptake and embryonation of the eggs. When infected with S. japonicum, wild-type mice developed less hepatic granulomatosis than CETP-transgenic mice by the ectopic egg embryonation. CD36RP is thus a candidate receptor of S. japonicum to facilitate uptake of HDL-CE necessary for egg embryonation. Abnormal HDL caused by CETP-deficiency retards this process and thereby protects the patients from development of hepatic lesions. S. japonicum infection is a strong candidate as a screening factor for CETP deficiency in East Asia.

There is no conflict of interest to declare for this work.
Alternative treatment of atherosclerosis using nanoparticles and nanocomposites

Abstract nr. 2
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Topic The Pathogenesis of Atherosclerosis; Immunity, Inflammation, and the Endothelium
Keywords Cardiovascular Disease, LDL, Therapy

Atherosclerosis is a disease characterized by its occurrence in the arterial wall at susceptible sites in major conduit arteries. This disease is initiated by lipid retention, oxidation and modification which will eventually cause chronic inflammation. This process can result in stenosis or thrombosis. Atherosclerosis and its thrombotic complications are currently the chief cause of morbidity and mortality in the developed world. The traditional drug treatments for atherosclerosis are limited to the prevention of the formation (generation) of new atheroma plaques in the body. In this respect, the development of functional nanostructures, to provide the removal of free-LDL from the bloodstream, is absolutely necessary for those patients for whom traditional treatments (statins) fails to prevent the negative effects of atherosclerosis. We developed SPIONS (magnetic nanoparticles) functionalized with monoclonal antibodies that are able to interact with low density lipoprotein (LDL). That is, these SPIONS will act as molecular / magnetic traps for free LDL. The SPIONS-LDL complexes will be trapped using a magnetic field during the short extracorporeal circulation. The prepared samples have its biocompatibility and its capacity to interact with free-LDL investigated. The studies for the control of nanonavigation are progressing with good results for static and low speed flow. This magnetic separation-based filtration system will provide for the rapid removal of LDL, offering the patient an opportunity to improve his or her quality and duration of life.

[i] Organisation modiale de la santé – MTN Profils de pays, 2011

Subdivision 2. Translational Research

Presentation Preference Oral presentation

Additional information
Whole exome sequencing identifies novel causal variants in ABCA1 gene associated with familial hypoalphaipoproteinemia

Abstract nr. 3
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Topic Dyslipidemia; Lipids, Lipoproteins and Apolipoproteins
Keywords Genetics, HDL

Background: Plasma high-density lipoprotein cholesterol (HDL-C) is a quantitative, heritable risk factor for coronary heart disease. Several genes are known to cause extremely low HDL-C level in Mendelian manner, including APOA1, ABCA1, and LCAT. However, it is onerous to determine molecular diagnosis through conventional genetic analysis.

Objectives: This study aimed to identify the causal variants in a family with hypoalphaipoproteinemia of unknown pathogenesis through whole exome sequencing.

Methods: A family with autosomal recessive, familial hypoalphaipoproteinemia was identified. Despite the extremely low HDL-C level (HDL-C = 2 mg/dl), the proband did not exhibit any apparent abnormalities in any organs, including coronary arteries. Her parents exhibited almost normo-HDL cholesterolemia, suggesting autosomal recessive pattern of inheritance. Exome capture and sequencing were performed in this family members (the proband and her parents). Variants were filtered for quality of the exome sequencing, rarity, predicted functional significance, and segregation pattern.

Results: Among 305,202 variants found in this family, we found 21,708 nonsense, missense, or splice site variants, of which 5,192 were rare (minor allele frequency ≤0.01 or not reported) in 1000 Genome (Asian population). Filtering assuming recessive pattern of inheritance successfully narrowed down the candidate to the compound heterozygous mutations in ABCA1 gene (c.7173G>T or P2077H and c.6223C>T or S2046N).

Conclusions: Whole exome sequencing identified novel causal variants in ABCA1 gene associated with hypoalphaipoproteinemia. Those results provide new insights into the novel pharmacological target for ABCA1.

Subdivision 3. Clinical Studies

Presentation Preference Oral presentation
Additional information
Predicting the Population at Risk of Atherothrombotic Disease (ATD)

Abstract nr. 4
Author Feeman, Jr., William, The Bowling Green Study, Bowling Green Ohio, United States of America
Topic Primary & Secondary prevention of CVD; Lifestyle Measures and Pharmacological Intervention
Keywords Atherosclerosis, Dyslipidemia, HDL, LDL

The cardinal risk factors for atherothrombotic disease (ATD) are dyslipidemia, cigarette smoking, and hypertension. Dyslipidemia is best defined in terms of LDL-cholesterol and HDL-cholesterol, and the author favors the Cholesterol Retention Fraction (CRF, or [LDL-HDL]/LDL). If only ATD of the heart is examined, then the population at risk of ATD can be defined in terms of CRF and LDL-cholesterol; however, if all forms of ATD are examined, then systolic blood pressure (SBP) must be added to the predictor.

There are 2841 patients in the author's general population database who have had full lipid profiles during the 1979-2003 time frame. If these people are arranged in a table stratifying the CRF values by their LDL-cholesterol values in a nested cohort manner, and if the incidence of ATD in each of these cohorts is examined, then three risk zones are evident. The highest risk zone includes all people whose CRF > 0.70 and LDL-cholesterol > 125 mg/dl (3.2 mmoles/L); 33% of these people sustained an ATD event. The medium risk zone includes all people whose CRF = 0.60-0.69 and LDL-cholesterol = 100-124 mg/dl (2.6-3.2 mmoles/L); 22% of these people sustained an ATD event. The low risk zone consists of all people whose CRF < 0.59 and LDL-cholesterol < 99 mg/dl (2.6 mmoles/L); 13% of these patients sustained an ATD event. If current cigarette smokers are excluded, the average age of ATD onset in the high risk zone is 66 years; in the medium risk zone, 72 years; and in the low risk zone, 75 years. These events are mainly ATD events of the coronary circulation.

When ATD events of the cerebral circulation are included, SBP must be included and the prediction of the population at risk of ATD evolves into a graph with CRF on the ordinate and SBP on the abscissa. The threshold line, above which lie the CRF-SBP plots of the vast majority of ATD patients have CRF-SBP loci of (0.74, 100) and (0.49, 140). The few ATD that occur in people with CRF-SBP plots below the threshold line do so in the aged and in the absence of current cigarette smoking, the prognosis is excellent.

Subdivision 4. Not applicable. Abstract matches with track c

Presentation Preference Oral presentation
Additional information
The Program on the Surgical Control of the Hyperlipidemias (POSCH) and the Lipid Regulatory Hypothesis

Abstract nr. 5
Author Feeman, Jr, William, The Bowling Green Study, Bowling Green Ohio, United States of America
Topic Primary & Secondary prevention of CVD; Lifestyle Measures and Pharmacological Intervention
Keywords Atherosclerosis, Dyslipidemia, HDL, LDL

The Lipid Regulatory Hypothesis of Esko Nikkila, MD, states that atherothrombotic disease ATD) is best stabilized/regressed when LDL-cholesterol is lowered simultaneously with HDL-cholesterol being raised. The POSCH study involved a trial of dietary therapy, with half the patient population being randomized to undergo a partial ileal bypass. Lipid profiles were obtained at baseline and at one year; angiograms were done at baseline and at three years. Changes in LDL-cholesterol and HDL-cholesterol were evaluated for their relationship to plaque outcomes. Since the Lipid Regulatory Hypothesis involves both LDL-cholesterol and HDL-cholesterol, a novel lipid predictor, the Cholesterol Retention Fraction (CRF, or [LDL-HDL]/LDL) was also used for evaluation.

Changes in LDL-cholesterol were stratified against changes in HDL-cholesterol, with the following results. Plaque stabilization/regression occurred if LDL-cholesterol levels fell so long as HDL-cholesterol levels did not fall too far or even if LDL-cholesterol levels provided that HDL-cholesterol levels rose sufficiently. Similarly, plaque progression occurred if LDL-cholesterol levels rose provided that HDL-cholesterol levels did not rise much, or if LDL-cholesterol levels fell provided HDL-cholesterol levels fell even more.

If the CRF rose, plaque progression occurred in all cases. If CRF values fell, plaque stabilization/regression occurred in all cases. Because the CRF predicted plaque outcome in all cases in POSCH, the CRF can serve as an indicator of plaque response to therapy.

Subdivision 4. Not applicable. Abstract matches with track c

Presentation Preference Oral presentation
Additional information
Cardiovascular risk profile and metabolic syndrome in young police officers

Abstract nr. 10
Author Domagala , Teresa, Jagiellonian University School of Medicine, Krakow, Poland
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Co-author(s) - Kotula-Horowitz , Katarzyna
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Topic Primary & Secondary prevention of CVD; Lifestyle Measures and Pharmacological Intervention
Keywords Cardiovascular Disease,Dyslipidemia,Lifestyle,Obesity

**Background:** There is an on-going debate about metabolic syndrome (MS) as a more viable predictor of cardiovascular disease (CVD) risk than individual risk factors. Stress also impacts prevalence of MS and coronary heart disease (CHD).

**Design:** The present study is focused on police officers whose occupation is deemed highly stressful.

**Methods:** 235 subjects mean aged 40.97 years were divided into two groups, with (46.38%) and without MS (53.62%). CV risk profile was assessed by interview, exercise ECG, measurement of endothelial function (flow-mediated dilation; FMD), carotid artery intima-media thickness (IMT) and select laboratory biochemical parameters. Coronary atherosclerosis was evaluated by computed tomography coronary angiography (CTCA). Levels of perceived stress were also assessed.

**Results:** MS was less associated with coronary artery atherosclerosis (OR=2.62, 95%CI 1.24-5.52) than with co-existence of classical CVD risk factors (OR=5.67, 95% CI 1.077-29.88; for 3 risk factors and OR = 9.0; 95% CI 1.24-66.23 for 6 risk factors), when compared to the subjects with 0-2 CVD risk factors. MS subjects had significantly higher IMT and no significantly lower FMD value. Perceived stress increased the chance of MS prevalence (OR 1.07; 95% CI 1.03-1.13; p=0.037), while in the multivariate regression model, stress impacted prevalence of coronary plaque (OR=1.05, 95% CI 1.001-1.010, p=0.04).

**Conclusions:** High prevalence of MS might be associated with exposure to job-specific hazards. Early comprehensive therapeutic intervention on CVD risk factors may potentially reduce overall risk of CV events in police officers.

Subdivision 5. Not applicable. Abstract matches with track d

Presentation Preference Electronic poster presentation
Additional information
Physical activity and lung function in young police officers with metabolic syndrome

Abstract nr. 11
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Topic Primary & Secondary prevention of CVD; Lifestyle Measures and Pharmacological Intervention
Keywords Cardiovascular Disease,Inflammation,Lifestyle,Obesity

Background: Prevalence of metabolic syndrome (MS) continues to spread becoming a major clinical and public health problem, mainly due to its association with cardiovascular disease. Lack of regular physical activity (PA) and impaired lung function are associated with obesity, MS and CVD.

Design: The present cohort study aimed to investigate the level of PA and lung function in young police officers with multiple cardiovascular risk factors.

Methods: 235 studied subjects mean aged 40.97 years were divided into two groups, with (46.38%) and without MS (53.62%). Coronary atherosclerosis was evaluated by computed tomography coronary angiography. Ultrasensitive CRP (hs-CRP) in the serum and tissue necrotic factor α (TNF-α) in the plasma. PA (International PA Questionnaire) and standard spirometry were also assessed.

Results: MS subjects had a higher prevalence of coronary artery atherosclerosis, as compared to the non-MS subjects (p<0.0017). Significantly higher hs-CRP (p=0.0001), and non-significantly higher TNF-α plasma concentration in the MS subjects were encountered. In the MS subjects significantly lower leisure-time PA (p=0.0001) and non-significantly lower PA associated with transportation and total walking (p=0.08) were established. Logistic regression revealed leisure-time PA to reduce the chances for developing MS (OR=0.98; 95% CI 0.96-0.99, p=0.022). There were no differences with regard to moderate, vigorous and total PA. The MS subjects had significantly lower some lung function parameters than the non-MS ones.

Conclusions: Regular, leisure-time PA induced protective effects on coronary artery disease. Lower pulmonary function in the MS group may have resulted from obesity and systemic inflammation.

Subdivision 4. Not applicable. Abstract matches with track c

Presentation Preference Electronic poster presentation
Additional information
Extreme Hypercholesterolemia Exacerbated by Breast Feeding: Infantile Cases of Sitosterolemia with Novel Mutations in ABCG5 and ABCG8 Gene

Abstract nr. 12
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Co-author(s) - Yamagishi, Masakazu
Topic Dyslipidemia; Lipids, Lipoproteins and Apolipoproteins
Keywords Dyslipidemia, Familial Hypercholesterolemia, Genetics, Lipoproteins

Background: Sitosterolemia is an extremely rare inherited disease characterized by increased levels of plant sterols such as sitosterol, the cause of which is ATP-binding cassette (ABC) subfamily G member 5 or member 8 (ABCG5 or ABCG8) gene mutations.

Methods and Results: We tried to determine the molecular diagnosis for 6 Japanese infantile cases with severe hypercholesterolemia and systemic xanthomas without any mutations in LDL receptor (LDLR), proprotein convertase subtilisin/kexin type 9 (PCSK9), and LDL receptor adaptor protein 1 (LDLRAP1) genes, then evaluated their clinical features, especially the responsiveness to variety of therapies. We performed genetic analysis for ABCG5, and ABCG8 genes for those 6 cases, and identified 2 pairs of mutations in ABCG5 or ABCG8 gene in each case, including 3 novel mutations (c.130C>T and c.1813_1817delCTTTT in ABCG5, and c.1256_1257TC>AA in ABCG8) and 3 known mutations (c.1306G>A and c.1336C>T in ABCG5, and c.1285A>G in ABCG8). During their clinical courses, significant reduction of their cholesterol levels could be obtained through their weaning alone (from 540 ± 164 mg/dl to 147 ± 60 mg/dl, p < 0.05). Also, a substantial reduction of their sitosterol levels were observed using ezetimibe without any apparent side effects (from 90 ± 69 μg/ml to 52 ± 38 μg/ml, p < 0.05).

Conclusion: We have identified infantile Japanese sitosterolemic subjects with extreme hypercholesterolemia exacerbated by breast feeding. Their unique manner of response to weaning as well as to ezetimibe could provide us novel insights into the metabolic basis for cholesterol and plant sterols in human.
Subdivision 3. Clinical Studies

Presentation Preference Oral presentation
Additional information
Effect of chronic hepatitis C infection on arterial stiffness is through systemic inflammation but not oxidative stress

Abstract nr. 13
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Topic The Pathogenesis of Atherosclerosis; Immunity, Inflammation, and the Endothelium
Keywords Atherosclerosis, Inflammation

Background
Our previous study has found both non-alcoholic fatty liver disease (NAFLD) and chronic hepatitis C virus (HCV) infection were associated with increased arterial stiffness. However, the possible mechanism has never been studied before.

Methods
We recruited 200 patients including 40 individuals were normal control (NC), 80 subjects were NAFLD, and 80 were HCV infection in this study. Arterial stiffness was assessed by Stiffness Index (SI) and Compliance Index (CI) derived from digital volume pulse by photoplethysmography. High-sensitive CRP (hsCRP) and TBARS (an oxidative stress marker) were measured in all subjects.

Results
HCV group had significantly higher SI (8.6 ± 2.2 m/s vs. 8.4 ± 2.4 m/s vs. 7.1 ± 1.5 m/s; p for trend = 0.001) and lower CI (3.06 ± 1.83 units vs. 3.82 ± 2.15 units vs. 4.93 ± 2.95 units; p for trend < 0.001) than NAFLD and NC. Using multi-variate linear regression analysis, we found that CI was independently correlated with HCV infection (beta = -0.212, p = 0.007). Furthermore, HCV had the highest hs-CRP (0.8 ± 0.8 ug/ml vs. 2.7 ± 2.5 ug/ml vs. 8.3 ± 7.7 ug/ml; p < 0.001) in all three groups. TBARS (17.9 ± 10.6 uM vs. 25.6 ± 11.4 uM vs. 18.7 ± 9.7 uM; p < 0.001) was significantly higher in NAFLD but not HCV group.

Conclusion
The underlying mechanism responsible for increased arterial stiffness in chronic HCV infection is different from NAFLD. It is possible due to systemic inflammation but not through increased oxidative stress.

Subdivision 3. Clinical Studies

Presentation Preference Electronic poster presentation
Additional information
Effects of Adiponectin on Vascular Strain of Carotid Artery Assessed by Speckle Tracking Echocardiography

Abstract nr. 15
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Topic The Pathogenesis of Atherosclerosis; Immunity, Inflammation, and the Endothelium
Keywords Atherosclerosis, Imaging

Background: Adiponectin is a cytokine from adipose tissue associated with atherosclerosis. Vascular strain of carotid artery can be assessed by speckle tracking echocardiography and has been found in association with stroke. However, effects of adiponectin on carotid strain were never been studied before.

Methods: We recruited 89 consecutive elder patients (mean age 72 ± 6 years, 31 men) from a community health survey program. Carotid B-mode image was acquired by using 10 MHz high resolution vascular probe equipped on an echocardiographic system. Cross sectional images of bilateral carotid artery 1 cm below carotid bulb were acquired and images were analysis offline. Circumferential strain (CS) and strain rate (CSR) of carotid artery were obtained by speckle tracking technique. We also measured carotid intima-medial thickness (IMT), and beta-index of carotid artery for local properties. The averages of bilateral measurements were used for analysis.

Results: Serum adiponectin was significantly correlated with carotid CS (r = 0.362, p = 0.001) and CSR (r = 0.313, p = 0.003) but not IMT and Beta-index. After multivariate analysis controlling age, blood pressure, body mass index, serum glucose level, adiponectin was still significantly correlated with CS (Beta = 0.313, p = 0.001) and CSR (Beta = 0.272, p = 0.010). Adiponectin was significantly correlated with procollage type I carboxyterminal propeptide, pro-matrix metalloproteinases I, and tissue inhibitor of metalloproteinases I.

Conclusions: Adiponectin was correlated with CS and CSR of carotid artery independently. This association was probably through the effects on matrix remodeling of carotid artery.

Subdivision 3. Clinical Studies

Presentation Preference Electronic poster presentation
Additional information
Mean Platelet Volume and Cardiovascular Outcomes in Acute Myocardial Infarction- a Prospective Cohort Study

Abstract nr. 16
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Topic The Pathogenesis of Atherosclerosis; Immunity, Inflammation, and the Endothelium
Keywords Pathogenesis, Thrombosis

Background: High levels of mean platelet volume (MPV) may be associated with adverse outcomes in patients with myocardial infarction (MI). We examined the association between MPV and the risk of death and adverse cardiovascular outcomes in patients with MI.

Methods: We studied consecutive patients with MI admitted to a tertiary care hospital during a period of 1 year. MPV was measured at admission and at third month. Patients were followed-up for one-year primary composite outcome of cardiovascular death, stroke, fatal or nonfatal MI and cardiac failure. Patients were classified according to tertile of baseline MPV.

Results: A total of 1206 MI patients, including 934 males (77.4%) and 272 females (22.6%) were studied. The mean age of the study population was 55.93 (SD11.07) years. At one-year follow-up, 292 (28.57%) primary outcome occurred: cardiovascular mortality 78 (7.6%), fatal or nonfatal MI 153 (15.0%), stroke 30 (2.9%), and cardiac failure 128 (12.52%). Highest tertile MPV patients had higher primary outcome as compared with those with MPV in the lowest tertile (adjusted OR=1.70; 95% CI: 1.18 to 2.45; p = 0.01). Total mortality was also more in high MPV group (adjusted OR 2.83; 95% CI: 1.49 to 5.35; p <0.001). There were no significant changes in mean MPV values at admission from those at third month interval [9.15, (SD 0.99) Vs 9.19 (SD 0.94); p=0.2].

Conclusions: Elevated MPV was associated with worse outcome in patients with acute MI. Elevated MPV in these patients may be due to inherently large platelets.

Subdivision 1. Basic Science

Presentation Preference Oral presentation

Additional information
Everolimus-eluting Stents Reduce Monocyte Expression Of Toll-like Receptor 4: A Reason For Systemic Use of Everolimus?

Abstract nr. 17
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Topic The Pathogenesis of Atherosclerosis; Immunity, Inflammation, and the Endothelium
Keywords Atherosclerosis, Inflammation, Intervention

Background: Toll-like receptors (TLR) are well known components of the innate immune system. Among them, TLR4 is related to the inflammatory responses after Percutaneous Coronary Intervention (PCI). Our purpose was to compare the monocytic expression of TLR4 following implantation of drug-eluting (DES) and bare stent (BMS).

Methods: The study was done in Shahid Madani Heart Hospital, Tabriz, Iran. Patients were divided into 2 groups: DES (n=95) and BMS (n=95). Blood collection was done before PCI, 2 hours and 4 hours after termination of PCI. Expression of TLR4 on monocytes was measured using flowcytometry (BD, US). Everolimus eluting stents were implanted for DES group (XIENCE, Abbott Vascular, US). Similar PCI protocols were performed.

Results: Figure A and B shows flowcytometry findings. No significant difference was seen in age, sex, use of medications, white blood cell count or the risk factors. A significant difference was present between DES and BMS before the intervention (P< 0.05). No significant difference was noted at 2 hours after PCI, however, patients in BMS group had higher expression of TLR4. Four hours after PCI, TLR4 expression was significantly lower in DES group than BMS group (30.1 ± 3.3% vs 39.2 ± 3.2%, P< 0.05).

Conclusion: Our findings suggest that eluted drugs can decrease PCI related inflammation by partial reduction of TLR4 expression on the surface of monocytes. Systemic use of these drugs may be a new field of research in order to decrease the likelihood of thrombosis formation.

Subdivision 3. Clinical Studies

Presentation Preference Electronic poster presentation
Additional information
Physician-prompts in an electronic medical record improve secondary prevention best-practices for cardiac risk factor targets and reduce utilization and costs.

Abstract nr. 18
Author Sheikh , Khalid, Health First Medical Group, Merritt Island, United States of America
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Topic Primary & Secondary prevention of CVD; Lifestyle Measures and Pharmacological Intervention
Keywords Cardiovascular Disease,Guidelines,Lipids,Risk Factor

Fewer than 50% of patients with known coronary heart disease (CHD) achieve best-practices for risk factor control. We tested the hypothesis that physician-prompts incorporated into an electronic medical record (EMR) that reinforce established clinical guidelines for best-practices in patients with established CHD would be superior to usual care. Over a 4 year period, 808 patients with known stable CHD, in a single managed care plan were followed. Clinical data was recorded in the GE Centricity EMR. Health care utilization and medical cost data were extracted from the managed care plan database. During 2009, 432 consecutive patients were assigned to usual care (UC). In 2011, the EMR was modified to post an immediate “pop-up” notification during the clinic visit if any parameter fell out of best-practices range. In this prompted care group (PC), 376 consecutive patients were enrolled.

**Results:**

PC UC p  
(n=376) (n=432)
Risk factor targets reached:  
Ideal HgA1c 48% 32% 0.001  
Ideal LDL-C 82% 51% 0.001  
Ideal BMI 12% 6% 0.001  
Ideal Mean BP 68% 39% 0.001  
Tobacco cessation 84% 77% 0.01  
Hospital Utilization & costs:  
ED visits 10.3% 16.4% 0.01  
Hospitalizations 13.1% 17.4% 0.01  
Length of stay (days) 0.39 0.66 0.01  
ED costs (per pt.) $ 22 $ 38 0.01  
Hospital costs (per pt.) $776 $908 0.01

The use of physician-prompts incorporated into an EMR in patients with established CHD is superior to usual care for improving parameters of cardiovascular risk and reducing health care utilization and costs.
Subdivision 3. Clinical Studies

Presentation Preference Electronic poster presentation
Additional information
Chronomics of BP/HR in terms of Double Amplitude, Acrophase, Hyperbaric Index and its relation with cortisol in night shift workers.

Abstract nr. 19
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Co-author(s) - Tiwari, Sandeep
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Topic Primary & Secondary prevention of CVD; Lifestyle Measures and Pharmacological Intervention
Keywords Blood pressure, Cardiovascular Disease, Lifestyle, Risk Factor

Objective: The present study was aimed to investigate the effects of rotating night shift on 24 hours chronomics of BP/HR in terms of Double amplitude, Acrophase and Hyperbaric index and its relation with salivary cortisol.

Material and Methods: 62 healthy nursing professionals, aged 20-40 year, performing day and night shift duties were recruited from the Trauma Center, GM and Associated Hospitals, King George’s Medical University, Lucknow, UP, India. BP and HR were recorded at every 30 min intervals in day time and each hour in night time synchronically with circadian pattern of salivary cortisol during shift duties.

Results: Highly Significant difference was found in double amplitude (2DA) of blood pressure between night and day shift (p<0.001). In night shift, hyperbaric index (HBI) of mean systolic blood pressure was found to be increased at 00-03 am (midnight) while during day shift, peak was found at 06-09 am. Highly significant difference was found in night cortisol levels among night (4.34 ± 3.37) vs day shift (2.70 ± 2.32), (p<0.001) due to recovery during day shift. Alteration in mean morning cortisol level was also found between night (3.73 ± 2.47) vs day shift (5.00 ± 2.73). Alterations in Acrophase of BP/HR were very common among most of the night shift workers and persistent during night and day shift due to incomplete recovery.

Conclusion: Ecphasia was also found in few night workers caused by internal desynchrononization which may be a risk factor of Cardiovascular diseases.

Subdivision 1. Basic Science

Presentation Preference Oral presentation
Additional information
Microalbuminuria is Associated with Endothelial Function and Vascular Arteriosclerosis.

Abstract nr. 20
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Co-author(s) - Teragawa, Hiroki
Co-author(s) - Nomura, Syuichi
Topic Epidemiology of CVD; The Risk Factor Concept
Keywords Atherosclerosis, Chronic Kidney Disease, Endothelium, Renal function

Background: Kidney function and cardiovascular disease are closely connected, and microalbuminuria is a proven marker of cardiovascular risk. The purpose of this study was to evaluate the relation of vascular parameter, renal function and microalbuminuria. Methods: Endothelial function was assessed by flow mediated vasodilatation (FMD) in the brachial artery by a novel semi-automatic vessel chasing system (UNEXEF18G), and nitroglycerin mediated vasodilatation (NMD) was used as a control test for FMD. Urinary albumin excretion rates (UAER), vascular and biochemical parameters were evaluated. Results: A total 119 patients enrolled in this study. The mean age was 67±11 years and 77 patients (65%) were men. Log UAER inversely correlated with FMD (r=-0.21 p=0.024) and NMD (r=-0.33 p=0.0004), but it was not correlated with eGFR (r=-0.04 p=0.650). Univariate analysis revealed that FMD correlated with age, blood sugar, log UAER and NMD correlated with log UAER. Multivariate analysis revealed that FMD independently correlations with log UAER, and NMD was independently correlations with log UAER. In addition, log UAER correlated with age, glucose, HbA1c, FMD, NMD, Carotid intima-media thickness (cIMT), carotid plaques (CP), Cardio Ankle Vascular Index (CAVI). Conclusions: These results suggest that the microalbuminuria might correlate the endothelial function and vascular arteriosclerosis, but not renal function.

Subdivision 3. Clinical Studies

Presentation Preference Electronic poster presentation
Additional information
Frequency dispersion on the vessel wall - the primary event in atherosclerosis.

Abstract nr. 21  
Author Beraia, Guram, Tbilisi, Georgia  
Co-author(s) - Beraia, Merab  
Topic The Pathogenesis of Atherosclerosis; Immunity, Inflammation, and the Endothelium  
Keywords Atherosclerosis, Imaging, Pathogenesis, Thrombosis

Purpose: The aim is to study the blood flow and vessel wall viscoelastic alterations at the boundary layer.

Methods and Materials: Peak velocity, net flow and the flow acceleration has been investigated in aorta by Magnetic Resonance Angiography in 40 healthy volunteers (age 18-51).

Results: At the outer curvature of the isthmus, flow acceleration in the initial diastole is 8.7 times higher than that in systole. Net flow from systole to diastole increases 2.5± 0.5 folds. From the end systole to the initial diastole flow separates into the opposite directed streams and there is a plateau on the net flow graph. Opposite flowing wave oscillation frequencies are 0.8Hz and 1.6Hz. Womersley number from ascending to abdominal aorta decreases from 13.2 to 8. At the outer curvature of isthmus, group wave at the boundary reflection, changes phase at 1800.

Conclusion: During the heart cycle, blood motion at the boundary layer, due to viscoelasticity of this system, forms the surface wave. At the end systole, at the outer curvature of the isthmus, pulse pressure at the reflection is in the resonance with the end systolic pressure drop and amplitude of the wall stress increases. In the initial diastole in the bulk flow, group wave, due to the frequency dispersion facilitates to the structural rearrangement of the cell aggregates, while at the boundary reflection, it shears the vessel wall.

Subdivision 1. Basic Science

Presentation Preference Oral presentation  
Additional information
Abstract nr. 22
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Topic Dyslipidemia; Lipids, Lipoproteins and Apolipoproteins
Keywords Atherosclerosis, Dyslipidemia, Inflammation, Reverse Cholesterol Transport

Objectives: To investigate the effects of cytokines on macrophage foam cell formation and to determine the underlying molecular mechanisms.

Background: Atherosclerosis is an inflammatory disorder of the vasculature regulated by cytokines. The effect of various cytokines on foam cell formation in human macrophages is poorly understood and was hence investigated using both classical cytokines, such as interferon-gamma (IFN-gamma) and transforming growth factor-beta (TGF-beta), and those identified more recently, such as tumour necrosis factor-like protein 1A (TL1A) and interleukin-33 (IL-33).

Methods: Foam cell formation was investigated in human macrophages, bone marrow-derived macrophages from wild type and knockout mice and apolipoprotein E-/- mice. Molecular mechanisms were delineated using a combination of RT-qPCR, western blot analysis, promoter analysis, pharmacological inhibitors, biochemical assays and RNA interference.

Results: IFN-gamma and TL1A stimulated foam cell formation by inducing the uptake of modified lipoproteins and inhibiting the efflux of cholesterol. Extracellular signal-regulated kinase was integral to the action of IFN-gamma. In contrast, TGF-beta and IL-33 attenuated foam cell formation by inhibiting the uptake of modified lipoproteins and storage of cholesterol, and stimulating the intracellular trafficking and efflux of this sterol. The action of these cytokines correlated with changes in the expression of key genes implicated in these processes. A dominant role for Smad2 in the action of TGF-beta was identified.

Conclusions: These studies provide novel insights into the regulation of macrophage cholesterol homeostasis by key cytokines implicated in atherosclerosis.

Funding: British Heart Foundation

Subdivision 1. Basic Science

Presentation Preference Oral presentation

Additional information
Serum lipid goal attainment in chronic kidney disease (CKD) under the Japan Atherosclerosis Society (JAS) 2012 guideline

Abstract nr. 23
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Topic Primary & Secondary prevention of CVD; Lifestyle Measures and Pharmacological Intervention
Keywords Chronic Kidney Disease, Guidelines, Lipoproteins, Risk stratification

Background:
In the Japan Atherosclerosis Society 2012 guideline (JAS2012-GL), chronic kidney disease (CKD) has newly been added to the high risk group for atherosclerotic cardiovascular diseases. We, therefore, have explored the lipid target level achieving rates under the JAS2012-GL in the real-world clinical practice.

Methods:
We retrospectively reviewed medical charts of patients who were hospitalized in the Nephrology Department at Kobe City Medical Center General Hospital from April 1, 2012 to May 31, 2013, and the serum lipid target level achieving rates were explored. Patients without lipid data, or undergoing regular dialysis because of chronic renal failure, were excluded. In this study, the CKD group (CKD-G) does not contain CKD patients with secondary prevention for coronary heart disease (CHD) or diabetes mellitus (DM).

Results:
CKD-G patients were 146 (81.1%) among 180 enrolled patients. According to the JAS2012-GL, 100% of the CKD-G patients were categorized into the high risk group, although only 12.1% of the CKD-G patients were at high-risk, according to the JAS2007-GL. Under the JAS2012-GL, LDL cholesterol (LDL-C) and non-HDL cholesterol (non-HDL-C) target level achieving rates for CKD-G were 71.4% and 68.1%, respectively. According to the JAS2007-GL, these rates were 81.3% and 79.1%, respectively. Under both guidelines, these rates were 71.7% and 72.1% for primary prevention DM (DM-G), and were 66.7% and 66.7% for CHD-G, respectively.

Conclusion:
After the revision of the JAS-GL in 2012, LDL-C and non-HDL-C target level achieving rates for CKD-G were reduced approximately by 10%; however, they remained similar to DM-G and higher than CHD-G.
Subdivision 3. Clinical Studies

Presentation Preference Oral presentation
Additional information
Rationale. Dyslipidemia that characterises Metabolic Syndrome (MetS) responds to weight loss. Superior comprehensive description of the dyslipidemia through lipidomic analysis and the effects of weight loss may identify further therapeutic targets.

Objectives. We have carried out 2 studies: firstly, comparing lipidomes in 95 subjects with MetS and 40 matched healthy subjects (HS) by liquid-chromatography-tandem mass spectrometry; secondly, in MetS subjects measuring effects of dietary weight loss n=19 (WL) or weight loss plus exercise n=17 (WLEX) during 12 weeks’ supervised intervention, 17 serving as controls (C).

Results. 334 lipid species were measured representing 23 classes and subclasses. MetS versus HS showed significantly higher (+43% to +58%) di- and tri-acylglycerols (DAG, TAG,) and cholesteryl esters (CE) (P<0.001 for all), but lower (-9% to -24%) di-and trihexosylceramides, lyso-, alkyl and alkenylphospholipid subclasses (P<0.001 for all) including plasmalogens with potential anti-oxidant property. Logistic regression odds ratios for MetS versus HS lipids were <0.5 for hexosylceramides, plasmalogens, lysophospholipids, (lower in MetS). Following WL and WLEX (similar falls in weight, glucose) lipid classes in MetS resembled HS values especially after WLEX (P<0.05 for DAG, TAG, CE, several ceramides and phospholipids).

Conclusions. Plasma lipidomic analyses of subjects with metabolic syndrome and healthy subjects showed higher values for DAG, TAG, CE, but significantly lower values for hexosylceramides and phospholipid species (as in diabetes). Improvement in these lipids occurred with dietary weight loss and even more with similar weight loss through an additional exercise program. Lipidomic analysis may improve therapeutic targeting.

Funding: National Health & Medical Research Council, Diabetes Australia.

Subdivision 3. Clinical Studies

Presentation Preference Oral presentation

Additional information
Epicardial fat volume is related to atherosclerotic calcification in multiple vessel beds

Abstract nr. 27
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Topic Epidemiology of CVD; The Risk Factor Concept
Keywords Atherosclerosis, Epidemiology, Imaging

Objective
Large amounts of epicardial fat have been associated with coronary artery atherosclerosis. It is unclear whether the amount of epicardial fat is also related to atherosclerosis in other vessels, and thereby represents a marker of systemic vascular risk. We explored relationships of epicardial fat volume with atherosclerosis in multiple vessel beds.

Methods
From the population-based Rotterdam Study, 2,298 participants underwent computed tomography examinations to quantify epicardial fat volume, and atherosclerotic calcification volume in the coronary arteries, aortic arch, extracranial and intracranial internal carotid arteries. Using linear regression modeling we investigated relationships of epicardial fat volume with atherosclerotic calcification volume in each vessel bed, adjusting for conventional cardiovascular risk factors. To test whether associations of epicardial fat with calcification per vessel bed were independent of calcification elsewhere, we created a model in which all vessel beds were entered together.

Results
We found that larger epicardial fat volume was associated with larger calcification volumes in all vessel beds. After adjustment for cardiovascular risk factors, larger epicardial fat volume was related to coronary and extracranial carotid artery calcification volume [Difference in standardized calcification volume per SD increase in epicardial fat volume: 0.10(95%C.I.:0.05;0.15), and 0.13(95%C.I.0.08;0.18)]. These associations remained present after entering all vessel beds in one model.

Conclusion
Larger volumes of epicardial fat are associated with larger amounts of coronary and extracranial carotid artery atherosclerosis, independent of cardiovascular risk factors. Epicardial fat may thus not only influence the local formation of atherosclerosis, but may also exert a more systemic effect on atherosclerosis development.
Subdivision 4. Not applicable. Abstract matches with track c

Presentation Preference Oral presentation
Additional information
Gelsolin (GSN) induces cardiomyocyte hypertrophy and BNP expression via p38 signaling and GATA-4 transcriptional factor activation.

Abstract nr. 28
Author Hu, Wei-Syun, Taipei, Taiwan
Topic The Pathogenesis of Atherosclerosis; Immunity, Inflammation, and the Endothelium
Keywords Atherosclerosis, Metabolism

Cardiomyocyte hypertrophy is an adaptive response of the heart to various types of stress. Gelsolin (GSN) is a member of the actin-binding proteins (ABPs), which regulate dynamic actin filament organization by severing and capping. Moreover, GSN also regulates cell morphology, differentiation, movement, and apoptosis. In this study, we used H9c2 and H9c2-GSN stable clones, in an attempt to understand the mechanisms of GSN overexpression in cardiomyocytes. This data showed that the overexpression of GSN in H9c2 induced cardiac hypertrophy and increased the pathological hypertrophy markers atrial natriuretic peptide (ANP) brain natriuretic peptide (BNP). Furthermore, we found that E-cadherin expression decreased with the overexpression of GSN in H9c2, but ß-catenin expression increased. These data presume that the cytoskeleton is loose. Further, previous studies show that the mitogen-activated protein kinase (MAPK) pathway can induce cardiac hypertrophy. Our data showed that p-p38 expression increased with the overexpression of GSN in H9c2, and the transcription factor p-GATA4 expression also increased, suggesting that the overexpression of GSN in H9c2-induced cardiac hypertrophy seemed to be regulated by the p38/GATA4 pathway. Moreover, we used both the p38 inhibitor (SB203580) and GSN siRNA to confirm our conjecture. We found that both of these factors significantly suppressed gelsolin-induced cardiac hypertrophy which through p38/GATA4 signaling pathway. Therefore, we predict that the gene silencing of GSN and/or the downstream blocking of GSN along the p38 pathway could be applied to ameliorate pathological cardiac hypertrophy in the future.

Subdivision 1. Basic Science

Presentation Preference Oral presentation

Additional information
Gelsolin (GSN) enhance cardiomyocyte apoptosis during hypoxia via reducing survival protein p-Akt and increasing HIF-1α.

Abstract nr. 29
Author Hu , Wei-Syun, Taipei, Taiwan
Topic The Pathogenesis of Atherosclerosis; Immunity, Inflammation, and the Endothelium
Keywords Atherosclerosis,Cardiovascular Disease,Inflammation

Cytoskeletal filaments play an important roles in cells such as cell shape, cell motility, intracellular transport and cellular division. Actin binding proteins (ABPs) have a lot of functions one of that is regulate the structure formation of actin to filament nucleation, elongation, severing, capping, crosslinking and actin monomer sequestration. Gelsolin (GSN) is one of actin binding proteins and it regulate actin filament formation and disassembly such as severing, capping, uncapping, nucleation of actin filament, and it regulate by pH, Ca2+, phosphoinositides (PIP2). Moreover, GSN also regulates cell morphology, differentiation, movement, and apoptosis. In our study, we used H9c2 and H9c2-GSN stable clones, in an attempt to understand the mechanisms of GSN overexpression in cardiomyocytes. This data showed that overexpression of GSN in H9c2 reduces the expression of survival markers p-Akt and Bcl-2. In hypoxia condition, overexpression GSN further reduce p-Akt expression and increase GSN, cleavage-GSN and HIF-1α expression more obviously. Moreover, overexpression GSN was more serious apoptosis compare with H9c2 cell during hypoxia.

Subdivision 1. Basic Science

Presentation Preference Oral presentation
Additional information
Genistein suppresses the isoproterenol-treated H9c2 cardiomyoblast cell apoptosis associated with P-38, Erk1/2, JNK and NFκB signaling protein activation

Abstract nr. 30
Author Hu, Wei-Syun, Taipei, Taiwan
Topic The Pathogenesis of Atherosclerosis; Immunity, Inflammation, and the Endothelium
Keywords Atrial fibrillation, Chronic Kidney Disease, Inflammation

Heart disease (HD) is greatly associated with gender and menopausal status because of estrogens. In addition, clinical evidence shows that increased level of serum norepinephrine is found in patients with HD. Therefore this study aimed to investigate the cardio-protective effect of genistein, a selective estrogen receptor modulator (SERM) from soy bean extract, in H9c2 cardiomyoblast cells treated with isoproterenol (ISO, a norepinephrine analog). In this in vitro model, image data and results from western blotting shown that ISO treatment was capable of inducing cellular apoptosis, especially mitochondrial dependent pathway. Treatment of genistein could suppress the expression of mitochondrial pro-apoptotic proteins including Bad, caspase-8, caspase-9 and caspase-3 in H9c2 treated with ISO. By contrast, several survival proteins were expressed in H9c2 treated with genistein, such as phosphor (p)-Akt, p-Bad and p-Erk1/2.

Furthermore, we confirmed that the protective role of genistein was partially mediated through the expression of Erk1/2, Akt and NFκB proteins by adding several pathway inhibitors. These in vitro data suggest that genistein may be a safe and natural SERM alternative to hormone therapy in cardio-protection.

Subdivision 1. Basic Science

Presentation Preference Oral presentation
Additional information
Antioxidant enzymes in hyperlipidemic patients treated with lovastatine

Abstract nr. 37
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Topic Primary & Secondary prevention of CVD; Lifestyle Measures and Pharmacological Intervention
Keywords Dyslipidemia, Hypolipidemic Drugs, Therapy, Triglycerides

Lovastatine belongs to the class of hypolipidemic drugs which are prescribed for lowering cholesterol levels in patients with hyperlipidemia or at risk of cardiovascular disease. The aim of our study was to determine the activity of antioxidant enzymes in hyperlipidemic patients treated with lovastatine.

Material and methods: Material of our study was the whole blood from 30 male subjects on lovastatine therapy and from 110 male healthy subjects. The enzyme activities were determined in erythrocyte lysate employing standard spectrophotometric methods. Lipid parameters were measured in serum by commercial kits. Statistical analyzes was done using WinStat statistical program.

Results: Gluthatione peroxidise activity was statistically significantly lower in the examined group in comparison to the control group (p<0.001). There was a significantly positive correlation between low density lipoprotein cholesterol level and glutathione peroxidise and superoxide dismutase activity (p<0.05 and p<0.01 respectively). Triglycerides negatively correlate with the superoxide activity (p<0.01). The activity of catalase and superoxide dismutase was statistically significantly increased in smokers in comparison with non smokers patients (p<0.05 and p<0.01 respectively).

Conclusion: We may conclude that determining the activity of gluthatione peroxidise and superoxide dismutase in patient on hyperlipidemic therapy with statins could serve as a useful parameter in the evaluation of the effectiveness of the therapy.

Subdivision 5. Not applicable. Abstract matches with track d

Presentation Preference Electronic poster presentation
Additional information
ASSOCIATIONS BETWEEN ANTIOXIDANT FOOD AND BEVERAGE INTAKES AND CORONARY ARTERY DISEASE (CAD) IN ELDERLY AND NON-ELDERLY JAPANESE PATIENTS

Abstract nr. 38
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Topic Primary & Secondary prevention of CVD; Lifestyle Measures and Pharmacological Intervention
Keywords Cardiovascular Disease, Elderly, Lifestyle

Green tea and soybeans are popular in Japanese, but such intakes may differ between elderly and non-elderly populations. We investigated antioxidant foods (soybeans, vegetables, fruits)(<3, 3-4, >4 times/week) and beverages (green tea, black tea, coffee, wine)(<1, 1-3, >3 cups/day) intakes by questionnaires in 725 Japanese patients undergoing coronary angiography, of whom 373 were elderly (>65 years old). CAD was found in 517 patients, of whom 225 had myocardial infarction (MI). Percentages of patients taking soybeans >4 times/week, fruits >4 times/week, and green tea >3 cups/day were higher in elderly than in non-elderly (39%, 53% and 38% vs. 28%, 38% and 31%, P<0.025). Among non-elderly patients, percentages of patients taking soybeans and fruits <3 times/week were higher in patients with CAD than without CAD (37% and 48% vs. 28% and 34%, P<0.05), especially high in CAD patients with MI (42% and 56%). Among elderly patients, percentage of green tea nondrinkers (<1 cup/day) tended to be higher in patients with CAD (18%) than without CAD (13%), but highest in MI patients (25%, P<0.01). In multivariate analysis, among non-elderly, soybeans intake was a factor for CAD and MI. Odds ratios were 1.8 (95%CI=1.1-2.8) and 1.9 (95%CI=1.1-3.2) for soybeans <3 times/week. Among elderly, green tea intake was a factor for MI. Odds ratio was 2.3 (95%CI=1.3-4.0) for green tea <1 cup/day.

CONCLUSIONS: Elderly patients had more soybeans and green tea than non-elderly. In elderly, green tea intake was a factor for MI, whereas, in non-elderly, soybeans intake was a factor for CAD and MI.

Subdivision 3. Clinical Studies

Presentation Preference Electronic poster presentation
Additional information
Hypolipidemic effect of Emblica officinalis seeds in diabetes-induced experimental rats

Abstract nr. 39
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Topic Dyslipidemia; Lipids, Lipoproteins and Apolipoproteins
Keywords Animal model, Diabetes, Dyslipidemia, Hypolipidemic Drugs

The antidiabetic and hypolipidemic potential of E. officinalis seeds have been reported for the first time by our research group. The present study was aimed to investigate the hypolipidemic effect of Emblica officinalis aqueous seed extract in long-term treatment of severely diabetic rats for 28 days. Rats were treated with the most effective dose of 300 mg kg\(^{-1}\) body weight of the extract identified in case of sub and mild-diabetic rats. Diabetes-induced enhanced levels of triglycerides (TG), total cholesterol (TC), low density lipoprotein-cholesterol (LDL-C) and very low density lipoprotein-cholesterol (VLDL-C) were brought down significantly to 43.6, 40.3, 53.0 and 43.6% from E. officinalis seed extract. Glipizide was used as a reference drug for comparison. The extract has gained much attention due to potential improvement of 35.1% in high density lipoprotein-cholesterol (HDL-C) level from the extract in severely diabetic treated group. Since, lipid abnormality along with premature atherosclerosis is the major cause of cardiovascular diseases in diabetic patients, therefore the ideal treatment for diabetes, in additional to glycemic control, should have a favourable effect on lipid profile. The study has clinical implications since E. officinalis seed extract may reverse dyslipidemia associated with diabetes and prevent cardiovascular complications which are extensively prevalent in diabetic patients.

Subdivision 1. Basic Science

Presentation Preference Oral presentation
Additional information
Obesity Paradox Still Exists After Percutaneous Coronary Intervention Independent of Metabolic Status

Abstract nr. 40
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Co-author(s) - Shin, Eak Kyun

Topic Epidemiology of CVD; The Risk Factor Concept
Keywords Cardiovascular Disease, Intervention, Obesity

**Background:** We aimed to investigate the impact of obesity and its relation with metabolic parameters on clinical outcomes in patients undergoing PCI.

**Methods:** A total of 714 consecutive patients who underwent PCI were divided into three groups according to BMI: normal weight (BMI < 23.0 kg/m², n=211), overweight (23.0 ≤ BMI < 27.5 kg/m², n=375), and obese groups (BMI ≥ 27.5 kg/m², n=128). Lipid profile, fasting glucose, insulin, HbA1c, and insulin sensitivity were measured. Primary endpoint was 1-year major adverse cardiovascular events (MACEs), defined as the composite of all-cause death, non-fatal myocardial infarction (MI), stroke, revascularization, or admission for heart failure.

**Results:** The overweight or obese group had a higher incidence of hypertension, diabetes, and hyperlipidemia than the normal weight group. Left ventricular systolic dysfunction was more frequent in the normal group compared to the overweight or obese group (14.1% vs. 7.3% vs. 8.6%, p=0.026, respectively). Fasting glucose, HbA1c, LDL-cholesterol did not differ significantly between groups. However, obese group had higher levels of fasting insulin than normal weight group (12.5±13.6μU/mL vs. 8.6±12.4μU/mL, p=0.007). In addition, there was a significant difference of QUICKI between normal, overweight and obese groups (0.345±0.048 vs. 0.336±0.040 vs. 0.321±0.038, p<0.05 for each groups, respectively). The cumulative incidence of MACEs at 1 year was 15.6% for the normal group, 5.9% for the overweight group, and 3.9% for the obese group (p<0.001).

**Conclusions:** Overweight or obese patients had better clinical outcomes compared with normal weight patients after PCI although overweight or obese patients have more metabolic abnormality.

Presentation Preference Electronic poster presentation
Additional information
The Prognostic Value of Mean Platelet Volume for Clinical Outcomes in Patients with Coronary Artery Disease Undergoing Percutaneous Coronary Intervention

Abstract nr. 41
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Co-author(s) - Shin, Eak Kyun

Topic The Pathogenesis of Atherosclerosis; Immunity, Inflammation, and the Endothelium
Keywords Atherosclerosis, Cardiovascular Disease, Thrombosis

**Background:** Platelet size, measured as mean platelet volume (MPV) has been reported to be correlated with platelet reactivity. Thus, we aimed to investigate the impact of MPV on 1-year clinical outcomes in patients undergoing PCI.

**Methods:** A total of 738 consecutive patients who underwent PCI were divided into two groups: the high MPV group (MPV ≥9.0fL, n=340, 46%) and the low MPV group (MPV <9fL, n=398, 54%). MACEs at 1year, defined as the composite of all-cause death, non-fatal myocardial infarction (MI), stroke, revascularization, or admission for heart failure, were compared.

**Results:** The mean level of MPV was 9.0±1.1fL. The prevalence of acute MI was significantly higher in the high MPV group than in the low MPV group (69.1% vs. 30.4%, p<0.001). The high MPV group had higher level of CK-MB than the low MPV group (median [interquartile range], 31.7 ng/mL [3.0-143.7] vs. 2.5ng/mL [1.3-11.2], p<0.001). In addition, systolic dysfunction was more frequent in the high MPV group compared with the low MPV group (13.3% vs. 5.6%, p<0.001). The cumulative incidence of MACEs at 1 year was significantly higher in the high MPV group than in the low MPV group (11.5% vs. 5.8%, p=0.004, respectively). By multivariate analysis adjusting for age, sex, peak level of CK-MB, or the presence of diabetes, acute MI or systolic dysfunction, the high MPV level was independently associated with 1-year MACEs (adjusted HR 2.52, 95% CI 1.34-4.76, p=0.004).

**Conclusion:** The level of MPV can be a powerful, independent predictor of 1-year MACEs in patients undergoing PCI.

Subdivision 3. Clinical Studies

Presentation Preference Electronic poster presentation
Additional information
ROLE OF SERUM LIPIDS AND CARDIOVASCULAR DISEASE IN PATIENTS WITH HYPERHOMOCYSTEINEMIA.

Abstract nr. 42
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Topic Epidemiology of CVD; The Risk Factor Concept
Keywords Cardiovascular Disease,Lipids,Lp(a)

Introduction: Hyperhomocysteinemia is associated with increased risk of atherosclerotic disease especially stroke. Its relation with serum lipids has not been completely clarified. Our aim is to study serum lipids in patients with hyperhomocysteinemia.

Methods: Patients with serum homocysteine higher than 15 mg/dL were included. Total cholesterol, HDL, LDL, VLDL, triglycerides (TG) and Lp(a) were measured. BMI, smoking, obesity, hypertension, type-2 diabetes, coronary artery disease (CAD), cerebrovascular disease (CVD), chronic kidney disease (CKD), and peripheral artery disease (PAD) were reported. Descriptive statistics as well as correlation test and ANOVA one-way were performed.

Results: A total of 38 (22 women/16 men) patients were included. Mean age 65 (range 41-87) years-old. Obesity was found in 50%, smoking 28.9%, hypertension 55.3%, type-2 diabetes 62.6%, CAD 36.8%, CVD 28.9%, and PAD 36.8%. Mean values of serum lipids were as follows: total cholesterol 258.76±22.85; TG 162.26±72.38; LDL 191.78±22.94; HDL 37.60±9.19; VLDL 11.15±7.78 and Lp(a): 7.55±10.02. All results are shown in mg/dl with standard deviation. Homocysteine: 20.94±3.25 μmol/l. Correlation test results: men smoked more than women (p=0.001), had more prevalence or PAD (p=0.035), and hypertensive patients had higher levels of VLDL (p=0.024). An ANOVA one-way test showed association between high level of Lp(a) and hyperhomocysteinemia (p=0.001).

Conclusions:
1.- In this hyperhomocysteinemic patients, the most common associated clinical conditions were type-2 diabetes, hypertension, obesity, CAD and PAD.
2.- Hypercholesterolemia and hypertriglyceridemia were predominant in these patients.
3.- Lp(a) was significantly increased in this group although few patients had a Lp(a) level higher than 30 mg/dL.

Presentation Preference Electronic poster presentation
Additional information
HIV protein Nef causes dyslipidemia and atherosclerosis

HIV resides in a limited number of very specific cell types, but complications of HIV disease include metabolic abnormalities in tissues that are not infected by the virus. We hypothesized that viral proteins secreted from infected cells impair metabolism in uninfected cells and systemically. We investigated the effects of Nef, a secreted HIV protein responsible for the impairment of cholesterol efflux, on the development of atherosclerosis in two animal models. In apoE−/− mice, injections of recombinant Nef increased the size of atherosclerotic lesions and caused vessel remodelling. Nef caused elevation of total cholesterol and triglyceride levels, while reducing high-density lipoprotein cholesterol levels in the plasma. These changes were accompanied by a reduction of Abca1 abundance in the liver but not in the vessels. In C57BL/6 mice on high fat/high cholesterol diet Nef caused a significant number of lipid-laden macrophages presented in adventitia of the vessels. Nef caused elevations of plasma triglyceride levels and obesity. We further investigated the lipoprotein profile of HIV patients infected with Nef-deficient virus (ΔNefHIV). The prevalence of hypoalphalipoproteinemia in these patients was reduced compared to patients infected with full virus approaching that of uninfected subjects. The size distribution of high-density lipoprotein particles was shifted toward smaller particles in HIV patients compared to uninfected subjects; this was absent in patients infected with ΔNefHIV. Our findings suggest that Nef causes dyslipidemia and accumulation of cholesterol in macrophages within the vessel wall, supporting the role of Nef in pathogenesis of atherosclerosis in HIV-infected patients.
Atherosclerosis in multiple vessel beds is related to a higher mortality risk: the Rotterdam Study

Abstract nr. 45
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Topic Epidemiology of CVD; The Risk Factor Concept
Keywords Atherosclerosis,Epidemiology,Imaging,Risk Factor

Objective
Atherosclerosis is a major contributor to global morbidity and mortality. We investigated whether atherosclerosis in different vessel beds contributes differentially to mortality, specifically focusing on cardiovascular mortality.

Methods
Between 2003 and 2006, a random sample of 2,413 participants from the population-based Rotterdam Study underwent computed tomography to quantify atherosclerotic calcification in the coronary arteries, the aortic arch, and the extracranial and intracranial internal carotid arteries. Follow-up for mortality was complete until January 1, 2012. We investigated relationships of calcification volume in each vessel bed with mortality using Cox regression models, adjusting for age, sex, and conventional cardiovascular risk factors. We additionally constructed a model in which we entered all vessel beds to investigate whether associations found per vessel bed were independent of calcification elsewhere.

Results
During 15,775 person-years of follow-up, 283 participants died, of whom 89 due to a cardiovascular cause. Larger calcification volumes in all vessels were related to a higher risk of all-cause mortality, cardiovascular mortality, and non-cardiovascular mortality, independent of cardiovascular risk factors. The strongest association was found for aortic arch calcification with cardiovascular mortality [age- and sex-adjusted hazard ratio per SD increase in calcification volume: 2.45(95%CI:1.69;3.57)]. The association between aortic arch calcification and cardiovascular mortality was independent of the amount of calcification elsewhere. We found no sex-specific differences.

Conclusion
Atherosclerotic load in major vessel beds is associated with an increased risk of death, independent of cardiovascular risk factors. In particular, aortic arch calcification yields unique information in addition to atherosclerosis elsewhere with regard to mortality.
Subdivision 4. Not applicable. Abstract matches with track c

Presentation Preference Oral presentation
Additional information
**Pigment Epithelium-Derived Factor is Associated with Necrotic Core Progression During Statin Therapy**

Abstract nr. 46  
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Topic Primary & Secondary prevention of CVD; Lifestyle Measures and Pharmacological Intervention  
Keywords Atherosclerosis, Prevention, Risk Factor, Vulnerable Plaque

**Background:** Pigment epithelium-derived factor (PEDF) is a potent inhibitor of angiogenesis and an important target molecule for preventing the progression of atherosclerosis. However, the relationship between PEDF and coronary atherosclerosis has not been fully examined. The aim of the present study is to evaluate the effects of statins on serum PEDF levels and the association between PEDF and coronary atherosclerosis.

**Methods:** Coronary atherosclerosis in non-culprit lesions of patients undergoing percutaneous coronary intervention (PCI) was evaluated using virtual histology intravascular ultrasound in 99 patients during PCI and after 8 months of statin therapy.

**Results:** Serum PEDF levels at baseline and at the 8-month follow-up did not differ. A significant decrease in the fibro-fatty component (-0.24 mm³/mm, p = 0.0003) and increases in the necrotic core (0.13 mm³/mm, p = 0.02) and dense calcium components (0.11 mm³/mm, p < 0.0001) were observed during the 8-month statin therapy. On univariate regression analyses, serum PEDF levels (r = 0.291, p = 0.004) and unstable angina pectoris (r = 0.203, p = 0.04) showed significant positive correlations with the percentage change in necrotic core volume. Multivariate regression analysis showed that serum PEDF level was a significant independent predictor associated with necrotic core progression during statin therapy (β = 0.218, p = 0.04).

**Conclusions:** Statin therapy had no effects on serum PEDF levels. Serum PEDF was a useful biomarker for predicting necrotic core progression during statin therapy, and its levels could be elevated as a counter-regulatory response mechanism to protect against necrotic core progression.
Subdivision 3. Clinical Studies

Presentation Preference Oral presentation
Additional information
Different Regulation of Complement Activation by Native and Acetylated LDL Influences LDL and acetylated LDL Binding to Complement Receptor 1

Abstract nr. 47
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Topic Dyslipidemia; Lipids, Lipoproteins and Apolipoproteins
Keywords Immunity, Inflammation, LDL, Lipoproteins

Introduction: Lipoproteins can induce complement activation potentially resulting in opsonization and binding of these complexes to complement receptors. We investigated the binding of native LDL and acetylated LDL (acLDL) to the complement receptor 1 (CR1).

Methods: Binding of complement factors C3b, IgM, C1q, mannose-binding lectin (MBL) and properdin to LDL and acLDL were investigated by ELISA. Subsequent binding of opsonized LDL and acLDL to CR1 on CR1-transfected Chinese Hamster Ovarian cells (CHO-CR1) was tested by flow cytometry.

Results: Upon incubation with normal human serum both native LDL and acLDL induced complement activation with subsequent C3b opsonization. Opsonized LDL and acLDL bound to CR1. Binding to CHO-CR1 was reduced by EDTA, whereas MgEGTA only reduced the binding of opsonized LDL, but not of acLDL, suggesting involvement of the alternative pathway in the binding of acLDL to CR1. In vitro incubations showed that LDL bound C1q, whereas acLDL bound to C1q, IgM and properdin, an initiator of the alternative pathway. MBL did neither bind to LDL nor to acLDL. The relevance of these findings was demonstrated by ex vivo upregulation of CR1 on human leukocytes by LPS with a concomitant increased binding of apolipoprotein B containing lipoproteins to these leukocytes.

Conclusion: CR1 is able to bind C3b-opsonized native LDL and acLDL. C3b opsonization of LDL...
is mediated via the classical pathway, whereas opsonization of acLDL is mediated via both the classical and alternative pathways. Binding of lipoproteins to CR1 may be of clinical relevance due to the ubiquitous cellular distribution of CR1.

Subdivision 1. Basic Science

Presentation Preference Oral presentation
Additional information
LincRNA-p21 Regulates Neointima Formation, Vascular Smooth Muscle Cell Proliferation, Apoptosis and Atherosclerosis by Enhancing p53 Activity

Abstract nr. 48
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Topic The Pathogenesis of Atherosclerosis; Immunity, Inflammation, and the Endothelium
Keywords Animal model, Atherosclerosis, Cardiovascular Disease, Genetics

Background -- Long non-coding RNAs (lncRNAs) recently have been implicated in many biological processes and diseases. Atherosclerosis is a major risk factor for cardiovascular disease. However, the functional role of lncRNAs in atherosclerosis is largely unknown.

Methods and Results -- We identified lincRNA-p21 as a key regulator of cell proliferation and apoptosis during atherosclerosis. The expression of lincRNA-p21 was dramatically down-regulated in atherosclerotic plaques of ApoE/− mice, an animal model for atherosclerosis. Through loss- and gain-of function approaches, we showed that lincRNA-p21 represses cell proliferation and induces apoptosis in vascular smooth muscle cells (VSMCs) and mouse mononuclear macrophage cells in vitro. Moreover, we found that inhibition of lincRNA-p21 results in neointimal hyperplasia in vivo in a carotid artery injury model. Genome-wide analysis revealed that lincRNA-p21 inhibition dysregulated many p53 targets. Furthermore, lincRNA-p21, a transcriptional target of p53, feeds back to enhance p53 transcriptional activity, at least in part, via binding to mouse double minute 2 (MDM2), an E3 ubiquitin-protein ligase. The association of lincRNA-p21 and MDM2 releases MDM2 repression of p53, enabling p53 to interact with p300 and bind to the promoters/enhancers of its target genes. Finally, we show that lincRNA-p21 expression is decreased in coronary artery disease patients.

Conclusions -- Our studies identify lincRNA-p21 as a novel regulator of cell proliferation and apoptosis and suggest that this IncRNA could serve as a therapeutic target to treat atherosclerosis and related cardiovascular disorders.

Subdivision 2. Translational Research

Presentation Preference Oral presentation

Additional information
Rosuvastatin induced carotid plaque regression in patients with inflammatory joint diseases: The RORA-AS study

Abstract nr. 49
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Co-author(s) - Semb, Anne Grete
Topic Primary & Secondary prevention of CVD; Lifestyle Measures and Pharmacological Intervention
Keywords Atherosclerosis, Inflammation, Lipids, Prevention

Objective: Patients with rheumatoid arthritis (RA) and carotid artery plaques (CP) have increased risk of acute coronary syndromes. Statin treatment with low density lipoprotein cholesterol (LDL-c) goal ≤ 1.8 mmol/L is recommended for patients with CP in the general population. In the RO suvastatin in Rheumatoid Arthritis, Ankylosing Spondylitis and other inflammatory joint diseases (RORA-AS) study, the aim was to evaluate the effect of 18 months intensive lipid lowering with rosuvastatin on change in CP height.

Methods: Eighty-six patients (60.5% female) with CP and IJD [RA (n=55), ankylosing spondylitis (n=21) and psoriatic arthritis (n=10)] were treated with rosuvastatin to obtain LDL-c goal. CP height was evaluated by B-mode ultrasound.

Results: Age was 60.8±8.5 years (mean±SD). Compliance of rosuvastatin use was median (IQR) 97.9% (96.0, 99.4). At baseline, median number and height of CP was 1.0 (range 1-6) and 1.80 mm (IQR 1.60, 2.10), respectively. Change in CP height after 18 months rosuvastatin treatment was -0.19±0.35 mm (p<0.001). Baseline and change in LDL-c was 4.0±0.9 mmol/L and -2.3±0.8 mmol/L (p<0.001). Mean LDL-c level during 18 months rosuvastatin treatment was 1.7±0.4 mmol/L (area under the curve). The degree of CP height reduction was independent of the LDL-c level exposure during the study period (p=0.36) (adjusted for age/gender/blood pressure). Attainment of LDL-c ≤ 1.8 mmol/L or the level of improvement in LDL-c did not influence the degree of CP height reduction (p=0.44 and p=0.46).

Conclusion: Intensive lipid lowering with rosuvastatin induced regression of CP height and reduced LDL-c significantly in patients with IJD.
Subdivision 3. Clinical Studies

Presentation Preference Oral presentation
Additional information
Geraniol a major component of essential oil ameliorates endothelial dysfunction induced by high-fat diet fed rats.

Abstract nr. 53
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Topic Primary & Secondary prevention of CVD; Lifestyle Measures and Pharmacological Intervention
Keywords Animal model, Cardiovascular Disease, Endothelium, Prevention

Purpose of the study: Geraniol a major component of geranium oil and also found in essential oils of various spices and aromatic herbs. Geraniola monoterpenoid is known for potent anti-inflammatory, antihypertensive, hypoglycemic and antioxidant activity. Hence, the present study was designed to explore the vasorelaxant and cardioprotective property of geraniol in high fat diet (HFD) induced metabolic complications in rats.

Methods: Metabolic complications were induced by feeding HFD containing 20 % fat (Tallow) for 12 weeks. After confirmation of hypercholesterolemia (total cholesterol >150 mg/dl) at the end of 6 weeks, different doses of geraniol (100, 200, 400 mg/kg p.o) were administered for next 6 weeks. At the end of study plasma glucose, insulin, OGTT, lipid profile, antioxidants levels, lipid peroxidation, serum NO level, NOS activity in aorta, ECG changes, mean arterial pressure and endothelial dependent and independent vascular function in aorta were assessed.

Main finding: Administration of geraniol in HFD fed rats exhibited a significant decline in glucose, insulin resistance, triglyceride, total cholesterol, LDL levels and increase in HDL levels. Decreased serum NO level and NOS activity, increased oxidative stress along with impaired glucose tolerance associated with HFD were restored significantly by geraniol in dose dependent manner. Also increased MAP and ECG changes were normalized and reduced acetylcholine-induced, endothelium-dependent relaxation was improved significantly in geraniol treated rats (89.26 ± 0.17%).

Conclusions: Geraniol ameliorates endothelial dysfunction and metabolic complications in HFD fed rats by repressing insulin resistance, oxidative stress, lipid lowering effect with normalizing MAP, ECG changes & NO bioavailability.

Subdivision 5. Not applicable. Abstract matches with track d

Presentation Preference Oral presentation
Additional information
Role of Arterial AT1 Receptor on the Regulation of GRK4 in Hypertension

Abstract nr. 54
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Topic Primary & Secondary prevention of CVD; Lifestyle Measures and Pharmacological Intervention
Keywords Blood pressure, Cardiovascular Disease, Hypertension

G protein-coupled receptor kinase 4 (GRK4) gene variants, via impairment of renal dopamine receptor and enhancement of renin-angiotensin system functions, cause sodium retention and increase blood pressure. Whether or not GRK4 and the angiotensin type 1 receptor (AT1R) interact in the aorta is not known. We report that GRK4 is expressed in vascular smooth muscle cells (VSMCs) of the aorta. Heterologous expression of the GRK4γ variant 142V in A10 cells increased AT1R protein expression and AT1R-mediated increase in intracellular calcium concentration. The increase in AT1R expression was related to an increase in AT1R mRNA expression via the nuclear factor κB (NF-κB) pathway. As compared with control, cells expressing GRK4γ 142V had greater NF-κB activity with more NF-κB bound to the AT1R promoter. The increased AT1R expression in cells expressing GRK4γ 142V was also associated with decreased AT1R degradation, which may be ascribed to lower AT1R phosphorylation. There was a direct interaction between GRK4γ wild-type (WT) and AT1R that was decreased by GRK4γ 142V. The regulation of AT1R expression by GRK4γ 142V in A10 cells was confirmed in GRK4γ 142V transgenic mice; AT1R expression was higher in the aorta of GRK4γ 142V transgenic mice than control GRK4γ wild-type (WT) mice. Angiotensin II-mediated vasoconstriction of the aorta was also higher in GRK4γ 142V than WT transgenic mice. This study provides a mechanism by which GRK4, via regulation of arterial AT1R expression and function, participates in the pathogenesis of conduit vessel abnormalities in hypertension.

Subdivision 1. Basic Science

Presentation Preference Mini-oral presentation
Additional information
Targeting MG53-mediated cell membrane repair for treatment of acute lung injury

Abstract nr. 55
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Topic The Pathogenesis of Atherosclerosis; Immunity, Inflammation, and the Endothelium
Keywords Inflammation

Injury to lung epithelial cells participates in the pathogenesis and progression of multiple lung diseases. Our previous studies identified mitsugumin 53 (MG53) as a key component of the cell membrane repair machinery in striated muscle cells. Here we present evidence that MG53 is also expressed in lung tissue. The mg53-/- mice show increased susceptibility to ischemia-reperfusion and over-ventilation induced injury to the lung when compared with wild type mice. In vitro studies demonstrate that extracellular application of the recombinant human MG53 (rhMG53) protein protects against injuries to lung epithelial cells. In vivo delivery of rhMG53 by intravenous or inhalation routes reduces symptoms in rodent models of acute lung injury and emphysema. Repetitive administration of rhMG53 improves pulmonary structure associated with chronic lung injury. Our data indicate a physiological function for MG53 in the lung and suggest that targeting membrane repair may be an effective means for treatment or prevention of lung diseases.

Subdivision 2. Translational Research

Presentation Preference Oral presentation
Additional information
Calpastatin counteracts pathological angiogenesis by inhibiting suppressor of cytokine signalling 3 degradation in vascular endothelial cells

Abstract nr. 58
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Topic The Pathogenesis of Atherosclerosis; Immunity, Inflammation, and the Endothelium
Keywords Angiogenesis, Endothelium

Pathological angiogenesis is known to exacerbate cancer growth and chronic inflammatory diseases including atherosclerosis. Janus kinase/signal transducer and activator of transcription (JAK/STAT) signals and their endogenous inhibitor suppressor of cytokine signalling 3 (SOCS3) in vascular endothelial cells (ECs) reportedly dominate the pathological angiogenesis. However, how these inflammatory signals are potentiated during pathological angiogenesis has not been fully elucidated. We suspected that an intracellular protease calpain, which compose the multifunctional proteolytic systems together with its endogenous inhibitor calpastatin (CAST), contributes to the JAK/STAT regulations. Our present data showed that the loss of CAST is detectable in neovessels in murine allograft tumours, some human malignant tissues and oxygen-induced retinopathy (OIR) lesions in mice. EC-specific transgenic introduction of CAST caused down-regulation of JAK/STAT signals, up-regulation of SOCS3 expression and depletion of vascular endothelial growth factor (VEGF)-C, thereby counteracting unstable pathological neovessels and disease progression in tumours and OIR lesions in mice. Neutralizing antibody against VEGF-C ameliorated pathological angiogenesis in OIR lesions. Small-interfering RNA-based silencing of endogenous CAST in cultured ECs facilitated µ-calpain-induced proteolytic degradation of SOCS3, leading to VEGF-C production through amplified interleukin-6-driven STAT3 signals. Interleukin-6-induced angiogenic tube formation in cultured ECs was accelerated by CAST silencing, which is suppressible by pharmacological inhibition of JAK/STAT signals, antibody-based blockage of VEGF-C and transfection of calpain-resistant SOCS3, while transfection of wild-type SOCS3 exhibited modest angiostatic effects. Hence, loss of CAST in angiogenic ECs facilitates µ-calpain-induced SOCS3 degradation, which amplifies pathological angiogenesis through interleukin-6/STAT3/VEGF-C axis. (Miyazaki T. et al., Circ Res., In press)
Subdivision 1. Basic Science

Presentation Preference Mini-oral presentation
Additional information
Improved endothelial function is associated with reduced arterial stiffness and atherosclerotic regression in rosuvastatin treated patients with inflammatory joint diseases.

Abstract nr. 59
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Topic Primary & Secondary prevention of CVD; Lifestyle Measures and Pharmacological Intervention
Keywords Atherosclerosis,Endothelium,Hypolipidemic Drugs,Inflammation

Background Endothelial dysfunction is the first step in the formation of atherosclerotic lesions and can be quantified by the degree of flow mediated vasodilation (FMD) of the brachial artery. Low FMD is a predictor of cardiovascular events. In addition, FMD is lower in patients with inflammatory joint diseases (IJD) compared to the general population. Our aim was to investigate if long-term rosuvastatin treatment in IJD patients with carotid plaques (CP) improves FMD. Furthermore, associations between change in FMD (ΔFMD) and change in CP height, arterial stiffness [aortic pulse wave velocity (aPWV) and augmentation index (AIx)], lipids and inflammatory variables were evaluated.

Methods Eighty five statin naïve IJD patients (rheumatoid arthritis: 53, ankylosing spondylitis: 24, psoriatic arthritis: 8) with ultrasound verified CP received treatment with rosuvastatin for 18 months to obtain low density lipoprotein cholesterol goal ≤1.8 mmol/L. All patients underwent assessment of FMD, aPWV, Alx and carotid ultrasound at baseline and at study end.

Results The mean±SD FMD was significantly improved from 7.10±3.14% at baseline to 8.70±2.98% at study end (p<0.001). Multiple linear regression analyses with ΔFMD as the dependent variable revealed a significant association with area under the curve erythrocyte sedimentation rate (p= 0.04), improvement in Alx (p=0.05) and CP height regression (p=0.001). The final linear regression model explained 31.1% of the variance in ΔFMD (R^2=0.311).

Conclusion Long-term intensive lipid lowering with rosuvastatin improved FMD in IJD patients with atherosclerotic disease. The improved endothelial function was associated with reduced arterial stiffness, CP height decrement and level of inflammation.
Rosuvastatin improves arterial stiffness in patients with inflammatory joint diseases and established atherosclerosis: Results from the RORA-AS study

Abstract nr. 60
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Topic Primary & Secondary prevention of CVD; Lifestyle Measures and Pharmacological Intervention
Keywords Atherosclerosis, Hypertension, Hypolipidemic Drugs, Inflammation

Background Arterial stiffness, as pulse wave velocity (PWV) and augmentation index (Alx), are early risk markers of cardiovascular disease (CVD). Intensive statin treatment induces carotid plaque (CP) regression in patients with inflammatory joint diseases (IJD). We evaluated the effect of rosuvastatin treatment on arterial stiffness in IJD patients with CP.

Methods The study population included 89 statin naïve IJD patients (rheumatoid arthritis: 55, ankylosing spondylitis: 23, psoriatic arthritis: 11). All patients had ultrasound verified CP and received rosuvastatin therapy over 18 months. PWV and Alx were measured at baseline and end of the study. Change in PWV and Alx from baseline was assessed with paired t-tests. Logistic regression analyses were performed with PWV and Alx as outcome variables, defined as decrease or no change/increase during the study, to assess for associations with other outcome measures.

Results From baseline to study end, mean (SD) Alx and PWV was significantly improved from 27.9 (7.7) % and 8.1 (1.6) m/s², to 26.2 (8.2) % (p=0.03) and 7.8 (1.5) m/s² (p=0.03), respectively. The logistic regression models revealed associations between: 1) PWV and change in systolic blood pressure (sBP) (p=0.008) and a lower area under the curve sBP (p=0.03), adjusted for antihypertensive medication. 2) Alx and change in CP height (p=0.03) and rosuvastatin dose (p=0.01). All associations were robust to adjustments for traditional CVD risk factors.

Conclusion Rosuvastatin therapy significantly improved arterial stiffness in IJD patients with CP. The improvement was associated with sBP change, rosuvastatin dose and atherosclerotic regression.

Subdivision 3. Clinical Studies

Presentation Preference Oral presentation
Additional information
Mechanisms underlying the vasorelaxation of human internal mammary artery induced by epicatechin

Abstract nr. 61
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Topic Primary & Secondary prevention of CVD; Lifestyle Measures and Pharmacological Intervention
Keywords Nutrition, Prevention

Aim: Many studies have indicated an association of an improved cardiovascular prognosis with flavanol-rich diets, which a major bioactive constituent seems to be epicatechin. Pure epicatechin has been reported to induce vasodilation and inhibit the vascular expression of proinflammatory and proatherogenic markers. Because the exact mechanisms by which epicatechin causes vasodilation are uncertain, we aimed to investigate vasorelaxant effect of epicatechin on the isolated human internal mammary artery (HIMA) and its underlying mechanisms.

Methods: Discarded segments of HIMA were collected from patients undergoing coronary artery bypass grafting and studied in organ baths.

Results: Epicatechin induced a concentration-dependent relaxation of HIMA rings pre-contracted by phenylephrine. Four-aminopyridine and margatoxin, blockers of voltage-gated K⁺ (Kᵥ) channels, and glibenclamide, a selective ATP-sensitive K⁺ (Kᵦᵣ) channels blocker, partly inhibited the epicatechin-induced relaxation of HIMA, while iberiotoxin, a most selective blocker of large conductance Ca²⁺-activated K⁺ channels (BKᵥCa), almost completely inhibited the relaxation. In rings pre-contracted by 80 mM K⁺, epicatechin induced partial relaxation of HIMA, whereas in Ca²⁺-free medium, epicatechin completely relaxed HIMA rings pre-contracted by phenylephrine and caffeine. Finally, thapsigargin, a sarcoplasmic reticulum Ca²⁺-ATPase inhibitor, slightly antagonized epicatechin-induced relaxation of HIMA pre-contracted by phenylephrine.

Conclusions: These results suggest that epicatechin induces strong endothelium-independent relaxation of HIMA pre-contracted by phenylephrine whilst 4-aminopyridine- and margatoxin-sensitive Kᵥ channels, as well as BKᵥCa and Kᵦᵣ channels, located in vascular smooth muscle, mediate this relaxation. In addition, it seems that epicatechin could inhibit influx of extracellular Ca
2+, interfere with intracellular Ca2+ release and re-uptake by the sarcoplasmic reticulum.

Subdivision 5. Not applicable. Abstract matches with track d

Presentation Preference Oral presentation
Additional information
Impaired dopamine D1 receptor-mediated vasorelaxation of mesenteric arteries in obese Zucker rats

Abstract nr. 62
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Topic Dyslipidemia; Lipids, Lipoproteins and Apolipoproteins
Keywords Cardiovascular Disease

Background: Obesity plays an important role in the pathogenesis of hypertension. Renal dopamine D1 receptor-mediated natriuresis is impaired in the obese Zucker rat. The role of arterial D1 receptors in the hypertension of obese Zucker rats is not clear.

Methods: Plasma glucose and insulin concentrations and blood pressure were measured. The vasodilatory response of isolated mesenteric arteries was evaluated using a small vessel myograph. The expression and phosphorylation of D1 receptors were quantified by co-immunoprecipitation and immunoblotting. To determine the effect of hyperinsulinemia and hyperglycemia on the function of the arterial D1 receptor, we studied obese Zucker rats fed vehicle or rosiglitazone, an insulin sensitizer, and lean Zucker rats, fed high-fat diet to induce hyperinsulinemia or injected intraperitoneally with streptomycin to induce hyperglycemia.

Results: In obese Zucker rats, the vasorelaxant effect of D1 receptors was impaired that could be ascribed to decreased arterial D1 receptor expression and increased D1 receptor phosphorylation. In these obese rats, rosiglitazone normalized the D1 receptor expression and phosphorylation and improved the D1 receptor-mediated vasorelaxation. We also found that D1 receptor-dependent vasorelaxation was decreased in lean Zucker rats with hyperinsulinemia or hyperglycemia. The ability of insulin and glucose to decrease D1 receptor expression and increase its phosphorylation were confirmed in studies of rat aortic smooth muscle cells.

Conclusions: Both hyperinsulinemia and hyperglycemia caused D1 receptor dysfunction by decreasing arterial D1 receptor expression and increasing D1 receptor phosphorylation, which is involved in the pathogenesis of obesity-related hypertension.

Keywords: D1 receptor, Vasorelaxation, Hyperinsulinemia, Hyperglycemia, Obesity-related hypertension

Subdivision 1. Basic Science

Presentation Preference Mini-oral presentation
Additional information
Development of A TransAtlantic Cardiovascular risk Calculator for Rheumatoid Arthritis (ATACC-RA) on behalf of the ATACC-RA consortium

Abstract nr. 63
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Topic Epidemiology of CVD; The Risk Factor Concept
Keywords Cardiovascular Disease, Risk Factor, Risk stratification

**Purpose:** Patients with rheumatoid arthritis (RA) have an increased risk of cardiovascular disease (CVD), which is not accurately predicted by risk calculators designed for the general population. Our aim was to develop a RA specific CVD risk calculator.

**Methods:** RA patients from 8 centres in 7 countries were included. CVD outcomes (MI, revascularization, angina, stroke, TIA, PAD and CVD death) were collected prospectively. RA characteristics (duration, seropositivity, disease activity (DAS28) and CRP/ESR) and traditional CVD risk factors were collected at baseline. Cox models stratified by centre were used to develop a CVD risk calculator considering traditional CV risk factors and RA characteristics. Model performance was assessed using discrimination and calibration.

**Results:** In total 3176 RA patients without prior CVD were included (mean age: 55 [SD: 14] years, 73% female). During a mean follow-up of 7.8 years (24733 person years), 314 had a CVD event. The multivariable risk evaluation revealed 2 models including either seropositivity or DAS28 along with age, sex, current smoking, presence of hypertension, and ratio of total cholesterol to high-density lipoprotein. Both 10-fold cross validation and multiple imputation analyses confirmed these findings. Both models demonstrated good discrimination (c-statistic: 0.76 and 0.74) and calibration (observed/predicted ratio: 1.00; 95% confidence interval: 0.89, 1.12). The ATACC-RA (mean: 11.5%, SD 14.1%) showed significantly improved discrimination compared to either Framingham (c-statistic: 0.71, p<0.001) or SCORE (c-statistic: 0.72, p<0.001) risk algorithms.

**Conclusions:** Development of an RA-specific CVD risk calculator is feasible by pooling resources from many centres. Further development including external validation is underway.

Subdivision 4. Not applicable. Abstract matches with track c

Presentation Preference Oral presentation
Additional information
ENDOTHELIAL DYSFUNCTION IN STREPTOZOTOCIN INDUCED DIABETES AND INFLUENCE OF GERANIUM OIL.

Abstract nr. 64
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Topic Primary & Secondary prevention of CVD; Lifestyle Measures and Pharmacological Intervention
Keywords Animal model, Diabetes, Endothelium, Inflammation

Aim: Endothelial dysfunction is a critical factor during the initiation of diabetic cardiovascular complications and antioxidant effect plays a pivotal role in this setting. The present study aimed to investigate whether the essential oil therapy with geranium oil and its major component like citronellol can provide protection against diabetes-associated endothelial dysfunction and elucidate the possible mechanism(s) underlying this effect.

Methods: Diabetes was induced by intraperitoneal injection of Streptozotocin (45 mg/kg) in rats. Influence of geranium oil (GO) and citronellol (each 100, 200 & 400 mg/kg, orally, 1 month) on TNF-α, oxidative stress parameters, NOS activity and vascular function were evaluated.

Results: Our results showed a marked increase in aortic superoxide anion (O$_2^-$) production and serum malondialdehyde level alongside attenuating antioxidant enzyme capacities in diabetic rats. This was associated with a significant increase in TNF-α serum level of diabetic rats alongside reducing aortic NOS activity and nitric oxide (NO) bioavailability. Administration of GO & its components citronellol significantly inhibited these changes. However, the vascular endothelium-dependent relaxation with acetylcholine in aorta of diabetic rat was significantly ameliorated by citronellol (90.16 ± 0.17%). Citronellol proves more promising component for beneficial effect of essential oil.

Conclusions: Collectively, our results demonstrated that the essential oil therapy of GO affords beneficial effects through its major component citronellol against diabetes-associated endothelial dysfunction, probably through normalizing the deregulated NOS and reducing the inflammation and oxidative stress in diabetic rats. It is noteworthy; that the essential oil therapy exhibited a significant response over the diabetic complications.

Subdivision 5. Not applicable. Abstract matches with track d

Presentation Preference Oral presentation
Additional information
Heterogeneity of traditional and un-traditional Cardiovascular Disease Risk Factors and Events in Patients with Rheumatoid Arthritis across 10 Countries

Abstract nr. 65
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Topic Epidemiology of CVD; The Risk Factor Concept
Keywords Cardiovascular Disease, Risk Factor, Risk stratification

**Purpose:** Cardiovascular disease (CVD) risk calculators for the general population do not accurately predict CVD events in rheumatoid arthritis (RA). We aimed to compare the impact of classical CVD risk factors and RA characteristics on CVD outcomes in RA patients across 10 countries.

**Methods:** CVD risk factors and RA characteristics from 13 rheumatology centers were collected at baseline. Cox-models were used to compare the impact of CVD risk factors and RA characteristics on events, and were adjusted for age/sex and age/sex/CVD risk factors.

**Results:** 5685 RA patients without prior CVD were included (mean age: 55 [SD: 14] years). During a mean follow-up of 6.1 years (31155 person-years), 476 patients developed CVD events. Mean age varied: 37-61 years. Norway and UK had the lowest CVD event rates, and South Africa, Netherlands, US-Mayo and Sweden the highest. Age effects were fairly consistent (hazard ratios [HR] from 1.6-1.8 per 10-year increase in age), but male sex varied from no effect to a doubled effect (HR=1.0-2.3). Varied effects were also seen for current smoking (HR=1.1-2.1), hypertension (HR=0.6-2.0), total cholesterol:high-density lipoprotein ratio (HR=0.9-1.2) and diabetes mellitus (HR=0.7-2.8). Effects varied also for RA characteristics, including rheumatoid factor and/or anti-citrullinated protein antibody seropositivity (HR=0.7-1.4), joint disease activity (HR=0.9-1.2) and RA disease duration (HR=0.7-1.1).

**Conclusions:** Major heterogeneity exists in CVD event rates and in impact of classical CVD risk factors and RA characteristics on CVD outcomes among RA patients across different countries, and is a challenge when developing an RA specific CVD risk calculator for international use.

Subdivision 4. Not applicable. Abstract matches with track c

Presentation Preference Mini-oral presentation
Additional information
Impact of asymptomatic atherosclerosis on cardiovascular risk stratification and consequences for lipid lowering prevention in patients with inflammatory joint diseases

Abstract nr. 66
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Topic Primary & Secondary prevention of CVD; Lifestyle Measures and Pharmacological Intervention
Keywords Cardiovascular Disease,Prevention,Risk Factor,Risk stratification

Purpose: Intensive lipid lowering treatment (LLT) is recommended for patients with carotid plaque (CP). Patients with inflammatory joint diseases (IJD) have a high frequency of CP, and we aimed to evaluate the impact of CP on cardiovascular disease (CVD) risk stratification and consequences for lipid lowering prevention in patients with IJD.

Methods: CVD risk stratification in IJD patients (n= 334) was performed using the SCORE algorithm and by performing ultrasound of the carotid arteries. Cross-tabulations, Chi² and ROC-curves were used to calculate sensitivity/specificty for the SCORE algorithm. The ROC curves closest point (0.1) and 80 % sensitivity were used for optimizing CVD risk classification.

Results: In 249 patients with IJD and a calculated risk <5%, 98 (39.4%) had CP and should receive intensive LLT. In patients with a calculated risk >5% & <10% + LDL>2.5 mmol/L (n=58), 38 (65.5 %) patients had CP and should receive intensive LLT. Thus, patients with CP who were wrongly classified to receive no or only moderate instead of intensive LLT, was 39.4% and 65.5%, respectively. Taken together, 136/307 (44.3%) of these patients would receive inadequate LLT. The sensitivity (correctly classifying patients with IJD + CP) was 0.39 and the specificity was 0.83. Optimizing SCORE cut off for very high risk, by area under the ROC curves' closest point (0, 1) or 80% sensitivity did not improve correct CVD risk stratification in congruence with recommended standards.

Conclusion: Carotid ultrasound contributes to optimized CVD risk classification with consequences for CVD preventive LLT in patients with IJD.

Subdivision 5. Not applicable. Abstract matches with track d

Presentation Preference Oral presentation
Additional information
A healthy diet is associated with less endothelial dysfunction and less low-grade inflammation over a 7-year period

Abstract nr. 67
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Topic Epidemiology of CVD; The Risk Factor Concept
Keywords Endothelium, Epidemiology, Inflammation, Nutrition

A healthy diet rich in fish, fruit and vegetables, but low in alcohol, dairy products and meat, has been associated with less incident cardiovascular disease (CVD). Endothelial dysfunction and low-grade inflammation play important roles in CVD. A healthy diet might modify these phenomena. We investigated the association between the above food groups and biomarker scores of endothelial dysfunction and low-grade inflammation. In 557 participants with increased CVD risk (baseline age 59.6 ± 6.9 years) we measured diet by FFQ. Biomarkers of endothelial dysfunction (von Willebrand factor, and soluble vascular cell adhesion molecule 1, endothelial selectin, thrombomodulin, intercellular adhesion molecule 1 (sICAM-1)) and low-grade inflammation (C-reactive protein, serum amyloid A, interleukin 6, interleukin 8, tumor necrosis factor α and sICAM-1) were measured and combined into overall scores (higher scores indicating worse function). Longitudinal data, at baseline and after 7 years, were analyzed with generalized estimating equations and adjusted for confounders.

Higher consumption of fish (per 100 g/wk), but not vegetables, fruit, alcohol-containing beverages, dairy products or meat, was associated with a lower endothelial dysfunction score over 7 years: \( \beta (95\% \text{ CI}) -0.027(-0.051;-0.004). \) No associations were observed with the overall low-grade inflammation score. Food component analyses indicated that more lean fish and raw vegetables, and less high-fat dairy products were associated with less endothelial dysfunction. Consumption of more fresh fruit, wine and poultry, and less high-fat dairy products was associated with less low-grade inflammation.

This suggests that dietary modification of endothelial dysfunction and low-grade inflammation, processes that are important in atherothrombosis, is possible.

Subdivision 4. Not applicable. Abstract matches with track c
Presentation Preference Oral presentation
Additional information
Blend of Unrefined Sesame and Rice bran oils Exhibits Lipid-lowering and Anti-hyperglycemic Potentials in Patients with Type 2 Diabetes Mellitus

Abstract nr. 68
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Topic Dyslipidemia; Lipids, Lipoproteins and Apolipoproteins
Keywords Diabetes, Lipids, Nutrition, Therapy

By considering the substantial health benefits of sesame and rice bran oils, the current study is to examine the extent to which the daily use of the blend of sesame and rich rice bran oils (20:80) as cooking oil beneficial in type 2 diabetes mellitus (T2DM). This open-label, randomized, dietary intervention comprised of 300 patients with T2DM and 100 normoglycemic subjects. Oils blend was supplied to T2DM patients, with (n=100; glibenclamide (5mg/d)) or without (n=100) anti-diabetic medication, and normoglycemic subjects while 100 T2DM patients were treated with glibenclamide (5mg/d) only. The groups supplied with the oils blend were instructed to use it as the only cooking oil for 60 days. Fasting and postprandial blood glucose was measured at days 0, 30 and 60. HbA1C and lipid profile (TC, TG, LDL-C and HDL-C) were measured at days 0 and 60. Blood glucose was significantly lowered from 30 days, and HbA1C and lipid profile were significantly improved at 60 days in T2DM patients substituted with the oils blend only while no significant changes were observed in normoglycemic subjects. Glibenclamide alone treatment significantly lowered blood glucose and HbA1C only where as glibenclamide plus oils blend treated group showed a remarkable reduction of glucose from 30 days, and significantly improved HbA1C and lipid profile after 60 days. The study reveals the fact that the blend of sesame and rice bran oils exhibits lipid-lowering and anti-hyperglycemic potentials and also exhibits additive effect with anti-diabetic drug for the effective management of T2DM.

Subdivision 3. Clinical Studies

Presentation Preference Oral presentation
Additional information
Prevalence of low high-density lipoprotein cholesterol stratified by risk category and gender among Arabian Gulf patients in the CEPHEUS

Abstract nr. 69
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Topic Dyslipidemia; Lipids, Lipoproteins and Apolipoproteins
Keywords Cardiovascular Disease, HDL, Hypolipidemic Drugs, LDL

Objective: To estimate the prevalence of low HDL-C among patients in the Centralized Pan-Middle East Survey on the undertreatment of hypercholesterolemia (CEPHEUS) stratified by risk category (according to the joint Consensus Statement of the American Diabetes Association (ADA) and American College of Cardiology (ACC) Foundation) and gender.

Methods: CEPHEUS was conducted in patients (≥18 years of age) in six Middle Eastern countries between November 2009 and July 2010 on lipid lowering drugs (LLDs). Serum samples were used to measure lipid parameters.

Results: The overall mean age of the cohort were 56±11 years and majority were males (58%). The overall prevalence of low HDL-C was 49%. Low HDL-C was more prevalent in female compared to male (53% vs 46%; p<0.001). In the high risk group the prevalence of low HDL-C was 40% compared to 53% in the highest risk group patients (p<0.001). The prevalence of low HDL-C in the high risk group in patients who achieved LDL-C target of <2.6 mmol/l was 48% compared to 52% in those who didn’t achieved LDL-C target of <2.6 mmol/l (p=0.073). In the highest risk group the prevalence of low HDL-C in patients who achieved LDL-C target of <1.8 mmol/l was 28% compared to 72% in those who didn’t achieved LDL-C target of <1.8 mmol/l (p<0.001).

Conclusions: Patients in the Middle East on LLDs have a high prevalence of low HDL-C and is more seen in the highest risk group and female patients. These patients may remain at increased residual risk for CVD.

Subdivision 3. Clinical Studies

Presentation Preference Oral presentation

Additional information
Hyperglycaemic spikes increase monocytes and atherosclerosis in normoglycaemic mice through a RAGE dependent mechanism.

Abstract nr. 70
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Topic The Pathogenesis of Atherosclerosis; Immunity, Inflammation, and the Endothelium
Keywords Animal model, Atherosclerosis, Diabetes

Introduction
Postprandial hyperglycaemic spikes are a major risk factor for cardiovascular disease in diabetes. We hypothesized that hyperglycaemic spikes increase circulating monocyte levels and atherosclerosis through receptor for advanced glycation endproducts (RAGE) signaling on monocyte precursors.

Methods
We injected wildtype female C57Bl/6 mice 4 subsequent times with glucose to induce hyperglycaemic spikes (~25mmol/l) and sacrificed them after 1 and 7 days of normoglycaemia. We quantified common myeloid (CMP) and granulocyte-monocyte precursors (GMP) and circulating monocyte subsets (Ly6C\text{hi} and Ly6C\text{lo}) with flow cytometry. To determine if this translated into accelerated atherosclerosis, we induced weekly hyperglycaemic spikes for 10 weeks in Apoe\textsuperscript{-/-} mice. To examine the role of haematopoietic RAGE, we transplanted Rage\textsuperscript{-/-} bone marrow into irradiated wildtype mice.

Results
We found in the bone marrow that the CMP and GMP were increased 2.2 and 1.3 fold after 1 day and normalized 7 days after glucose spiking, resulting in a significant increase in monocytes after 7 days (especially Ly6C\text{hi} subset). Hyperglycaemic spikes increased atherosclerotic burden in the aortic arch 2-fold. Interestingly, 1 day after glucose spiking, the expression of RAGE ligand S100A8/A9 in white blood cells and expression of RAGE on CMPs were increased. Subsequently, mice transplanted with Rage\textsuperscript{-/-} bone marrow were protected against monocytosis induced by hyperglycaemic spikes.

Conclusion
These results reveal potential harm of hyperglycaemic spikes by acting on haematopoietic progenitors, stimulating monocyte production. This is dependent on RAGE signaling, with S100A8/A9 as a potential ligand. Preventing hyperglycaemic spikes or RAGE signaling may reduce cardiovascular risk in people with diabetes.

Subdivision 2. Translational Research

Presentation Preference Oral presentation
Additional information
**Metalloproteinases behaviour in epicardial adipose tissue and its association with coronary artery disease**

Abstract nr. 71
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**Topic** The Pathogenesis of Atherosclerosis; Immunity, Inflammation, and the Endothelium

**Keywords** Angiogenesis, Cardiovascular Disease, Risk Factor

**Background:** Epicardial adipose tissue (EAT) is a metabolically active visceral adipose tissue surrounding and infiltrating myocardium and coronary arteries. An excessive amount of EAT may represent injury for the myocardium. Metalloproteinases are endopeptidases involved in expansion of adipose tissue as well as in atherosclerosis; however, there is no evidence about MMP’s behavior in EAT. **Objective:** evaluate MMP-2 and -9 in EAT from patients with coronary artery disease (CAD) and their relationship with morphologic EAT characteristics.

**Subjects and Results:** EAT and subcutaneous adipose tissue (SAT) were obtained from patients undergoing heart surgery for coronary artery bypass graft (CAD, N=17) or valve replacement (No CAD, N=15). In EAT and SAT, MMP-2 and -9 localization and activity, vascular density (VD), size and adipocyte density and inflammatory cell infiltration were determined. MMP-2 activity was significantly increased in EAT from CAD compared to No CAD patients (1.86±0.54 vs 1.43±0.23 RU, p=0.031). In EAT from CAD patients, we observed an increase in MMP-2 (1.86±0.54 vs 1.39±0.33 RU, p=0.038) and MMP-9 (1.53±0.61 vs 1.19±0.28 RU, p=0.049) activities compared to SAT. VD was significantly higher in EAT from CAD compared to No CAD (p=0.015) and it was directly correlated with MMP-2 (p=0.006) and MMP-9 (p=0.02) activity. **Conclusions:** EAT from CAD patients presents higher gelatinases activity than EAT from No CAD patients and it could be responsible for the higher VD observed. The increased of MMPs activity and inflammatory infiltrate in EAT could be linked to the plaque vulnerability and the higher cardiometabolic risk in CAD.

Subdivision 3. Clinical Studies

Presentation Preference Electronic poster presentation

Additional information
Role of SN1 Lipases on Plasma Lipids in Metabolic Syndrome and Obesity

Abstract nr. 72
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Topic Dyslipidemia; Lipids, Lipoproteins and Apolipoproteins
Keywords Lipoproteins, Metabolism, Obesity

Objective: To assess the phospholipase activity of endothelial (EL) and hepatic lipase (HL) in postheparin plasma of subjects with metabolic syndrome (MS)/obesity and their relationship with atherogenic and antiatherogenic lipoproteins. Additionally, to evaluate lipoprotein lipase (LPL) and HL activity as triglyceride (TG)-hydrolyses to complete the analyses of SN1 lipolytic enzymes in the same patient.

Results: Plasma EL, HL, and LPL activities were evaluated in 59 patients with MS and 36 controls. A trend toward higher EL activity was observed in MS. EL activity was increased in obese compared with normal weight group (P=0.009) and negatively associated with high-density lipoprotein–cholesterol (HDL-c) (P=0.014 and P=0.005) and apolipoprotein A-I (P=0.045 and P=0.001) in control and MS group, respectively. HL activity, as TG-hydrolase, was increased in MS (P=0.025) as well as in obese group (P=0.017); directly correlated with low-density lipoprotein–cholesterol (P=0.005) and apolipoprotein B (P=0.003) and negatively with HDL-c (P=0.021) in control group. LPL was decreased in MS (P<0.001) as well as in overweight and obese compared with normal weight group (P=0.015 and P=0.004, respectively); inversely correlated %TG-very low-density lipoproteins (P=0.04) and TG/apolipoprotein B index (P=0.013) in control group. These associations were not found in MS.

Conclusions: We describe for the first time EL and HL activity as phospholipases in MS/obesity, being both responsible for HDL catabolism. Our results elucidate part of the controversies about SN1 lipases in MS and different grades of obesity. The impact of insulin resistance on the activity of the 3 enzymes determines the lipoprotein alterations observed in these states.

Subdivision 3. Clinical Studies

Presentation Preference Electronic poster presentation
Additional information
EFFECT OF EMAP-II TO CARDIOHEMODYNAMICS IN HYPERTENSION.

Abstract nr. 73
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Topic The Pathogenesis of Atherosclerosis; Immunity, Inflammation, and the Endothelium
Keywords Endothelium, Hypertension

Endothelial monocyte-activating polypeptide-II (EMAP-II) is a multifunctional polypeptide with proinflammatory and antiangiogenic activity. Enhancing of low-grade chronic inflammation is associated with cardiovascular diseases and hypertension. However, the role of this cytokine in hypertension is not understood.

The aim of study was investigate effect of EMAP II on heart function of spontaneously hypertensive rats (SHR). The researches were conducted on six-month SHR male rats. The functional cardiohemodynamic indicators registered via Pressure-Volume System.

It was shown that stroke volume increased by 18.2%, cardiac output – by 22% after EMAP II in SHR. The end-diastolic myocardial stiffness reduced in 4.7 times, arterial stiffness decreased by 23.2 in SHR after EMAP II.

Thus, in hypertension EMAP II has the positive effect on the reduction of arterial stiffness, end-systolic- and maximum myocardial stiffness, increase indices of heart pump function, improvement of left ventricular relaxation.

Subdivision 1. Basic Science

Presentation Preference Electronic poster presentation
Additional information
Targeted Next-Generation Sequencing to Diagnose Abnormalities of HDL Cholesterol

Abstract nr. 74
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Topic Dyslipidemia; Lipids, Lipoproteins and Apolipoproteins
Keywords Genetics, HDL, Lipids, Lipoproteins

Background: A low level of high-density lipoprotein cholesterol (HDL-C) is the most common lipid abnormality in patients with premature coronary artery disease. Individuals with very low or very high levels of HDL-C frequently have rare mutations in one of several genes, suggesting that a molecular diagnosis could be made in these patients. However, identification of the specific molecular abnormality in patients with extreme HDL-C is rarely performed in clinical practice. The objective of this study was to investigate the analytic validity and diagnostic yield of a targeted next-generation sequencing (NGS) assay for extreme levels of HDL-C.

Methods and Results: We developed a targeted NGS panel to capture the exons, intron/exon boundaries and untranslated regions of genes with highly penetrant effects on plasma lipid levels. We sequenced 92 patients with very low or very high levels of HDL-C recruited from a large specialty lipid clinic. We also included 6 patients with known Mendelian disorders of HDL in whom pathogenic mutations had previously been identified, and 1 family with a suspected Mendelian disorder of HDL in whom no mutation had previously been identified. We prioritized variants in accordance with medical genetics guidelines. All variants subsequently underwent validation by bidirectional Sanger sequencing. Overall, we established a molecular diagnosis in 40% of patients with low HDL-C and 8% of patients with high HDL-C. One hundred percent of prioritized variants were confirmed by Sanger sequencing and all previously known variants in patients with Mendelian disorders of HDL were accurately detected by NGS. Functional studies on a subset of these variants confirmed that they resulted in loss-of-function of the encoded proteins.

Conclusions: Our results suggest that a molecular diagnosis can be established in a substantial proportion of patients with low HDL-C, but in only a small percentage of patients with high HDL-C. Our customized NGS assay has positive predictive value and sensitivity approaching 100% for identifying these variants. Molecular diagnosis of disorders of lipid metabolism has the potential to refine diagnostic categories and may lead to new therapeutic strategies.
Subdivision 2. Translational Research

Presentation Preference Oral presentation
Additional information
Different effect of statins on inducing diabetes mellitus: An experimental study

Abstract nr. 77

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Topic Primary & Secondary prevention of CVD; Lifestyle Measures and Pharmacological Intervention

Keywords Diabetes, Intervention

Background: To determine whether individual statins had differing effects on inducing diabetes mellitus process.

Methods: Four kinds of statins, atorvastatin, pravastatin, rosuvastatin, and pitavastatin were selected to determine the insulin secretion and resistance. The cytotoxicity, insulin secretion and glucose-stimulated insulin secretion were investigated in human pancreas islet β cells. The decrease of glucose uptake in human skeletal muscle cells was also investigated.

Results: Human pancreas islet β cells treated with 100 μM of atorvastatin, pravastatin, rosuvastatin, and pitavastatin. Cell viability was reduced by 32.12%, 41.09%, 33.96%, 29.19% relative to control cells, and insulin secretion rate was reduced by 34.07%, 30.06%, 26.78%, 19.22% relative to control cells, respectively. The insulin secretion stimulated by high glucose concentration (28 mmol/L) was significantly higher than by the physiological concentration (5.6 mmol/L) all the treatment groups, which ranged from 53.44 ng/mL to 78.32 ng/mL vs. from 35.78 ng/mL to 54.22 ng/mL. The glucose uptake rates of human skeletal muscle cells treated with 100 μM of the four statins, which were atorvastatin (58.76%) < pravastatin (60.21%) < rosuvastatin (72.54%) < pitavastatin (89.96%). The atorvastatin and pravastatin inhibited GLUT2 expression and induced p-p38 MAPK expression in human pancreas islet β cells. The atorvastatin, pravastatin and rosuvastatin inhibited GLUT4, p-AKT, p-GSK-3β, and p-p38 MAPK in human skeletal muscle cells.

Conclusions: Differences between individual statins likely exist that may cause to different effect of inducing islet cells damage and insulin resistance. Pitavastatin may have the lowest diabetes mellitus inducing effect among the four statins.

Subdivision 5. Not applicable. Abstract matches with track d

Presentation Preference Electronic poster presentation

Additional information
Nurse interventions for early restarting of physical activity in people with prior acute myocardial infarction: the Fitwalking® Project.

Abstract nr. 78
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Topic Primary & Secondary prevention of CVD; Lifestyle Measures and Pharmacological Intervention
Keywords Cardiovascular Disease, Lifestyle, Prevention

Aim: To evaluate effect of nurse-led aerobic exercise (Fitwalking® (FW), a brisk walking conceived by Maurizio Damilano) on body size and exercise tolerance in people with prior Acute Myocardial Infarction (AMI).

Methods: 17 consecutive people (13 males, 58.4±6.5 years) from Coronary Unit (CU), performed a 40-minutes long FW session twice a week. Inclusion criteria: prior AMI; CU admission at least 6 months before; ejection fraction >45%; age <70 years; negative stress test for ischemia/angina; no disabling diseases; consent by attending cardiologist. For educational purposes, 9 people were included in Group 1 (G1; 17 sessions performed), 8 people in Group 2 (G2; 22 sessions performed). Body size, distance walked (DW) and, only in G2, Borg Scale score (BS) were collected at baseline and at the end of study. Results were compared within each group and whole sample (WS) by T-test variance analysis.

Results: Study showed significant improvement of performance in G1 (DW: 2.8±0.0 vs 5.3±0.6 km, P=0.025), not significant improvement of exercise tolerance (G2, WS) and not significant reduction in body size (G1, WS).

Conclusion: In a short observational period and small sample, a positive trend in reducing body size and improving performance was seen. In contrast with literature, with increasing distance a reduction in BS was seen: the better shape, the better wellness? It may be likely, since some people in G1, feeling fit, continued practice with G2. A nurse-led pedagogical approach based on educational, relational and motivational competence, able to highlight trainees’ progress, made the Project possible.

Subdivision 5. Not applicable. Abstract matches with track d

Presentation Preference Electronic poster presentation
Additional information
Maternal and infant adiposity and lipid profile are associated with maternal and cord blood inflammation.

Abstract nr. 79
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Topic Dyslipidemia; Lipids, Lipoproteins and Apolipoproteins
Keywords Dyslipidemia, Epidemiology, Inflammation, Metabolism

Lipid dysregulation is exacerbated by inflammation. We investigated associations between maternal and infant lipid profiles, adiposity and inflammation.

Materials/Methods
Paired maternal (28-weeks gestation) and infant (umbilical cord) blood samples were collected from a population-derived birth cohort (Barwon Infant Study, n=1074). Data on maternal co-morbidities, infant birth weight and adiposity (standardised skin-fold thickness) were compiled. In a randomly selected subgroup of term infants (n= 227 pairs), matched maternal and cord lipids and high sensitivity C-reactive protein (hsCRP) were measured.

Results
Mean maternal age was 32.4 years (sd 4.2) with a pre-pregnancy BMI median 24.4 kg/m² (IQR 21.7-28.1); 92% of the cohort was caucasian. Caesarian births accounted for 33% of deliveries, and mean birth weight was 3.6kg (sd 0.44).
Preliminary data show that maternal cholesterol and LDL were elevated compared to non-pregnant normal ranges. Infant lipid concentrations were higher in female infants (e.g cholesterol mean difference 0.4 (95%CI 0.1-0.6) mmol/L). Infant cholesterol (r=0.40, p<0.001), HDL (r=0.30, p<0.001), LDL (r=0.37, p<0.001), ApoA (r=0.46, p<0.001) and ApoB (r=0.43, p<0.001) appeared to correlate with infant hsCRP.
After adjusting for maternal age, smoking status, mode of delivery and infant gender, multivariate regression analysis demonstrated an association between increased maternal hsCRP and increasing pre-pregnancy BMI (β=0.3 mg/L per kg/m²; p<0.001), birth weight (β=0.003 mg/L per kg, p<0.001) and infant skin fold thickness (β=0.8mg/L per mm; p=0.003). For infant hsCRP, similar patterns were observed.

Conclusion
Increased infant cholesterol positively correlated with increased infant hsCRP, whilst higher pre-pregnancy BMI and markers of infant adiposity are associated with higher maternal hsCRP. These
findings are in keeping with a relationship between inflammation, adiposity and lipid metabolism in the perinatal period.

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Kate McCloskey is funded by a Sidney Myer PhD scholarship

Subdivision 2. Translational Research

Presentation Preference Electronic poster presentation
Additional information
Impact of five novel mutations and five known mutations in endothelial lipase on HDL cholesterol levels.

Abstract nr. 82
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Topic Dyslipidemia; Lipids, Lipoproteins and Apolipoproteins
Keywords Genetics,HDL,Risk stratification

High density lipoprotein (HDL) has multiple functions. High HDL-cholesterol (HDL-C) concentrations, generally viewed as favourable, may be due to several causes that may have different effects on composition and function. Endothelial lipase (LIPG) mutations were found to cause increased HDL-C concentrations with unresolved impact on cardiovascular disease. We aimed to seek LIPG mutations in a cohort of patients with high HDL-C and to determine their prevalence in a range of HDL-C concentrations in patients attending a referral clinic for dyslipidaemia.

Patients with hypercholesterolaemia >7.5mmol/L and consenting to research were assessed clinically in conjunction with a fasting lipogram and tests for secondary dyslipidaemia. Mutations in LIPG were first sought in those with HDL-C >2.5mmol/L, whereafter these mutations were sought in categories of 200 random samples in HDL-C ranges 1.2-1.6, 1.6-2.0, 2.0-2.5mmol/L.

Polymerase chain reaction products were analysed by high resolution melting and heteroduplex patterns were analysed by sequencing.

Five unreported mutations and five known mutations in LIPG were identified in the following numbers of patients: Q249L(1), A277D(1), T298S(9), S310G(2), R315H(1), N396S(18), E417Q(1), R442W(1), R448L(1), R450G(3). Two common mutations were found across the range of HDL-C levels. Six uncommon mutations were found in the higher HDL-C categories.

Mutations in LIPG were identified. The known N396S and T298S mutations appear not to raise HDL-C powerfully while six of the mutations are likely powerful modulators of HDL-C. Further investigation is required to determine the functional and clinical impact of these mutations.

Funding: South African Medical Research Council

Subdivision 3. Clinical Studies

Presentation Preference Electronic poster presentation

Additional information
The influence of exenatide on monocytes/macrophages' phenotype, TNF alpha release and ROS generation – an in vitro study.

Abstract nr. 83
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Topic The Pathogenesis of Atherosclerosis; Immunity, Inflammation, and the Endothelium
Keywords Atherosclerosis, Diabetes, Inflammation

Introduction: Diabetic patients experience accelerated atherosclerosis. Macrophages are key cells accelerating the development of atherosclerotic plaques. There are at least two major subpopulations of macrophages: M1 - associated with atherosclerosis progression (high inducible nitrous oxide synthase [iNOS] expression) and M2 – anti-inflammatory and healing promoting cells (high arginase 1 [arg1] expression). Effects of novel antidiabetic incretin-based therapies exceed its hypoglycaemic properties (e.g. a decrease in markers of low-intensity inflammation). Therefore authors aimed at the assessment of the influence of in vitro exenatide (a glucagon-like peptide-1 [GLP-1] receptor agonist) on macrophages' phenotype, inflammatory and oxidative stress markers.

Materials and Methods: Monocytes were isolated from 18 patients with recently diagnosed type 2 diabetes. Cells were exposed in vitro to exenatide, LPS and combination of the both compounds. The impact of exenatide on the phenotype of macrophages (iNOS and arg1), TNFalpha and ROS level was studied.

Results: Exenatide alone did not affect iNOS expression but it significantly inhibited iNOS expression in LPS pre-treated cells (376±76RODvs.478±112ROD; p<0.05). Compared to controls, exenatide effectively induced arg1 expression in macrophages pre-treated (100±31RODvs.379±51ROD; p<0.05) or untreated with LPS (100±31RODvs.212±66ROD; p<0.05). Exenatide diminished the level of ROS (321.5±65RUvs.401.3±75RU; p<0.05) and TNFalpha (379.3±51pg/ml vs. 451.1±42pg/ml; p<0.05) in LPS pre-treated macrophages. However no effect of exenatide was observed in cells unexposed to LPS.

Conclusion: We showed that exenatide influenced basic markers of the macrophage phenotype, skewing the population toward alternative activation and limiting classical activation induced by LPS. Additionally a reduction in inflammatory and oxidative stress markers was achieved.

Subdivision 1. Basic Science

Presentation Preference Electronic poster presentation
Additional information
Coronary artery disease risk estimation with combination of visual and biochemical markers

Abstract nr. 84
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Topic Epidemiology of CVD; The Risk Factor Concept
Keywords Cardiovascular Disease, Lipoproteins, Risk Factor, Visceral Fat

Aim: To investigate whether carotid artery dopplerography parameters and blood biomarkers concentrations are associated with coronary artery disease (CAD).

Methods: This study included 205 consecutive patients (M/F 136/69; mean age 62.8±9.0 yrs). All patients were underwent coronary angiography and carotid artery ultrasound dopplerography with the mean common carotid artery intima-media thickness (IMT) and carotid atherosclerotic plaques (ASP) assessment; 70.7% of patients had CAD; 92.4% of patients were treated with statins.

Results: CAD patients didn’t differ by lipid profile parameters, but exhibited significantly lower serum levels of apolipoprotein (apo) AI (154.5±26.3 vs. 166.4±29.7 mg/dl; p=0.000), apo B (87.7±24.4 vs. 98.1±25.3 mg/dl; p=0.000), as well as that for leptin (28.5±22.6 vs. 44.4±59.4 ng/ml; p=0.000), as compared to the patients without CAD. Meanwhile, there were significant differences in leptin (p=0.000), apo AI (p=0.000) and apo B (p=0.009) levels between patients with single-, two, and multiple-vessel disease upward in group without atherosclerotic coronary lesion. Logistic regression analysis indicated that the IMT >0.9 mm (OR=2.7, 95% CI=1.4-5.4, p=0.004) and presence of carotid ASP ≥3 (OR=4.6, 95%CI=1.9-11.4, p=0.001) independently associated with CAD. Multiple regression analysis demonstrated that presence of carotid ASP ≥3 (OR=2.5; 95%CI=1.0-5.9; p=0.045) and blood adiponectin level below median (8.0 mkg/ml) (OR=3.1; 95%CI=1.3-7.6; p=0.014) were associated with CAD.

Conclusion: Combination of three and more carotid ASP with low blood adiponectin level <8.0 mkg/ml can be used as a risk marker of atherosclerotic burden and might be helpful in non-invasive CAD prediction.

Subdivision 3. Clinical Studies

Presentation Preference Mini-oral presentation
Additional information
Complement receptor 1 (CR1) is involved in the binding of apo B-containing lipoproteins to circulating leukocytes.

Abstract nr. 85
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Co-author(s) - Castro Cabezas, Manuel
Topic Dyslipidemia; Lipids, Lipoproteins and Apolipoproteins
Keywords Apolipoproteins, Inflammation, Triglyceride-Rich Proteins

Background: Apolipoprotein (apo) B is present on the surface of blood cells. Several candidate receptors may be involved. Emerging evidence suggests a role for complement activation. Complement Receptor 1 (CR1) is a candidate receptor to contribute to cell-bound apo B-containing lipoproteins. We investigated whether apo B-containing lipoproteins bind to CR1 on native leukocytes.

Materials and methods: Complement activation ex vivo (15 minutes at 37 C°) was induced by bacterial lipopolysaccharides (LPS) and artificial triglyceride-rich lipoproteins (Lipoplus®). The expression of apo B and CR1 by monocytes and neutrophils was measured using flow cytometry. The expression of apo B and CR1 was expressed as mean percentage ± SD from baseline.

Results: Whole blood incubation with LPS resulted in an increase in apo B expression by both monocytes and neutrophils (211% ± 40%, p<0.05; 180% ± 18, p<0.05). A simultaneous increase in CR1 expression by monocytes and neutrophils was observed (586% ± 258% p<0.05; 1042% ± 758%, p<0.05), but no changes in LDL-R expression were observed. Similar results were obtained with Lipoplus, suggesting that triglycerides may induce complement activation in vivo.

Conclusions: Stimulation of leukocytes by LPS or Lipoplus resulted in a simultaneous increase in apo B and CR1 expression. This provides indirect evidence of CR1-mediated binding of apo B-containing lipoproteins to blood cells. Triglyceride-rich lipoproteins stimulate CR1 expression on leukocytes and may be the physiological trigger for the binding of apo B-containing lipoproteins to CR1 in vivo.

Subdivision 1. Basic Science
Presentation Preference: Oral presentation
Additional information
Complement Receptor 1 may be responsible for the binding of apolipoprotein B to circulating erythrocytes providing protection against atherosclerosis.

Abstract nr. 86
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Co-author(s) - Castro Cabezas, Manuel
Topic Dyslipidemia; Lipids, Lipoproteins and Apolipoproteins
Keywords Apolipoproteins, Atherosclerosis, Genetics

Background: Apolipoprotein (apo) B is present on the surface of circulating erythrocytes. A high presence of apo B on erythrocytes (ery-apoB) has been associated with protection against cardiovascular disease (CVD). Since erythrocytes do not carry classical LDL-receptors, other mechanisms must be involved. We aimed to investigate the role of Complement Receptor 1 (CR1) in the binding of apo B to erythrocytes.

Materials and methods: Subjects with and without CVD were included. Ery-apoB and CR1 expression were measured by flow cytometry. Functional CR1 polymorphisms (Pro1827Arg) were determined.

Results: In total 431 subjects were included. Ery-apoB was lower in males than in females (1.00±0.75 au vs. 1.18±0.96 au, p=0.035). Subjects with clinical CVD had lower ery-apoB (0.99±0.80 au) than healthy subjects (1.17±0.90 au, p=0.028). Ery-apoB was lower in subjects with high intima media thickness (IMT, >0.700mm) (0.94±0.81 au) than subjects with low IMT (1.15±0.87 au, p=0.016). Ery-apoB was inversely correlated with BMI (Spearmans rho=-0.138, p=0.004), diastolic blood pressure (rho=-0.108, p=0.026), triglycerides (rho=-0.137, p=0.004), complement C3 (rho=-0.144, p=0.003) and CRP (rho=-0.135, p=0.007) and positively correlated with serum HDL-C (rho=0.119, p=0.019). In 99 subjects functional CR1 polymorphisms were determined. Subjects with the wildtype CR1 polymorphism, associated with high erythrocyte CR1 expression, had higher levels of ery-apoB (n=65; 1.354±1.17 au) than subjects with a mutated CR1 polymorphism (n=34; 0.955±0.88 au; p=0.085).

Conclusions: These data suggest a role of CR1 in the binding of atherogenic lipoproteins to circulating erythrocytes, reflecting an anti-atherogenic mechanism. Surprisingly, several cardiovascular risk factors seem to be associated to ery-apoB.
Subdivision 1. Basic Science

Presentation Preference Oral presentation
Additional information
Korean traditional Chungkookjang improves lipid profile and atherogenic indices in overweight/obese subjects: a clinical trial

Abstract nr. 88
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Topic Primary & Secondary prevention of CVD; Lifestyle Measures and Pharmacological Intervention
Keywords Apolipoproteins, Lipids, Nutrition, Obesity

Chungkookjang is Korean representative fermented food with soybean, like Ganjang, Doenjang, Gochujang, and so on. This study was investigated to develop awareness and preference about Korean traditional Chungkookjang among young generation, by validating its health promoting benefits especially against lipid profile and atherogenic indices. There were 166 subjects as cross-over design; 83 subjects of 120 volunteers completed all procedure; aged 19–29 years old. They were randomized to double-blind treatment with either Chunkookjang 35g or placebo on a regular daily basis for 12 weeks. After 12 weeks wash-out period, the groups were crossed over. Chungkookjang group showed a significant decrease in serum levels of hs-CRP and LDL-C/HDL-C. Moreover, Apo A1 and Apo B were significantly improved in the Chungkookjang group. These results indicate that Chungkookjang has favorable effects on preventing and improving lipid profile and atherogenic indices in overweight and obese individuals.[This research was supported by the Globalization of Korean Foods R&D program, funded by Ministry of Food, Agriculture, Forestry and Fisheries, Republic of Korea.]
Keywords: Chungkookjang, fermented food, lipid profile and atherogenic indices

Subdivision 3. Clinical Studies

Presentation Preference Electronic poster presentation
Additional information
High-sensitivity C-reactive protein and cardiovascular risk factors in Type 2 diabetic patients with acute coronary syndrome

Abstract nr. 89
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Topic Epidemiology of CVD; The Risk Factor Concept
Keywords ACS, Diabetes, Risk Factor

Introduction. Elevated high-sensitivity C-reactive protein (hs-CRP) levels have frequently been shown to be associated with type 2 diabetes (T2D). Additionally, hs-CRP has also emerged as a powerful predictor of cardiovascular disease. Inflammation, indicated by hs-CRP and hyperglycemia, indicated by glycosylated haemoglobin (HbA1c), jointly contribute to the cardiovascular risk of patients with advanced atherosclerosis.

Objective. In this study, we assessed the correlation between hs-CRP and cardiovascular risk factors such as obesity, serum lipids and HbA1c in our local setting.

Methodology. A cross sectional study was conducted on 81 male patients with T2D who were admitted for acute coronary syndrome in the medical ward. This population was ethnically diverse comprising patients of Malay, Chinese and Asian Indian descent. Variables tested included HbA1c, serum triglyceride, high density lipoprotein (HDL) and body mass index (BMI). Hs-CRP was measured using ELISA technique.

Results. There was no significant correlation between hs-CRP and BMI (p=0.985), hs-CRP and HDL (p=0.939) and hs-CRP and triglyceride (p=0.404). However, there was significant correlation between hs-CRP and HbA1c (95%CI 0.18, 0.32 and p<0.001). The observed correlation coefficient, r=0.645, suggests positive and moderate correlation.

Conclusion. Our study showed that there was a positive correlation between hs-CRP and HbA1c levels in our local population. There was no significant correlation between hs-CRP and obesity and serum lipids. Future studies are required to evaluate the influence of modulators including genetic variations on the elevation of hs-CRP levels in this population subgroup.

Subdivision 4. Not applicable. Abstract matches with track c

Presentation Preference Electronic poster presentation
Additional information
Leukocyte Thrombomodulin Mediates Leukocyte Adhesion to Endothelium in Vascular Inflammation

Abstract nr. 90
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Topic The Pathogenesis of Atherosclerosis; Immunity, Inflammation, and the Endothelium
Keywords Atherosclerosis, Cardiovascular Disease

Thrombomodulin (TM) is a transmembrane glycoprotein composed of multiple domains and expressed in a variety of cell types. In response to vascular injury, endothelial cell-expressed TM can modulate inflammation through thrombin and protein C-dependent pathways. However, it is not clear whether leukocyte TM is involved in inflammation. We previously demonstrated that the lectin-like domain of TM can bind LewisY (LeY), which is upregulated in endothelial cells upon vascular inflammation and mediates cell adhesion. In this study, we investigated the interaction of leukocyte TM and LeY in facilitating the adhesion of leukocyte under inflammation. To test the role of TM in regulating leukocyte recruitment, carotid artery ligation was performed to induce vascular injury. Reduced leukocyte recruitment and neointima formation were observed in myeloid-specific TM deficient mice compared with those of wild-type mice. Knockdown of TM expression in human monocytic THP-1 cells resulted in decreased adhesion to activated endothelium under shear flow. We further investigated the involvement of LeY in the TM-dependent adhesion. Knockdown of TM or treatment of TM specific antibodies reduced the adhesion of THP-1 cells to LeY-immobilized surface under shear flow, indicating that the binding of TM and LeY facilitates THP-1 adhesion. The phosphorylation of p38, as well as, the activation of β2-integrin in THP-1 cells was induced by the addition of soluble LeY. In contrast, the effects were ameliorated when TM was knocked down. In conclusion, our results show that leukocyte TM interacts with LeY to elicit signal transduction leading to leukocyte adhesion to endothelium under vascular inflammation.

Subdivision 1. Basic Science

Presentation Preference Electronic poster presentation
Additional information
Initiation and progression of coronary atherosclerosis in WHHLMI rabbits

Abstract nr. 91
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Topic The Pathogenesis of Atherosclerosis; Immunity, Inflammation, and the Endothelium
Keywords Animal model, Atherosclerosis, Pathogenesis

Objectives: Myocardial infarction-prone Watanabe heritable hyperlipidemic (WHHLMI) rabbits shows severe coronary atherosclerosis spontaneously. It is unclear that the detailed process of the initiation and progression of coronary atherosclerosis in WHHLMI rabbits.

Methods: Coronary arteries were excised from 136 WHHLMI rabbits (1-29 months old). These arteries were fixed by neutral buffered formalin and sliced at 500 micro meter intervals. Sections were stained histopathologically and immunohistochemically (CD31 for endothelial cells, 1A4 for smooth muscle cells, or SMC and RAM-11 for macrophages), and lesion thickness and cross-sectional narrowing (CSN) were evaluated.

Results: Early lesions showed mainly intimal thickening with SMC proliferation at the bifurcation of arteries. However, infiltrations of macrophages were relatively dominant in the trunk compared to lesions at the bifurcation. Fibrous plaques were mainly observed in 30-<50% CSN. Layered plaques consisting of fibromuscular components and lipids/foam cells were increased with plaque growth. Pre-fibroatheroma, which has foam cell accumulation instead of lipid core, were decreased, and fibroatheroma were increased with further progression of plaques, respectively. Thin-capped fibroatheroma were frequent in >90% CSN. Vasa vasorum were observed in plaques with >50% CSN. Although macrophage/foam cell-rich lesions were rare in WHHLMI coronary plaques, foam cell-clusters layered on the plaque surface were observed occasionally.

Conclusions: This study suggest that the development of coronary lesions in WHHLMI rabbits are as follows; 1) the initiation of coronary lesions is intimal thickening, 2) macrophage infiltration and increase in fibromuscular components promote coronary plaques; 3) these lesions transfer to fibroatheroma and thin-capped fibroatheroma over time.

Subdivision 1. Basic Science

Presentation Preference Oral presentation
Additional information
Thrombomodulin interacts with fibronectin and promotes angiogenesis

Abstract nr. 92
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Topic The Pathogenesis of Atherosclerosis; Immunity, Inflammation, and the Endothelium
Keywords Angiogenesis,Atherosclerosis

Objective: Angiogenesis in an atherosclerotic plaque may contribute to the growth of lesions and lead to the recruitment of inflammatory cells to the plaque, resulting in chronic inflammation. Interaction of endothelial cells with extracellular matrix is critical for angiogenesis. Thrombomodulin (TM) is a cell surface glycoprotein; however, it remains unknown whether TM binds to extracellular matrix. Here, we investigate the interaction of TM with extracellular matrix and its biological roles in angiogenesis.

Methods: Solid-phase binding assays were used to assess recombinant TM lectin-like domain 1 (rTMD1) binding to extracellular matrix. The effects of TM expression on cell adhesion and migration were determined. We examined the association of TM in endothelial cells with fibronectin and analyzed the effects of TM knockdown on endothelial cell tube formation in vitro.

Results: The solid-phase binding assays showed that rTMD1 bound directly to the extracellular matrix fibronectin. Mapping analysis using various fibronectin fragments identified the N-terminal 70-kDa region of fibronectin as the TMD1-binding site. Overexpression of TM in TM-negative A2058 melanoma cells enhanced cell adhesion and migration on fibronectin, and led to increased focal adhesion kinase phosphorylation. Up-regulation of TM expression in endothelial cells promoted tube formation on Matrigel, whereas knockdown of TM expression by RNA interference reduced the tube formation. In addition, confocal microscopy analysis revealed that TM colocalized with fibronectin at tube-like structures during endothelial tube formation.

Conclusions: TM promotes cell adhesion, migration and angiogenesis by interacting with fibronectin. This implies that TM may play a role in angiogenesis-related diseases such as atherosclerosis.

Subdivision 1. Basic Science

Presentation Preference Electronic poster presentation
Additional information
CD40-Filamin A interactions are required for translocation of CD40 to lipid rafts in endothelial cells and for endothelial cell activation

Abstract nr. 93
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Topic The Pathogenesis of Atherosclerosis; Immunity, Inflammation, and the Endothelium
Keywords Atherosclerosis, Cardiovascular Disease, Endothelium, Inflammation

**Background and Aim:** CD40 is a member of the co-stimulatory tumor necrosis factor receptor superfamily that is constitutively expressed not only on professional antigen presenting cells like macrophages dendritic cells and B-cells, but also on endothelial cells. Interactions between CD40 and its ligand, CD40 ligand (CD40L) are crucial for proper immune cell activation. Activation of CD40 signaling plays a role in chronic diseases such as rheumatoid arthritis, inflammatory bowel disease and atherosclerosis. However, since CD40-CD40L interactions are also important in thrombosis, blocking these interactions has severe adverse side-effects. Therefore, in search for new therapeutic targets, we aimed to identify new CD40-binding partners.

**Methods and Results:** We created a cDNA library of murine aortas containing atherosclerotic plaques at various stages and performed a yeast-two-hybrid with the C-terminal domain of CD40 as bait. We identified filamin A as a novel CD40 binding partner in atherosclerosis, which was confirmed by co-immunoprecipitation. By confocal microscopy we showed in endothelial cells that, upon activation of CD40, filamin A was recruited to CD40. Filamin A binds to the intracellular domain of CD40, near the transmembrane domain, at a site distinct from the tumor necrosis receptor associated factor (TRAF) binding sites. Previous studies have shown that disruption of the lipid rafts in endothelial cells disrupts part of the CD40 signaling cascade and we found that knock-down of filamin in endothelial cells using siRNAs inhibits the translocation of CD40 to lipid rafts upon activation of CD40 signaling. This inhibition of CD40 translocation resulted in repression of CD40-mediated Akt signaling but not of CD40-mediated JNK signaling and subsequent inhibition of VCAM-1 and CCL-2.

**Conclusions:** We show that CD40 interacts with filamin A in endothelial cells. This interaction is involved in translocation of CD40 to the lipid rafts and CD40-mediated activation of the Akt pathway. The reduced upregulation of VCAM-1 and CCL-2 makes this an interesting target for novel therapies where reduced leukocyte recruitment is favorable.

Funding: The Netherlands Organization for Scientific Research, a Vici grant to E.L.
Subdivision 1. Basic Science

Presentation Preference Oral presentation
Additional information
In vitro oxidation of LDL and its in vivo implication: A comparative study of Iranians living in IRAN and in India

Abstract nr. 94
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Topic Epidemiology of CVD; The Risk Factor Concept
Keywords Atherosclerosis, HDL, LDL, Lifestyle

According to the Cholesterol-Diet-Heart theory, Low Density Lipoprotein associated cholesterol (LDL-C) was the cause of atherosclerosis. However, over three decades of rigorous efforts to reduce LDL-C have not resulted in any significant decrease in the mortality rates due to heart diseases. On the contrary, oxidized LDL (ox-LDL) correlated with the risk of heart diseases and was a far superior marker than all other lipid markers.

Since in vitro studies aim at understanding the in vivo mechanisms, we undertook a study to compare the in vitro oxidation on serum LDL of Iranians living in Iran and in India. The isolated LDL was subjected to oxidation in vitro by water soluble and fat soluble antioxidants. Iranians living in Iran had lower levels of oxidized lipids in their serum compared with Iranians living in India. The lag phase of oxidation was significantly longer (P<0.05) and they had higher level of antioxidants in their serum compared with the Iranians living in India. Iranians living in India had higher levels of oxidized lipids in the serum, the lag phase of LDL oxidation was short, there were protein oxidation products in the LDL and the antioxidant levels in the serum were low. The LDL oxidation profile resembled that of Indians living in similar conditions. The High Density Lipoprotein (HDL) of Iranians living in India was highly oxidized and was comparable to that of the Indians.

A major significant difference in the lifestyle of Iranians living in Iran and in India was the dietary oil they used. Iranians in India used popular brands of cooking oils. These oils are rich in polyunsaturated fatty acids and in ω-6 fatty acids. These fatty acids would become incorporated into the LDL and would be highly susceptible to oxidation. Although the HDL could prevent the LDL oxidation, since it is already oxidized it may be unable to prevent LDL oxidation.

Taken together, these results suggest that the dietary oil may be responsible for higher level of oxidized LDL in Iranians living in India and of Indians.

Subdivision 4. Not applicable. Abstract matches with track c

Presentation Preference Electronic poster presentation
Additional information
Probucol rescued litter size and gender ratio in reproduction of hypo-lipoproteinemia model mice

Abstract nr. 95
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Topic Dyslipidemia; Lipids, Lipoproteins and Apolipoproteins
Keywords HDL, Lipoproteins

Low plasma HDL mice, such as ABCA1-null mice, Lcat-null and ABCA1 inactivator, probucol-fed mice have significantly low cholesterol content in their adrenal glands and ovaries. Upon reproduction between heterozygotes, the reproduction of ABCA1-null weaned pups were reduced to 30% of that expected by Mendelian genetics, and ABCA1 heterozygote male pups was reduced to 75% of female heterozygote pups. Lcat-null male pups was also reduced to 31% of that expected by Mendelian genetics. Gender ratio in reproduction of wild type, and 0.2% probucol fed mice were 1 to 1 in the same mating condition. Interestingly, although 0.2% probucol-fed mice reduced its plasma HDL only to 5% within 2 weeks, probucol-fed mice reproduced normally. This result suggesting some beneficial functions of probucol may protect pups’ from death by this chow treatment. Thus, we fed probucol containing chow to ABCA1 heterozygote or LCAT heterozygote mice upon mating to the lactation period. Here, significance in the Chi- squared analysis disappeared on the gender ratio in these weaned mice as well as the litter size. HMGCoA reductase expression was increased in adrenal of probucol-fed wild type mice indicate increased cholesterol de novo synthesis may supply enough cholesterol for steroid synthesis during their reproduction in these low HDL mice. Probucol-HDL (1.00 µg probucol / µg HDL-protein) derived probucol into NCI-H295 human adrenal cortex cells (0.73±0.12 µg probucol / mg cellular protein). The expression of HMGCoA reductase was significantly increased compared to b-actin. The further mechanism to increase cellular cholesterol synthesis by Probucol will be examined.

Subdivision 1. Basic Science

Presentation Preference Electronic poster presentation
Additional information
The differential roles for Nox isoforms in the development of diabetes associated atherosclerosis

Abstract nr. 96
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Topic The Pathogenesis of Atherosclerosis; Immunity, Inflammation, and the Endothelium
Keywords Atherosclerosis, Cardiovascular Disease, Diabetes

Individuals diagnosed with diabetes have accelerated development of atherosclerosis; however the mechanisms are poorly understood. Oxidative stress appears to play a significant role, specifically Nox-derived ROS, for which there are two principal isoforms Nox1 and 4 which are upregulated in activity by glucose. The aim of this study was to delineate the role of Nox-derived oxidative stress in the development of diabetes-related atherosclerosis.

Nox isoform specific-ApoE-/- double knockout mice, Nox1-/-ApoE-/- and Nox4-/-ApoE-/- mice were rendered diabetic by streptozotocin (55mg/kg/day for 5 days), with non-diabetic wildtype mice serving as controls. Animals were diabetic for 20 weeks at which point aortas were removed and cleaned for analysis.

After 20 weeks, diabetic wildtype mice had a significant elevation in atherosclerosis compared to non-diabetic counterparts. Deletion of the Nox1 isoform in diabetes resulted in a 50% reduction in atherosclerosis development. In contrast, deletion of the Nox4 isoform in diabetes resulted in a 65% increase in atherosclerosis development. Aortic RT-PCR demonstrated a significant reduction in gene expression of markers for oxidative stress, inflammation (MCP-1, IL1β, TNFα) and fibrosis (Collagen I) in Nox1-/-ApoE-/- diabetic mice, which were significantly elevated in diabetic Nox4-/-ApoE-/- diabetic mice. Immunohistochemistry analysis of the aorta identified a significant decrease in pro-oxidant markers and macrophage infiltration in diabetic Nox1-/-ApoE-/- mice, which were significantly elevated in diabetic Nox4-/-ApoE-/- mice.

These data demonstrate opposing effects of two Nox isoforms in diabetes associated atherosclerosis, Nox1 playing a pathological role, where in turn Nox4 derived ROS plays a vasculo-protective role in atherosclerosis development.

Subdivision 1. Basic Science

Presentation Preference Oral presentation
Additional information
Pharmacological inhibition of Nox as both a Primary and Delayed Intervention Attenuates Atherosclerosis Development in Diabetes.

Abstract nr. 97
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Topic Primary & Secondary prevention of CVD; Lifestyle Measures and Pharmacological Intervention
Keywords Atherosclerosis,Diabetes,Prevention

The development of atherosclerosis in diabetes is significantly accelerated, contributing to increase incidence of stroke and heart attack. The cause for the acceleration in atherosclerosis development in diabetes is largely unknown; however, oxidative stress appears to be an essential mediator in its development. Members of the NAD(P)H oxidase (Nox) family have been identified to play a causative role in the promotion of atherosclerosis development. It has been demonstrated that Nox1, when deleted in diabetic mice attenuates atherosclerosis development. Targeting these enzymes pharmacologically is of novel interest to attenuate atherosclerosis development, particularly in diabetes.

We aimed to explore the pharmacological potential of Nox inhibition using GKT137831 in attenuating the development of atherosclerosis in diabetes.

ApoE\(^{-/-}\) mice were rendered diabetic at 6 weeks of age using streptozotocin injections, saline injected ApoE\(^{-/-}\) mice served as controls. Mice were randomly allocated into three groups, vehicle treated, primary GKT137831 intervention (30mg/kg/day, 0wks to 20wks) and delayed GKT137831 intervention (30mg/kg/day, 10wks to 20wks). After 20 weeks animals were culled with aortas removed for assessment of atherosclerosis development, immunohistochemical analysis, RT-PCR and ELISA.

After 20wks of diabetes, atherosclerosis was significantly increased compared to controls. Administration of GKT137831 as both a primary and delayed intervention was able to attenuate the development of atherosclerosis in diabetes. Assessment of the oxidative stress marker Nitrotyrosine demonstrated a significant increase in vehicle treated diabetic mice; with a significant attenuation in diabetic mice administered GKT137831 as both primary or delayed intervention. Analysis of pro-inflammatory and chemotaxis markers by RT-PCR identified significant upregulation in MCP-1 and TNFα expression in vehicle treated diabetics, which was attenuated with GKT137831 treated as both a primary and delayed intervention.

Taken together, these results highlight the potential of targeted Nox inhibition in the prevention of
atherosclerosis and attenuation of established atherosclerosis.

Subdivision 1. Basic Science

Presentation Preference Oral presentation
Additional information
Abnormal HDL particles distribution in coronary artery disease patients

Abstract nr. 98
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Topic Dyslipidemia; Lipids, Lipoproteins and Apolipoproteins
Keywords Atherosclerosis, HDL, Lipoproteins

Low concentration of HDL-C is associated with higher cardiovascular disease risk. HDL are composed of heterogeneous particles with different in size, density, composition and functions.

Aim. To study the HDL particles distribution in patients differing by coronary artery disease (CAD) severity.

Materials and methods. Patients with CAD verified by coronary angiography (n=130; 30-80 yrs) were included into study. All patients were treated with statins. HDL subfractional distribution was analyzed using Lipoprint System (Quantimetrix, USA).

Results. Patients were divided into three groups according to CAD severity estimated by Gensini score (GS): group 1 - GS=0, n=40; group 2 - GS =1-34, n=40; group 3 - GS ≥35, n=50. No differences between groups in HDL-C level were found. CAD patients (groups 2 and 3) as compared to group 1 had higher portion of small HDL (20,3±7,5 and 19,0±7,2 vs 16,1±5,9%; p<0,01) and intermediate HDL (46,4±4,8 and 46,2±4,6 vs 44,6±4,5%; p<0,05) and the lower portion of large HDL (32,9±7,5 and 34,6±9,0 vs 39,2±9,0%; p<0,01). The negative Spearman rank correlation between TG level and large, intermediate and small HDL particles was obtained in CAD-free patients (R= -0,354; -0,509; and -0,435; p=0,005). In group 2 the correlation was found only between TG level and intermediate HDL particles (R= -0,369; p<0,02).

Conclusions. The difference in HDL particles distribution is associated with cardiovascular manifestations severity with the predominance of smaller HDL particles and lower portion of large HDL particles. Thus, an abnormal distribution of HDL particles was found already in patients with mild-to moderate atherosclerosis (GS 1-34).

Subdivision 1. Basic Science

Presentation Preference Electronic poster presentation
Additional information
Efficacy and Safety of Pitavastatin at Adult Doses in Children between 6 and 17 years at High Future Cardiovascular Risk

Abstract nr. 99
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Topic Primary & Secondary prevention of CVD; Lifestyle Measures and Pharmacological Intervention
Keywords Dyslipidemia, Familial Hypercholesterolemia, Pharmacology, Prevention

Objectives:
Elevated low-density lipoprotein cholesterol (LDL-C) is a risk factor for coronary heart disease (CHD) in adults, but the underlying atherogenesis begins in childhood. Therefore guidelines recommend consideration of statin therapy in children at high future CHD risk. The aim of the study was to assess the safety and efficacy of the adult dose range of pitavastatin, a relatively new member of the statin class, in hyperlipidemic children and adolescents, the youngest starting at the age of 6.

Study design:
A total of 106 hyperlipidemic children and adolescents, (48 boys and 58 girls; 43 between 6-9 years; 50 between 10-14 years; 13 ≥15 years) were enrolled in a 12 week randomized, double blind, placebo controlled study and randomly assigned to pitavastatin 1 mg, 2 mg, 4 mg or placebo. During a 52 week extension period, subjects were up-titrated from 1 mg pitavastatin to a maximum dose of 4 mg in an effort to achieve an optimum LDL-C treatment target of <110 mg/dL (2.8 mmol/L). Safety was assessed in terms of adverse events rates, including abnormal clinical laboratory variables, vital signs and physical examination.

Results:
Mean baseline LDL-C was 232.9 (±52.0) mg/dL and 97.2% of the children had genetically confirmed familial hypercholesterolemia. At 12 weeks LDL-C was reduced by 24.5%, 31.1% and 40.3% against placebo in the 1 mg, 2 mg and 4 mg group, respectively. In the open label study 20.5% of the subjects reached the LDL-C goal <110 mg/dL (2.8 mmol/L). Drug-related treatment emergent adverse events were present in 10 subjects (8.9%) of the open label study, most commonly musculoskeletal/connective tissue disorders (2.7%) and nervous system disorders (2.7%). All were considered of mild (7.1%) or moderate intensity (1.8%) by the investigator and not dose related. No clinically significant differences in clinical laboratory variables, vital signs and
physical examination were observed.

**Conclusion:**
The whole adult dose range of pitavastatin is well tolerated and efficacious in hypercholesterolemic children and adolescents aged 6-17 years.

**Subdivision 3. Clinical Studies**

**Presentation Preference** Oral presentation

**Additional information**
Gender differences in the adipose tissue macrophage subpopulation

Abstract nr. 100
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Topic The Pathogenesis of Atherosclerosis; Immunity, Inflammation, and the Endothelium
Keywords Elderly, Inflammation, Visceral Fat

Aim: The presence of pro-inflammatory macrophages (CD14+CD16+) in inflamed tissue has been documented in several inflammatory conditions including atherosclerosis. The aim of the study is to analyse the proportion of pro-inflammatory macrophages in the perirenal fat of men and women of pre-menopausal and menopausal age.

Methods: Samples of perirenal fat were obtained while kidneys were isolated in living donors, then the samples were dissected into small pieces and exposed to collagenase. Stroma vascular fraction (SVF) was eluted and analysed using flow cytometry. Mononuclear cells expressing CD14 were identified as macrophages and further divided according to the co-expression of CD16.

Results: We found no differences in the total macrophage content between men (n=15) and women (n=28). However, we observed a higher proportion of double positive CD14+CD16+ macrophages in post-menopausal women (age<51 years, n=14) than pre-menopausal women (n=14) (45±14 vs. 58±8%; p<0.01). In addition, a correlation (p<0.05) between CD14+CD16+ macrophage content and age was found in post-menopausal women, whereas no such relationship was found in the other groups.

Conclusion: The macrophage subpopulation in adipose tissue may depend on gender and age.

Subdivision 1. Basic Science

Presentation Preference Electronic poster presentation

Additional information
UNVEILING THE PLAYERS OF OBESITY

Abstract nr. 101
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Topic Epidemiology of CVD; The Risk Factor Concept
Keywords Diabetes, Obesity

BACKGROUND
Obesity is a silent killer and a forerunner of many complications if persists long. Various studies with animal model have identified the role of leptin, the hormone of adipose tissue; in obesity and its associated complications like diabetes and atherosclerosis in later stages. The exact mechanism to know how leptin influences insulin action in body and thereby leading to diabetes or post diabetic atherosclerosis is still not completely evaluated. Hypercholesterolemia was only found common to all these three states. The present study, therefore, evaluated the role of obesity on the expression of LDLR receptor, INSULIN receptor and LEPTIN receptor.

METHOD
Receptor expression was done by immunohistochemistry/ western blot. The serum level of lipids were measured by enzyme based kit method. The serum level of insulin and leptin and its soluble receptor were measured by elisa based kit.

RESULTS
The blot for insulin expression shows no change with body weight; the blot for leptin receptor shows decrease expression with weight gain and blot for LDLR shows decrease expression with weight gain. The serum levels of insulin and leptin are increased with weight gain but soluble receptor for leptin did not change significantly. Even the obese group showed decrease tyrosine phosphorylation of insulin receptor.

CONCLUSION
This study has given some possible reasons of the inter-association of hyperleptinemia, hypercholesterolemia and hyperinsulinemia by showing possibilities of inactivation of insulin and LDLR receptor with leptin resistance.

Subdivision 3. Clinical Studies

Presentation Preference Mini-oral presentation

Additional information
P-Hydroxybenzyl alcohol-containing biodegradable nanoparticle improves functional blood flow perfusion through angiogenesis in a mouse model of hindlimb ischemia

Abstract nr. 102
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Topic Primary & Secondary prevention of CVD; Lifestyle Measures and Pharmacological Intervention
Keywords Angiogenesis

Therapeutic angiogenesis has achieved promising results for ischemic diseases or peripheral artery disease in preclinical and early-phase clinical studies. We examined the therapeutic angiogenic effects of HPOX, which is biodegradable polymer composing the antioxidant p-hydroxybenzyl alcohol (HBA), in a mouse model of hindlimb ischemia. HPOX effectively stimulated blood flow recovery, compared with its degraded compounds HBA and 1,4-cyclohexandimethanol, via promotion of capillary vessel density in the ischemic hindlimb. These effects were highly correlated with levels of angiogenic inducers, vascular endothelial cell growth factor (VEGF), heme oxygenase-1 (HO-1), and Akt/AMPK/endothelial nitric oxide synthase (eNOS) in ischemic mouse hindlimb muscle. Blood perfusion and neovascularization induced by HPOX were reduced in eNOS-/- and HO-1+/- mice. HPOX also elevated the endothelial cell markers VEGF receptor-2, CD31, and eNOS mRNAs in the ischemic hindlimb, indicating that HPOX increases endothelial cell population and angiogenesis in the ischemic muscle. However, this nanoparticle suppressed expression levels of several inflammatory genes in ischemic tissues. These results suggest that HPOX significantly promotes angiogenesis and blood flow perfusion in the ischemic mouse hindlimb via increased angiogenic inducers, along with suppression of inflammatory gene expression. Thus, HPOX can be used potentially as a noninvasive drug intervention to facilitate therapeutic angiogenesis.
HPOX increases angiogenesis-regulatory gene expression in the ischemic mouse hindlimb.

HPOX improves blood flow recovery and neovascularization in the ischemic mouse hindlimb.

Subdivision 1. Basic Science

Presentation Preference Electronic poster presentation

Additional information
THE SIGNIFICANCE OF TRACE ELEMENTS IN THE DEVELOPMENT OF CAROTID ATHEROSCLEROSIS

Abstract nr. 103
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Topic The Pathogenesis of Atherosclerosis; Immunity, Inflammation, and the Endothelium
Keywords Atherosclerosis, Pathogenesis

Purpose: Study of relationships of intima - media thickness of common carotid artery (IMT CCA) and trace elements in hair at patients with carotid atherosclerosis (CA)

Methods and Materials: 132 patients with CA and 18 healthy individuals (mean age 61.2 and 64.4 years) were included in study. IMT CCA is measured at duplex scanning by HD3 ultrasound Phillips) with linear transducer 5-7.5 MHz. The levels of trace elements (TE) in hair were determined by ICP -OES (Optima-2400DV (USA). Examined trace elements Fe, Cu, Al, Zn, Cd, Se, Ca, K, Na, Mg and the relationship Cu / Fe, Mg / Fe, Zn / Fe, Mg / Zn, Ca / Mg, K / Na, Zn / Cu, Cu / Zn in hair.

Results: IMT CCA in patients was higher than in healthy group (0.98 ± 0.37 mm vs. 0.78 ± 0.27 mm, p <0.005). Revealed a significant negative correlation between IMT CCA and the level of Zn in hair (r = -0.48, p <0.05), while a positive correlation between IMT CCA and Cu levels in hair (r = 0.42, p <0.05), Mg (r = 0.47, p <0.05), Cd (r = 0.44, p <0.05) and the ratio of Cu / Zn (r = 0.41, p <0.05). Linear regression analysis was confirmed that the levels of Mg and Cd in hair and the ratio of Cu / Zn positively correlated with IMT CCA.

Conclusion: Identified relationships can be useful to clarify the pathogenetic mechanisms of atherosclerosis.

Subdivision 3. Clinical Studies

Presentation Preference Electronic poster presentation
Additional information
Association between Carotid Arteriosclerosis and Cardio Ankle Vascular Index (CAVI)

Abstract nr. 104
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Topic Epidemiology of CVD; The Risk Factor Concept
Keywords Atherosclerosis

[Aim] CAVI is a simple and useful examination to estimate arterial stiffness, but carotid arteries are not included among the target arteries in this examination. The aim of this study was to determine the relationship between carotid arteriosclerosis and CAVI.

[Methods] The study population was comprised of 1418 individuals (839 men and 579 women; mean age 55.9±11.5 years) who underwent annual health checks at our institute. This study was a cross-sectional analysis using clinically-relevant demographic and biochemical data. Carotid arteriosclerosis was estimated by intimal-media thickening (IMT) using ultrasonography; IMT value of <1.1 was considered normal. The thickest IMT of 6 sections of right and left common carotid artery, bifurcation, and internal carotid artery was defined as max IMT. CAVI was measured using pulse wave velocity. A mean of right and left CAVI value of <9 was considered normal. Data were analyzed using t-test, chi-square test, and multiple regression analysis; significance was considered at p<0.05.

[Results] Among various laboratory data, age, mean blood pressure, fasting plasma glucose (FPG), and max IMT were significantly higher in the high CAVI group (n=146). The correlation ratio of max IMT with CAVI was 0.351. Multiple regression analysis showed that age (β=0.616), waist circumference (β=-0.168), mean blood pressure (β=0.187), FPG (β=0.062), HDL-cholesterol (β=-0.067), and max IMT (β=0.044) were independent predictors of CAVI (R²=0.482).

[Conclusion] Carotid arteriosclerosis is associated with CAVI

Subdivision 4. Not applicable. Abstract matches with track c

Presentation Preference Electronic poster presentation
Additional information
Perivascular adipose tissue and coronary atherosclerosis

Abstract nr. 105
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Topic The Pathogenesis of Atherosclerosis; Immunity, Inflammation, and the Endothelium
Keywords Atherosclerosis, Inflammation, Pathogenesis

Ectopic fat plays an important role in the development of insulin resistance and pro-atherogenic metabolic conditions. Recently, studies have shown a more direct effect of adipose tissue surrounding artery.

Methods: We analyzed perivascular adipose tissue size around the left coronary artery as well as macrophage content of this tissue and the coronary artery wall in 96 explanted hearts during heart transplantation. Two groups with different reasons for heart failure were compared – coronary heart disease (CHD n=49) and dilatation cardiomyopathy (DCMP n=47).

Results: Perivascular adipose tissue size around the left coronary artery was not different in CHD (96.4 ± 83.1 mm²) and DCMP groups (91.1 ± 77.1 mm²). This result is in disagreement with indirectly analyzed literary data using computer tomography. The fraction area occupied by macrophages (CD68+ cells) in the coronary artery was five times higher in CHD patients (1.27 ± 1.68) compared to patients with DCMP (0.26 ± 0.28, p<0.001), whereas we detected no difference in the surrounding adipose tissue. During analysis of the correlation between macrophages in the arterial wall and the surrounding adipose tissue, we found no correlation in the DCMP group (A) but a highly significant correlation in the CHD group (p<0.005) (B).

Conclusion: Perivascular adipose tissue size does not play any role in the development of atherosclerosis in the coronary artery. It is supposed that an interplay between adipose tissue and artery wall macrophages is very important in CHD but is not involved in DCMP.

Supported by grant IGA MZ CR NT 14009/3.
Subdivision 1. Basic Science

Presentation Preference Oral presentation

Additional information
HOMOCYSTEINEMIA AND DEVELOPMENT OF CORONARY ARTERY DISEASE

Abstract nr. 106
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Topic Epidemiology of CVD; The Risk Factor Concept
Keywords Atherosclerosis

Objective. The aim of the study was to establish if there is correlation between total plasma homocysteine (tHcy) levels with occurrence and development of coronary artery disease (CAD).

Material and methods. Total number of 165 patients were examined which were divided into 3 groups based on 10 years risk for CAD established according ATP III and Framingham criteria: high risk group consist 60 patients with CAD risk above 20%; group of 49 patients with angiographyally proven CAD and 56 patients, control group, with CAD risk less than 10%. All patients were evaluated for the following risk factors and markers: sex, age, smoking status, hypertension, family history of CAD, lipids, lipoproteins, glucose, white blood cells, urea and creatine.

Results. Mean plasma tHcy levels in high risk group were 16.0 micromol/L (p<0.04), in the group with CAD, 15.3 micromol/L respectively (p<0.02) vs. control (13.0 micromol/L). There was correlation between tHcy and total CAD risk (p<0.04) and white blood cells count (0.02) in high risk group. In the group with CAD, tHcy correlated with the frequency of high grade of coronary artery stenosis, >95% of arterial lumen (0.04).

Conclusion. We concluded that elevated tHcy correlated with the total CAD risk and the stage of coronary artery disease.
Intrplaque hemorrhage of basilar artery atherosclerosis: Prevalence and Clinical Relevance

Abstract nr. 107
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Topic Epidemiology of CVD; The Risk Factor Concept
Keywords Atherosclerosis, Vulnerable Plaque

Purpose: The aim of this study was to evaluate the prevalence and clinical relevance of intraplaque hemorrhage (IPH) in patients with basilar artery (BA) atherosclerosis using high-resolution magnetic resonance imaging (HRMRI).

Methods: We retrospectively analyzed the HRMRI and clinical data of 74 patients (44 symptomatic and 30 asymptomatic) with >50% BA stenosis. High-signal intensity within a BA plaque on magnetization-prepared rapid acquisition with gradient echo (MPRAGE) and/or simultaneous noncontrast angiography and intraplaque hemorrhage imaging (SNAP) was defined as an area with an intensity >150% of the signal of adjacent muscle. The relationship between IPH within BA plaque and clinical presentation was analyzed.

Results: IPH was revealed on HRMRI in 30 patients (42.3%, 24 symptomatic and 6 asymptomatic). IPH of BA plaque in symptomatic patients was significantly higher prevalence compared with asymptomatic patients (54.5% vs 20%, p = 0.006). The stenotic degree of BA plaque between IPH group and non-IPH group was significantly different (72.9 ±8.7 vs 62.2 ± 31.2, p = 0.001).

Conclusions: IPH within BA plaque on HRMRI is relatively high prevalence and associated with acute stroke.

Subdivision 3. Clinical Studies

Presentation Preference Electronic poster presentation
Additional information
ERECTILE DYSFUNCTION IS ASSOCIATED WITH LOW TOTAL SERUM TESTOSTERONE LEVELS AND IMPAIRED FLOW-MEDIATED VASODILATION

Abstract nr. 108
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Topic The Pathogenesis of Atherosclerosis; Immunity, Inflammation, and the Endothelium
Keywords Atherosclerosis, Endothelium

Background: The value of testosterone levels and erectile dysfunction (ED) as early markers of atherosclerosis is not well understood.

Objectives: To analyze the relationship between plasma testosterone levels in men with both endothelial function (EF) and ED.

Methods: We enrolled 802 asymptomatic, intermediate cardiovascular risk patients, according to the Framingham Risk Score, aged 40 to 80 years, who underwent the study of EF, evaluation of ED and dosage of plasma testosterone.

Results: Testosterone levels correlated both with FMD (r = 0.85; p<0.0001) and IIEF-5 score (rs = 0.65; p<0.0001). At multivariable logistic regression analysis, lower serum testosterone levels were strongly associated (p < 0.001) with severe (OR 0.78; CI 0.62 - 0.86), and moderate ED (OR 0.85; CI 0.72 - 0.97), while worse EF was strongly associated (p < 0.001) with severe (OR 0.68; CI 0.59 - 0.79), moderate (OR 0.76; CI 0.63 to 0.83) and mild to moderate ED (OR 0.8; CI 0.69 to 0.94). Even mild ED resulted statistically associated worse EF (OR 0.94; CI 0.82 - 1.07; p=0.03) but not with serum testosterone levels. These relations were not substantially affected by adjustments for further potential confounders including smoking status, hypertension, diabetes mellitus and body mass index.

Conclusions: We demonstrated a significant correlation between ED, worse EF and testosterone plasma levels in a primary prevention population, therefore low testosterone levels may be considered as early markers of atherosclerosis.

Subdivision 3. Clinical Studies

Presentation Preference Oral presentation
Additional information
Interaction of the Adipophilin with Acyl-coenzyme A:Cholesterol Acyltransferse 1 and Neutral Cholesterol Ester Hydrolase in Lipid-loaded Macrophages

Abstract nr. 109
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Topic The Pathogenesis of Atherosclerosis; Immunity, Inflammation, and the Endothelium
Keywords Atherosclerosis,Lipids,Metabolism

**Aim** To explore whether adipophilin interact with acyl-coenzyme A:cholesterol acyltransferse 1 (ACAT1) and neutral cholesterol ester hydrolase (NCEH) in lipid-loaded RAW264.7 cell induced by oxidized low density lipoprotein (ox-LDL). **Methods** RAW264.7 cells were incubated with 50 mg/L ox-LDL for different time. The expression of mRNA and proteins of adipophilin, ACAT1 and NCEH were detected by semi-quantitative reverse transcription-polymerase chain reaction and western blot respectively. Interactions between adipophilin and ACAT1 or NCEH were detected by co-immunoprecipitation. **Results** As the incubation time of ox-LDL was extended in RAW264.7 cells, the expression of mRNA and proteins of adipophilin, ACAT1 and NCEH were significantly increased compared with 0 h group (P<0.05, n3). Co-immunoprecipitation showed that there were interactions between adipophilin and ACAT1 in RAW264.7 macrophages with ox-LDL treatment at 0, 0.5, 1 h and 3 h, and no interactions at 6 h. There were not interactions between adipophilin and NCEH in RAW264.7 macrophages with ox-LDL treatment at 0, 0.5 h and 1 h, and interactions at 3 h and 6 h. **Conclusion** There were interactions between adipophilin and ACAT1 or NCEH in RAW264.7 macrophages with ox-LDL treatment. It suggests that adipophilin may have synergistic effects with ACAT1 and NCEH in lipid-loaded RAW264.7 cell.

Subdivision 1. Basic Science

Presentation Preference Electronic poster presentation

Additional information
Association between the estimated glomerular filtration rate and subclinical atherosclerosis in patients with and without hypertension

Abstract nr. 110
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Topic Epidemiology of CVD; The Risk Factor Concept
Keywords Atherosclerosis, Cardiovascular Disease, Hypertension, Prevention

Purpose: Atherosclerosis as a chronic, progressive, inflammatory disease with a long asymptomatic phase can be undiagnosed through years, until the occurrence of acute cardiovascular and/or cerebrovascular events. Revealing of factors, which are simple and cheap to assess and might indicate subclinical atherosclerosis, have highest importance. Aim of the study was to investigate relationship between existence and severity of coronary and carotid artery atherosclerosis and glomerular filtration rate (GFR).

Methods: 447 patients (mean age±SD, 63.9±11.6 years), 238 females and 209 males were included in the study. 334 of them had arterial hypertension (AH) and 113 normal blood pressure. Assessment of GFR, coronary angiography and carotid artery ultrasound was performed in all patients. Gensini score was used for assessment of coronary artery disease severity.

Results: In comparison with hypertensives, normotensive subjects had significantly higher GFR (78.6±19.2 vs 70.8±20.8; P=0.001). GFR showed negative correlation with the stage of AH (r=-0.195; P=0.000). According to the Gensini score level, hypertensive patients had more severe atherosclerotic lesions of coronary arteries than normotensives (43.47±49.41 vs 21.81±37.00; P<0.05). GFR showed strong negative correlation with the Gensini score independent from the having of AH (r=-0.252, P=0.000 in Hypertensives and r=-0.297, P=0.000 in Normotensives, consequently). Right carotid artery (RCA) was more frequently and markedly damaged with atherosclerosis in comparison with left carotid artery (LCA). GFR showed significant correlation with the level of carotid artery damage in hypertensive and normotensive populations (r=-0.258, P=0.000 in hypertensives and r=-0.362, P=0.000 in normotensives, consequently). There was revealed strong positive correlation between coronary artery atherosclerosis expressed in Gensini scores and carotid artery atherosclerotic damage severity in both, hypertensive and normotensive populations (r=0.791, P=0.000 LCA, r=0.802, P=0.000 RCA in normotensives and r=0.745, P=0.000 LCA, r=0.769, P=0.000 RCA in hypertensives, respectively).

Conclusions: Results of our study point out that existence and severity of coronary and carotid artery atherosclerosis is significantly related with GFR. Possibility of coronary and carotid artery atherosclerosis rises with decrease of GFR. Therefore, patients with decreased GFR may be considered as a high risk group for subclinical atherosclerosis and undergo carotid and coronary artery atherosclerosis assessment examinations.
Subdivision 3. Clinical Studies

Presentation Preference Oral presentation
Additional information
Liposomal prednisolone inhibits vascular inflammation and enhances maturation of arteriovenous fistulas in mice

Abstract nr. 111
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Topic Primary & Secondary prevention of CVD; Lifestyle Measures and Pharmacological Intervention
Keywords Animal model, Inflammation, Intervention

BACKGROUND
Arteriovenous fistulas (AVFs) for hemodialysis access have a 1-year primary patency of only 60%, mainly as a result of maturation failure that is caused by insufficient outward remodeling (OR) and intimal hyperplasia (IH). The exact pathophysiology remains unknown, but the local inflammatory vascular response is thought to play an important role. Corticosteroids are powerful inhibitors of inflammation that suffer from unwanted side effects when given systemically. In the present study, we evaluated the effect of prednisolone on AVF maturation using a targeted liposomal delivery method in a murine model of AVF failure.

METHODS
First, the effect of liposomal prednisolone on vascular smooth muscle cells (VSMCs) and macrophages was evaluated in vitro. Next, AVFs between the jugular vein and common carotid artery were created in and end-to-side manner in C57BL/6 mice. The animals were then injected (dose 10 mg/kg) with liposomal prednisolone phosphate, liposomal PBS, prednisolone phosphate or PBS at days 0, 2, 5 and 10. Fluorescent-labeled liposomes were injected in a separate group of mice. At time of scarification (day 14), the labeled liposomes were visualized using near-infrared fluoroscopy. In addition, histomorphometric analysis of the venous outflow tract was performed and the composition of the venous wall was evaluated using immunohistochemistry.

RESULTS
Incubation with liposomal prednisolone resulted in a strong reduction of IL-6 and MCP-1 in cultured macrophages while no effect of VSMC proliferation was observed. The in vivo studies revealed that the fluorescent liposomes were mainly detected in macrophages in the anastomotic
area of the AVF (Fig 1). Histomorphometrically, mice treated with liposomal prednisolone had an increased venous circumference and lumen (p<0.01; p<0.03) when compared to the PBS group (Fig 2). Furthermore, we observed a strong reduction in infiltrating CD45+ cells in the liposomal prednisolone group (p<0.01).

**CONCLUSION**

Liposomes proved to be an effective delivery method to target vascular inflammation in AVFs. Liposomal prednisolone results in enhanced outward remodeling of murine AVF.

**Figure 1**

Green-fluorescent-labeled liposomes accumulated at the anastomosis of the AVF. a: carotid artery. v: jugular vein. colocalization of gold-labeled liposomes and CD68+ macrophages in the anastomatic area of murine AVF.

**Figure 2**

Representative HPS-stained sections of the venous outflow tract of murine AVF of (A) PBS-treated, (B) prednisolone-treated and (C) liposomal prednisolone-treated mice.

**Presentation Preference** Oral presentation

**Additional information**
Cardiometabolic risk factors and epicardial adipose tissue in children and adolescents

Abstract nr. 112
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Topic Epidemiology of CVD; The Risk Factor Concept
Keywords Lipids, Obesity, Risk Factor, Visceral Fat

Background: Epicardial adipose tissue (EAT) is the visceral fat deposit around the heart and is commonly increased in obese subjects. EAT is related to cardiometabolic risk factors and non-alcoholic fatty liver disease (NAFLD) in adults, but this relationship is not well known in children.


Study groups and methods: In 25 (mean age 13.0 ± 2.3) overweight and obese subjects and 24 lean controls, blood pressure (BP), WC, fasting plasma glucose and insulin, lipids, uric acid and hepatic enzymes were measured. EAT thickness was measured by transthoracic echocardiography.

Results: In overweight and obese subjects, EAT was significantly higher compared to normal weight children. Overweight and obese children had significantly higher body mass index (BMI), WC, BP, triglycerides (TAG), low-density lipoprotein and total cholesterol, hepatic enzymes alanine aminotransferase (ALT) and g-glutamyl transferase, and lower high-density lipoprotein cholesterol (HDL-C). EAT correlated significantly with BP, TAG, uric acid, HDL-C, apoprotein B and ALT. Correlation coefficients were similar or better than for WC, but similar or lower than for BMI.

Conclusion: EAT thickness in children is associated with an unfavourable cardiometabolic risk profile including biochemical signs of NAFLD and hyperuricaemia, but is not a stronger indicator than BMI.

Subdivision 3. Clinical Studies

Presentation Preference Oral presentation
Additional information
Correlation of some markers of inflammation, thrombosis and homocystein with carotid arteries stenosis in patients with heart ischemic disease

Abstract nr. 113
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Topic The Pathogenesis of Atherosclerosis; Immunity, Inflammation, and the Endothelium
Keywords Atherosclerosis, Inflammation, Prevention, Thrombosis

The purpose of the work was to find correlation which may exist between IL1β, IL6, HSCRP, fibrinogen, D dimer, SFMC and homocystein, levels and the degree of Carotid Arteries (CA) stenosis in patients with heart ischemic disease.

According to CA stenosis, 75 patients (45 female and 30 male) with chronic heart disease (mean age 55.7±1.6 years) were divided into 2 groups. Group I comprised 33 patients, who had hemodynamically insignificant stenosis of CA (<50%). Group II consisted of 42 patients with hemodynamically significant stenosis (>50%). CA intima media thikness of all patients was 1.18±1.02 mm. D dimer, SFMC, as well as homocystein, interleukins, fibronogen and HSCRP were defined.

The value of D dimer and SFMC in Group I was increased up to 900.0±3.0 ng/ml and 8.0±0.03g/l. Homocystein was 18.8±0.06 mkmol/l, IL1β 53.3±1.0 pg/ml, IL6 49.3±0.8 pg/ml, HSCRP 6.9±0.02 mg/l and fibrinogen 5.9±0.07 g/l accordingly. The relation between these parameters and CA stenosis degree appeared to be positive (from r=0.473, to r=0.533). In Group II, The value of D dimer was 1100.9±3.0 ng/ml, SFMC 9.0±0.0.6 g/l. Homocystein increased up to 26.0±0.3 mkmol/l, IL1β up to 59.3 and IL6 55.4 pg/ml, HSCRP was 9.1±0.3 mg/l, fibrinogren 6.1±0.06g/l. Correlation between these parameters and CA stenosis was positive (from r=0.500 to r=0.621).

Taking into consideration the result obtained, we think it is possible to use positive correlation between the degree of CA stenosis, D dimer, SFMC, homocystein and inflammation parameters as the markers of development of carotid atherosclerosis in the patients with heart ischemic disease.

Subdivision 1. Basic Science

Presentation Preference Electronic poster presentation
Additional information
Relationships between Protectin CD59 positive mononuclears and lipid levels in progressing atherosclerosis

Abstract nr. 114
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Topic The Pathogenesis of Atherosclerosis; Immunity, Inflammation, and the Endothelium
Keywords ACS,Atherosclerosis,Immunity,Lipoproteins

Background. It's known that the complement activation is involved in the pathogenesis of clinical complications of coronary atherosclerosis via Membrane Attack Complex (MAC) formation and following cell lysis. Simultaneously a defense mechanism against the damaging effect of complement is activated. An important factor of the complement inhibition is Protectin CD59 which binds to cell membranes and stops MAC formation.

Purpose. The aim of this study was to investigate the relationship between the number of circulating CD59-"positive" (CD59⁺) mononuclear cells and lipid levels in patients with acute coronary syndrome.

Methods. Blood samples of 87 (53 male and 34 female) patients with clinical and instrumental signs of acute coronary syndrome (ACS) and blood samples of 43 volunteers as controls were examined in this study. The control group was corresponding on average age, sex and lipid profile however with no or minimal signs of atherosclerosis progression. Flow cytometry with fluorescently labeled monoclonal antibodies was used to determine CD59⁺ peripheral mononuclears during admittance and within two weeks after discharge. Antibodies to oxidized LDL (ab-oxLDL) have been determined by ELISA. Blood levels of HDL-cholesterol, LDL-cholesterol and Lipoprotein(a) were measured with usage of routine lab kits.

Results. It has been shown that the mean quantity of CD59⁺ cells was significantly higher in group with documented ACS in comparison with control group. In patients with transmural myocardium infarction the expression of CD59⁺ was more intensive then in those with unstable angina. During treatment the levels of CD59⁺ mononuclears were decreased. We found in patients with acute coronary syndrome the negative correlation between the number of circulating CD59⁺ mononuclear cells and HDL-cholesterol levels (r= -0,64). On the other hand the significant positive correlation (r= +0,61) was found between CD59⁺ and Lipoprotein(a). The correlation between LDL-cholesterol levels and CD59⁺ was absent, while the positive correlation between ab-oxLDL and CD59⁺ was significantly high (r= + 0,63)

Conclusion. The expression of CD59 - lipid-anchored inhibitor of complement lysis is correlated with lipoprotein blood levels in patients with clinical manifestation of atherosclerosis.

Subdivision 2. Translational Research

Presentation Preference Oral presentation
Additional information
Potential therapeutic use of anti-electronegative LDL single chain fragment variable vectorized in nanocapsules on atherosclerosis

Abstract nr. 115
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Topic Primary & Secondary prevention of CVD; Lifestyle Measures and Pharmacological Intervention
Keywords Atherosclerosis, Inflammation, LDL, Therapy

The electronegative low-density lipoprotein [LDL(-)], a native LDL modified subfraction, plays a key role in atherosclerosis, since its modifications are capable of inducing foam cells formation. The immune system is crucial in atherogenic process and therapeutic strategies directed to the immunoregulation of this process have been used. In this context, it is suggested that antibody fragments such as scFv (single chain fragment variable) may be used as new alternatives in prevention of development and/or progression of atherosclerosis. In order to increase efficiency of scFv, nanoparticles have been combined with these fragments.

Given the role of LDL(-) in atherosclerosis, this study aimed to evaluate the effects of a nanostructured system containing anti-LDL(-) scFv fragments derivatized on the surface of nanocapsules (NC-scFv) and to determine endocytic mechanisms related to its internalization by murine and human primary macrophages.

Foam cell formation was evaluated by LDL(-) uptake and the impact of different endocytic pathways were determined by NC-scFv uptake in the presence of specific endocytosis inhibitors. It has been demonstrated that treatment of primary murine and human macrophages with NC-scFv significantly decreased the uptake of LDL(-) (84.67% and 86.50%, respectively) and that this formulation is internalized by macrophages through different mechanisms of endocytosis (phagocytosis, macropinocytosis and dynamin dependent endocytosis). In human primary macrophages, both scFv anti-LDL(-) and the formulation NC-scFv significantly decreased the gene expression of IL1B (interleukin 1 beta) and MCP1 (monocyte chemoattractant protein-1). These results provide evidence for the atheroprotective action of the NC-scFv, suggesting it as a therapeutic strategy with potential use in atherosclerosis.
Funding: FAPESP (grant to D.S.P.A. and scholarship to M.F.C. and S.M.K.), CAPES/DAAD/PROBRAL and CNPq/INCT_if.

Subdivision 1. Basic Science

Presentation Preference Electronic poster presentation
Additional information
Renal Oxidation of ESS diabetic rats is minimized by EPA

Abstract nr. 116
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Topic The Pathogenesis of Atherosclerosis; Immunity, Inflammation, and the Endothelium
Keywords Animal model, Blood pressure, Diabetes, Dyslipidemia

Salt sensitivity (SS) is associated with increased cardiovascular risk in diabetic patients due to increased renal oxidation and decreased urinary sodium excretion. Western diet has limited content of w3 polyunsaturated fatty acids, with antioxidant capacity, such as eicosapentaneoico acid (EPA). Therefore we hypothesized that nutritional supplementation with EPA, prevents SS in DM rats by decreasing renal oxidative stress. Methods: Wistar rats were used as healthy controls. Type II diabetic rat group (eSS), 3 months old, were divided in 3 groups, diabetic control (eSS), eSS treated with arachidonic acid (pro-oxidant)(2.5mg/ip, monthly) (eSS+AA) and eSS treated with EPA (2.5mg/ip month) (eSS+EPA). Animals were treated during 1 year, then placed in metabolic cages and subsequently underwent 2 subsequent experimental periods of 7 days each with normal sodium diet (0.4% NaCl)(NNaD) and high salt diet (4% NaCl)(HNaD). At the end of each period, weight, systolic blood pressure (SBP), HbA1c, triglycerides (Trig), cholesterol (Chol), creatinine (Cre), kidney γ-glutamyl transpeptidase activity (γGTP), urinary protein excretion (UprotV) were assayed. Results eSS rats had elevated HbA1c, Tri, Chol and reduced body weight vs. Wistar control group. Renal function was normal all along the experimental period. The eSS+AA group also showed elevation of HbA1c, Trig, with no change in Cre and Chol. During NNaD SBP was 119±3mmHg and after HNaD 125±1mmHg (p<0.05). In contrast, in EPA+eSS lower values of HbA1c (5.6±0.3% vs 7.0±0.2%, p<0.05), Trig (175±1mg/dl vs 245±12mg/dl p<0.05), and increased body weight (424±11gr vs 511±22gr, p<0.05) vs eSS were observed. EPA supplementation prevented the increase of SBP during the HNaD (126±2mmHg vs. 128±2mmHg p>0.5). eSS+AA did not differ from eSS group. No significant difference was observed in UprotV among groups. Renal interstitium γ-GT activity in eSS group was 0.65±0.04au and 0.61±0.02au in eSS+AA group, while in EPA+eSS 0.5±0.03 (p<0.05). Conclusion. The salt sentitive eSS rats have hypertriglyceridemia and elevated HbA1c. Supplementation with w3 EPA prevented the salt sensitivity, increment of HbA1c and triglycerides. These beneficial changes were associated with lower kidney γ-GT activity, suggesting that the EPA dietary supplement can be used in diabetic patients to prevent salt sensitivity and improve metabolic abnormalities.
Subdivision 1. Basic Science

Presentation Preference Oral presentation
Additional information
Homocystein-lowering effects of VCRESC® (a vitamin micronutrient beverage) in patients with coronary artery disease

Abstract nr. 117
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Topic Primary & Secondary prevention of CVD; Lifestyle Measures and Pharmacological Intervention
Keywords Cardiovascular Disease, Nutrition

INTRODUCTION: Increased homocysteine (Hcy) level is a risk factor of atherosclerotic cardiovascular diseases (ASCVD). One of possible approach to reduce Hcy levels is an oral supplementation of B-vitamins and folic acid. However, it would be hard to take sufficient amount of these micronutrients by altering daily food consumption. Aim: In the present study, we examined long-term effects of B-vitamins (B6, B12) and folic acid supplementation by commercially-available beverage on Hcy level in patients with ASCVD. Subjects and Methods: Fifteen patients with angiographically-proven stable coronary artery disease (54.4±3.0 years old) were enrolled. Fasting blood levels of vitamin B6, B12, and folic acid were measured before and after over six month-intervention period with consumption of 125 ml of VCRESC® (Nutri Co. Ltd, Mie, Japan) after breakfast. Fasting plasma Hcy levels were also measured. Results: Mean levels (±SD) of vitamin B6 (pyridoxal) significantly increased (9.2±1.0 to 31.8±3.3 ng/ml, p<0.01), and B12 levels remained unchanged (556±140 to 538±39 pg/ml, n.s.). Baseline folic acid levels remained low, and increased significantly after the period with considerable variation (6.7±0.5 to 16.2±1.8 ng/ml, p<0.01). In response to these changes, Hcy levels significantly decreased from 10.2±0.5 to 7.9±0.4 nmol/ml (p<0.01). None of adverse events potentially related to VCRESC® consumption was noted. Conclusion: Levels of vitamin B6 and folic acid significantly increased by six-month consumption of VCRESC® in association with significant reduction of Hcy, suggesting that a vitamin micronutrient beverage appears to be a novel alternative to reduce plasma Hcy levels in patients with ASCVD.

Subdivision 3. Clinical Studies

Presentation Preference Mini-oral presentation
Additional information
A VERY LOW CALORIE DIET AMELIORATES ENDOTHELIAL FUNCTION AND INFLAMMATION MARKERS IN OBESE PATIENTS WITH TYPE 2 DIABETES

Abstract nr. 118
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Topic Primary & Secondary prevention of CVD; Lifestyle Measures and Pharmacological Intervention
Keywords Diabetes, Endothelium, Nutrition, Obesity

Introduction: Obesity and type 2 diabetes (T2D) increase the risk of cardiovascular diseases. This increased risk is associated with impairment of endothelial function and increased systemic inflammation. We investigated the effect of diet-induced weight loss on biomarkers of endothelial function and inflammation in overweight patients with T2D.

Methods: 132 T2D patients with BMI > 27 were put on a 750 kcal/day diet for 2 months, followed by 1000-1300 kcal/day diet for another 2 months. At baseline and at the end of the intervention, the endothelial markers sICAM-1, sVCAM-1, vWF, and inflammation markers CRP and IL-6 were measured in plasma.

Results: The diet intervention resulted in a 9.8±5.2 % weight loss. sICAM-1, vWF and CRP levels were significantly reduced (p < 0.01), while sVCAM-1 and IL-6 remained unaffected. The intervention reduced the number of patients with a high-risk CRP level (>3 mg/L; p=0.033) and increased the number of patients with a low-risk CRP level (<1 mg/L; p<0.0001) (figure 1). In multiple linear regression models, the diet-induced reduction in sICAM-1 level was significantly associated with baseline sICAM-1 (p<0.0001), reduction in CRP levels (p<0.0001) and reduction in bodyweight (p=0.016). The decrease in vWF was associated with baseline vWF (p<0.0001), fall in waist circumference (p=0.016) and fall in fasting glucose (p=0.028). The reduction in CRP was associated with baseline CRP (p<0.0001).

Conclusion: In conclusion, a 4-month (very) low calorie diet is a therapeutic option for improving endothelial function and reducing systemic inflammation in overweight and obese type 2 diabetes patients, ameliorating cardiovascular risk. The positive effect of this dietary regimen was most clear in the patients that presented with the highest sICAM-1, vWF and CRP plasma levels before initiation of the diet.

This study is internally funded by the Erasmus Medical Center within the funding program: ‘zorgonderzoek Erasmus MC’.
Figure 1: The effect of the dietary intervention on the distribution of participants among CRP risk categories
Subdivision 5. Not applicable. Abstract matches with track d

Presentation Preference Oral presentation
Additional information
ASYMPTOMATIC PATIENTS WITH SEVERE VASCULAR DISEASE AND FIBROCALCIC PLAQUES DO NOT EVIDENCE INTRAPLQUE INFLAMMATION WHEN STUDIED BY 18-FDG PET.

Abstract nr. 119
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Co-author(s) - Martire, Maria Victoria
Co-author(s) - De Pierris, Carlos
Topic The Pathogenesis of Atherosclerosis; Immunity, Inflammation, and the Endothelium
Keywords Atherosclerosis, Imaging, Inflammation, Pathogenesis

Background: Recent although scarce evidence indicates that symptomatic patients (P) with peripheral or carotid artery disease with levels of high ultra sensitive C-reactive protein (US-CRP) and/or echo-translucent fibrous-lipid plaques present high 18-FDG uptake in PET studies. However, there is no clinical information as to whether patients with severe vascular disease who are asymptomatic and evidence fibrocalcic plaques present the same inflammatory pattern and 18-FDG uptake. With this purpose we designed a metabolic study protocol for this type of patients by correlating PET with US-CRP findings.

Materials and Methods: A total of 18 consecutive asymptomatic P were followed up, 14 males and 4 females, with an average age of 69 ± 12 years old, with multiple vascular risk factors (hypertension: 18, dyslipidemia:15, diabetes:8, tobacco:10, obesity: 10), with evidence of severe fibrocalcic lesions in carotid (n:18), aortic (n:4), iliofemoral (n:4) territories with an average of 2.3±0.7 lesions per patient. US-CRP was determined (normal reference value ≤ 4 mG/liter) and all underwent 18-FDG PET-CT metabolic study, administering 15 mCi/patient and obtaining images after 90 minutes.

Results: 1-. US-CRP: 1, 97±0, 5 mG/l; 2-PET-CT: no patient evidenced uptake of 18-FDG in territories with severe vascular lesions with fibrocalcic plaques.

Conclusion: Unlike what was observed in symptomatic P or P with echo-translucent fibrous-lipid plaques, these sampling patients, who were stable and showed no laboratory-based evidence of inflammation, did not present uptake of the radioactive tracer, this being in agreement with the clinical response, though severe lesions were present.

Subdivision 3. Clinical Studies

Presentation Preference Electronic poster presentation
Additional information
Validation of carotid artery disease as marker of coronary disease and inducible ischemia in asymptomatic patients with multiple risk factors.

Abstract nr. 120
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Co-author(s) - Martire, Maria Victoria
Co-author(s) - Perelestein, Sergio
Topic Epidemiology of CVD; The Risk Factor Concept
Keywords Atherosclerosis, Imaging, Risk stratification

Background: The carotid intima-media thickness (IMT) as a long-term risk marker and the correlation between carotid plaques (CP) and SYNTAX score, have been well demonstrated. However, it has recently been known that there is information about the incidence of myocardial ischemia depending on the different degrees of severity of the carotid artery disease (CAD).

Objective: To assess the incidence and severity of inducible myocardial ischemia in patients (P) with different degrees of CAD, using quantitative data of Carotid Doppler (CD) and of the functional study of radioisotope myocardial perfusion (SPECT) as assessment test of ischemia.

Materials and Methods: A total of 397 consecutive asymptomatic P were followed up, 251 males and 146 females, with an average age of 65 ± 9 years old, with multiple cardiovascular risk factors and high pre-test probability for coronary artery disease according to clinical scores, They were indicated color Doppler echocardiography CDE and SPECT and divided into 5 groups (G) according to the degree of CAD, assessed by means of the thickness summation in mm in both carotid territories: Plaque Score (PS).

G1 (Control, n: 50): With no carotid alterations: PS: <1.1 mm; G2 (n: 150): With thickening of IMT: PS: between 1.1-1.5 mm; G3 (n: 88): PS: between 1.5-6, G4 (n: 62): PS: between 6-12; G5 (n: 47): PS: > 12. Determination of ischemic incidence in each group, correlation (r) between PS by means of CDE with summed difference score (SDS) by means of SPECT and ROC curve.

Results: From the total of 397 P, 169 (42%) developed ischemia under SPECT. For each group: G1:14 (28%), G2:41 (26%), G3:30 (34%), G4:45 (72%) *, G5:39 (83%) *. Correlation: r=PS/SDS: G1:0.13. G2:0.23. G3:0.25. G4:0.47 *. G5:0.65 *. (* = p: <0.01). ROC curve: 0.72 ± 0.04 (PS cutting line SP: ≥ 6).

Conclusion: The quantification of carotid vascular disease and its increasing complexity predicted elevated occurrence and severity of inducible ischemia in patients with higher risk, reasserting the clinical value as an additional risk marker to the scores available at present.
Subdivision 3. Clinical Studies

Presentation Preference Electronic poster presentation
Additional information
Incidence and severity of alterations in calcium phosphorus metabolism in patients with multiple cardiovascular risk factors and high Framingham score.

Abstract nr. 121
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Co-author(s) - Martire, Maria Victoria
Co-author(s) - Perelestein, Sergio
Topic Epidemiology of CVD; The Risk Factor Concept
Keywords Cardiovascular Disease, Metabolism, Risk Factor

**Background:** Contradictory and non concluding data refer to the clinical and therapeutical importance of alterations in calcium phosphorus metabolism (CPM) in patients with multiple cardiovascular risk factors (CVRF) and high Framingham point score (PFS) (≥ 20).

**Objective:** To assess the incidence and severity of CPM alterations on a first model of clinical high risk, through the determination of paratohormone (PTH), Vitamin D (Vit D), plasma calcium (P-Ca), fasting (F-Ph) and postprandial phosphatemia (Pp-ph).

**Material and Methods:** Having successively studied 88 patients (61 males aged 60±9 years), all of them with FPS ≥ 20, PTH was determined through chemiluminescence (normal reference value (RV): 7-53 pG/ml), Vit D through electrochemiluminescence (RV: 20-100 nG/ml), calcemia and phosphatemia through colorimetric, complexometric and UV methods (RV: 8,6-10,2 mgs/dl and 2,5-4,5 mgs/dl respectively). Those patients with renal clearance < 40ml/min, calcium supplement or Vit D intake, and hypercalciuria remained excluded.

**Results:** A-Incidence. 84/88 patients (95%) presented abnormal determination (elevated) of PTH, 82/88 (93%) severe lack of Vit D, 0/88 (0%) abnormal calcemia, and 88/88 (100%) abnormal postprandial response to dietary phosphate (F-Ph, Pp-Ph, 3 h after intake). (F: fast, Pp: post prandial)

B-Magnitude of monitored alterations. PTH: 91±27 pG/ml, Vit D: 10±6 nG/ml, Ca-P: 9,01±0,25 mgs/dl, F-Ph: 3,26±0,47 mgs/dl, Pp-Ph: 4,03±0,65 mgs/dl (p< 0,01). (pG: picograms, nG: nanograms, mgs: milligrams, dl: deciliter.)

**Conclusion:** In this model to identify clinical high risk there is evidence of a very high incidence and severity of paratohormone and Vit D alterations, as well as abnormal postprandial management of dietary phosphate, showing the need of a physiopathological and eventually therapeutic new approach in this insufficiently explored area.
Subdivision 3. Clinical Studies

Presentation Preference Electronic poster presentation

Additional information

Monitored alterations. (scale log 2)

PTH: pG/ml
Vit D: ng/mL
Ca, Ph: mG/dl
Herbal Commiphora Mukul Flavonoids Improves Chymase Enzyme Inhibition in Human Chymase Transgenic Mice a Novel Therapeutic Regimen against Atherosclerosis

Abstract nr. 122
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Topic Primary & Secondary prevention of CVD; Lifestyle Measures and Pharmacological Intervention
Keywords Cardiovascular Disease, Pharmacology, Therapy, Vulnerable Plaque

BACKGROUND: This insilico study was designed to investigate the effects and mechanism of inhibition action of the Indian herbal plant flavonoids, Phytosterols, Gugulipids and Guggulsterones from Commiphora mukul, on chymase enzyme inhibition through its validation on human chymase transgenic mice

METHODS: We will evaluate and study on downloaded different 3D X-ray crystallographic structures of chymase Enzymes, 3N7O, 1T31, 3SON, and 2HVX to incorporate molecular docking techniques using Commiphora mukul herbal Flavanoids: Phytosterols, Gugulipids and Guggulsterones into the active site of chymase enzyme. The Molecular dynamics simulations of chymase with Commiphora mukul Flavanoids were performed to reveal its binding orientations to depict any conformational changes in the active site. At last, validation studies implies specificity, effects of computational active herbal extract of Commiphora mukul Flavanoids on the signal transduction pathway in heart remodeling of human chymase transgenic mice

RESULTS: The inhibition mechanism of chymase gives key structural focus conceptualizing rational design of novel herbal inhibitors of the enzyme. The results conferring about 3D chymase structure as well as the novel benefits of Commiphora mukul Flavanoids Phytosterols, Gugulipids and Guggulsterones in hydrolase function

CONCLUSIONS: Novel Commiphora mukul herbal flavanoids benefits in chymase inhibition for the vulnerability and treatment of cardiovascular diseases, allergic inflammation, and fibrotic disorders. Binding mode prediction reveals substitution of a heavier atom on most active site inferring about to change of its variation and orientation causing other groups to interact with Phytosterols, Gugulipids and Guggulsterones residues. Dynamics simulations depict conformational variation in inhibitor regions, binding convinced alteration, thus changing its interactions with it. Chymase with the active Phytosterols, Gugulipids and Guggulsterones inhibitors utilizing pharmacophore modeling which is enforced in databases screening for other novel potent herbal drugs. Finally, hits which constrained best at the active site, presented key interactions and favourable electronic features for chymase and clinical validation studies on human chymase transgenic mice shows how individual mutation and variation deals pathologies or "silent" protein changes in Atherosclerosis

Subdivision 2. Translational Research
Presentation Preference Oral presentation
Additional information
Association between body mass index and existence and severity of coronary artery disease in normotensive patients

Abstract nr. 123
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Topic Epidemiology of CVD; The Risk Factor Concept
Keywords Atherosclerosis, Cardiovascular Disease, Obesity

Introduction: Link between obesity and coronary artery disease (CAD) was proved in clinical trials and like hypertension, it is considered as a strong risk factor for CAD. Therefore, association between body mass index (BMI) and existence and severity of atherosclerotic lesion of coronary arteries still has interest in different ethnic groups.

Objectives: Study purpose was to investigate relationship between existence and severity of CAD and body mass index in patients with normal blood pressure values without any history of high blood pressure and its treatment.

Materials and Methods: 80 patients (mean age±SD, 58.15±13.69 years), 47 females and 33 males, with normal blood pressure values and no history of hypertension were included in the study. Calculation of BMI and coronaroangiography for assessment atherosclerotic process and its severity was performed in all study participants. Gensiny score was used for assessment of CAD severity. Patients with diabetes mellitus, smokers as well as with renal/liver insufficiency were excluded from the study.

Results: According to the BMI, all the study participants were divided into three groups: patients with normal weight (n=26, mean BMI = 21.34±2.66 kg/m²), overweight (n=29; mean BMI = 27.03±1.45 kg/m²) and obese (n=25; mean BMI = 35.6± 6.13 kg/m²). In comparison with normal weight patients, overweight and obese patients had significantly higher rate of CAD (46.15% vs. 62% and 60%; P<0.05, respectively). Diffuse type atherosclerotic lesion of coronary arteries was significantly frequent in obese patients in comparison with normal and overweight (36% vs. 15.4% and 1.65%). Local atherosclerotic lesions i.e. plaques were more frequent in overweight patients, than in obese and normal weight (55 % vs. 24% and 30.8%). Therefore, highest level of Gensini score appeared in patients with obesity in comparison with normal and overweight subjects (44.8±21.9 vs. 23.43±27.6 and 38.43±24.8).

Conclusions: Results of our study points out that severity of coronary atherosclerosis is significantly related with BMI. Namely, as high is BMI, as severe is atherosclerotic damage – diffuse or local. Therefore, possibility of existence and severity of coronary artery atherosclerosis rises with an increase of BMI.
Subdivision 4. Not applicable. Abstract matches with track c

Presentation Preference
Electronic poster presentation
Additional information
“New thiazolidine compounds improve metabolic syndrome”

Abstract nr. 124
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Topic Primary & Secondary prevention of CVD; Lifestyle Measures and Pharmacological Intervention
Keywords Diabetes, Dyslipidemia, Hypolipidemic Drugs, Obesity

The thiazolidinediones (TZDs) are anti-diabetic oral drugs used for type 2 diabetes treatment. However, clinical practice shows important adverse effects, such as weight increase and bone density loss. Thus, new thiazolidine compounds (NTC) have been developed to identify more effective drugs with less adverse effects. In this study we investigated biological effects promoted by NTC (GQ-02, GQ-11, GQ-177 and Lyso-7) on a metabolic syndrome animal model. C57BL/6J and C57BL/6J LDLr -/- mice high fat diet fed were treated with NTC, water, vehicle and pioglitazone (control). Relative gene expression in epididymal adipose tissue was quantified by RT-PCR (ΔΔct analysis method). Glucose tolerance test (GTT) was done according to protocol guidelines, serum leptin and insulin were measured by ELISA and lipid profile was evaluated by enzymatic/colorimetric assays.

All mice treated with NTC showed decreased values for GTT (AUC) and serum insulin, besides increase of adiponectin and glut-4 expression in adipose tissue, indicating hypoglycemic and insulin sensitizer effects. Treatment with NTC also showed decreased serum leptin and leptin mRNA in adipose tissue, indicating improvement of leptin resistance and hyperleptinemia condition. Moreover, one of NTC (GQ-…) modulated lipid profile by increasing HDL-cholesterol and decreasing LDL-cholesterol. Moreover, srebp expression was down-regulated in hepatic tissue.

Our data show improvement of metabolic syndrome with beneficial effects on insulin, glucose and leptin resistance besides hypercholesterolemia. These results warrant further studies with these NTZ that can be drug candidates helpful for metabolic syndrome treatment.

Funding: FAPESP (grant to D.S.P.A. and scholarship to J.A.C. and M.F.C.), CNPq/INCT_if.

Subdivision 1. Basic Science

Presentation Preference Electronic poster presentation

Additional information
Increased aortic valve calcification in familial hypercholesterolemia: Prevalence, extent and associated risk factors in a case-control study

Abstract nr. 125
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Topic Dyslipidemia; Lipids, Lipoproteins and Apolipoproteins
Keywords Cardiovascular Disease, Familial Hypercholesterolemia, Imaging, Pathogenesis

Background
Severe aortic valve calcification is seen in patients with extreme LDL-C levels as are seen in patients with homozygous familial hypercholesterolemia (FH). Although patients with heterozygous FH have lower levels of LDL-C, the prevalence of AoVC in heterozygous FH is unknown. We quantified AoVC and compared the results with controls without FH, using cardiac CT.

Methods
145 asymptomatic, statin treated, patients with FH (93 men; mean age 52, SD=8) and 131 controls without FH (78 men; mean age 56, SD=9) underwent cardiac CT calcium scoring. The amount of calcium at the aortic valve leaflets was expressed in Agatston units as the AoVC-score. The AoVC-score was compared between patients with and without FH.

Results
Prevalence of AoVC and the AoVC-score (median, IQR) were higher in FH than in controls: 41%, 51(9-117) and 21%, 21(3-49), (P<0.001 and P=0.007). LDLR-negative mutational FH was associated with the highest prevalence of AoVC (53%, P<0.001) that was generally more severe (OR 3.17 (CI 1.43-7.02; P=0.004). Age, maximum untreated total cholesterol, diastolic blood pressure, LDLR-negative mutational FH and coronary artery calcification were independently associated AoVC.

Conclusion
This is the first study to show that heterozygous FH is associated with high prevalence and extent of subclinical AoVC, and that there seems to be an LDL-C gene dosage effect as causative factor for this development.
Subdivision 3. Clinical Studies

Presentation Preference Oral presentation
Additional information
Lipoprotein (a) is not associated with carotid plaque presence and carotid intima media thickness in statin treated FH patients

Abstract nr. 126
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Topic Dyslipidemia; Lipids, Lipoproteins and Apolipoproteins
Keywords Familial Hypercholesterolemia,Imaging,Lp(a),Risk stratification

**Background:**
Familial hypercholesterolemia (FH) leads to elevated low density lipoprotein cholesterol and thereby increases risk of premature cardiovascular disease (CVD). An additional risk factor in FH is lipoprotein (a) (Lp(a)). However, it is unknown if Lp(a) causes a higher atherosclerotic burden in these patients. Subclinical atherosclerotic burden can be visualized by carotid ultrasound measurements, and we investigated whether carotid plaque presence, and the carotid intima media thickness (C-IMT) are associated with Lp(a) in statin treated FH patients.

**Methods and results**
191 FH patients were included in this study, and were split in to two groups. The first, with high Lp(a) (≥0.3g/L) and the second, with low Lp(a) (<0.3g/L). These groups did not differ at baseline. Carotid plaque presence was evaluated, and C-IMT was measured twice from two different angels at both common carotid arteries. For the analysis the mean of these four measurements was used.

The association between Lp(a) and plaque presence was tested using a Chi-Square test showing no differences in plaque presence between the groups (p=0.448). C-IMT was tested with an ANOVA, and was the equal in the high Lp(a) group (CIMT= 0.588±0.133 mm) as in the low Lp(a) group (C-IMT=0.593±0.127 mm) (p=0.842).

Finally the results did not change when other cut-off values (Lp(a) 0.5g/L and 1.0g/L) were used or when Lp(a) was used as a continuous variable (data not shown).

**Conclusions**
Lp(a) is not associated with subclinical atherosclerosis defined as plaque presence or an increased C-IMT in statin treated FH patients. A possible explanation is that adequate statin treatment results in normalisation of C-IMT.

Subdivision 3. Clinical Studies
Presentation Preference Mini-oral presentation
Additional information
**Inter observer variability and intra observer variability of automatic carotid intima media thickness measurements**

Abstract nr. 127  
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Topic Epidemiology of CVD; The Risk Factor Concept  
Keywords Imaging,Risk stratification

**Introduction:** Evaluation of subclinical atherosclerosis can be done with the use of carotid ultrasound, in which the presence of carotid plaques can be evaluated and the carotid intima media thickness (C-IMT) can be measured. The aim of this study was to evaluate the measurement error of the Panasonic CardioHealth station when used for carotid plaque scan and C-IMT measurement.

**Methods and Results:** Two experienced physicians performed plaque scans and C-IMT measurements. Plaque scans were done bilaterally in the internal, external, and common carotid arteries. C-IMT was measured bilaterally from two different angles. For the intra observer variability both physicians measured 15 separate individuals twice in a blinded matter. Both physicians measured 50 patients for the inter observer variability. Intra observer plaque presence was excellent with a 100% accuracy for both observers. Inter observer plaque presence agreed in 92% of the cases, with an equal error for the observers.

The ICC of both observers where similar 0.93 (0.89-0.96) vs 0.90 (0.84-0.94). Furthermore the LOA were also showed a similar SD change (0.0049±0.074) vs (-0.015±0.075).

The intra class coefficient (ICC) between the two observers was 0.92 (0.89-0.94), and the line of agreements (LOA) where -0.0057 (±0.076).

**Conclusion:** The Panasonic CardioHealth station shows reliable reproducible results between different and individual observers. The LOA were higher than expected per measurement, which can be caused by the device. However, since no big differences were found between observers it is more likely that the difference is caused by the unreliability of the C-IMT measurement per sé.

Subdivision 3. Clinical Studies

Presentation Preference Electronic poster presentation

Additional information
**Dunaliella salina modulates the adhesion molecules of endothelia and the cell migration of vascular smooth muscles to ameliorate inflammatory responses**

Abstract nr. 128  
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Topic The Pathogenesis of Atherosclerosis; Immunity, Inflammation, and the Endothelium  
Keywords Inflammation, Pharmacology

The inflammatory responses of blood vessels involve up-regulation of vascular adhesion molecules such as vascular cell adhesion molecule (VCAM-1) and intercellular adhesion molecule (ICAM-1). Migration of vascular smooth muscle cells (VSMC) via MMP activities also occurs at inflammation so becomes a marker of atherosclerosis. *Dunaliella salina* has shown its capability to prevent hyperlipidemia-induced atherosclerosis. However, the molecular mechanisms in its prevention effects are still not yet explored. The aim of this study is to investigate the effects of *Dunaliella salina* extracts on expression of biomarkers that participates in atherosclerosis. RAW246.7 macrophages were activated by LPS (1ug/ml). Endothelial cells (SVEC4-10 cell line) and VSMC (A7r5 cell line) were treated with 50% RAW-conditioned medium (i.e. 50% DMEM culture medium plus 50% LPS-activated macrophage culture medium) with and without various concentrations of *Dunaliella salina* extracts(from 0.01 to 1 mg/ml). Production of nitric oxide, TNF-alpha and Monocyte chemoattractant protein-1 (MCP-1) in macrophages and production of VCAM-1 and ICAM-1 in SEVC cells were measured by ELISA assay. Matrix metalloproteinases (MMP)-2 and MMP-9 protein levels and cell migration in VSMC were evaluated by Western blotting and wound healing assay, respectively. Results showed that production of MCP-1, ICAM-1 and VCAM-1 and expression of MMP-2 were significantly suppressed by *Dunaliella salina* extracts (at both 0.5 and 1 mg/ml). Furthermore, VSMC migration was also decreased by *Dunaliella salina* extracts. These data indicate that *Dunaliella salina* extracts provides protective effects against proinflammation-induced atherosclerosis via prevention of adhesion molecules production and migration of VSMC.

Subdivision 1. Basic Science

Presentation Preference Electronic poster presentation

Additional information
K-877, a potent and selective PPARα modulator, increases plasma FGF21 and improves triglyceride metabolism in Zucker fatty rats.

Abstract nr. 129
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Topic Dyslipidemia; Lipids, Lipoproteins and Apolipoproteins
Keywords Hypolipidemic Drugs, Lipids, Triglycerides

In clinical trials of hypertriglyceridemia (triglyceride (TG) up to 500 mg/dL), K-877 showed reduction of plasma triglycerides and markedly increased plasma fibroblast growth factor 21 (FGF21) levels, whereas fenofibrate had little effect on FGF21. We investigated the effect of K-877 on TG metabolism, using Zucker fatty (ZF) rats as a model of severe hypertriglyceridemia (TG>500 mg/dL).

After 2 weeks of treatment with K-877 3 mg/kg, significant reduction (67%) in plasma TG was observed compared with fenofibrate 100 mg/kg (41%). We examined TG clearance in blood and TG secretion rate from liver, using soybean-oil emulsion and tyloxapol (Triton WR-1339), respectively. K-877 accelerated TG clearance ($t_{1/2}$:16.3 min) compared with fenofibrate (23.7 min) and control (25.7 min). Meanwhile, TG secretion rate was reduced compared to control (892.9 mg/dL/h) but there was no significant difference between K-877 (593.6 mg/dL/h) and fenofibrate (663.0 mg/dL/h). These data suggest that accelerated TG clearance has an important role in TG-lowering by K-877 in this model.

FGF21 is known as a hormonal regulator of lipid metabolism, and decreases plasma TG while enhancing TG clearance. K-877, but not fenofibrate, increased liver FGF21 mRNA and plasma FGF21. Moreover, in primary human hepatocytes, K-877 increased secretion of FGF21 compared with fenofibric acid.

In conclusion, these results suggest that the action of K-877 on FGF21 may contribute to its potency in improving dyslipidemia. We intend to verify the effects of K-877 on severe hypertriglyceridemia in human in future clinical studies.

Subdivision 2. Translational Research

Presentation Preference Electronic poster presentation
Additional information
Effect of Diets With Different Protein Composition in Weight and Lipids in Overweight and Obese Women: A Randomized Controlled Study

Abstract nr. 131
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Topic Primary & Secondary prevention of CVD; Lifestyle Measures and Pharmacological Intervention
Keywords Lifestyle, Lipids, Nutrition, Obesity

Background: High-protein hypocaloric diets have been shown to be effective in promoting weight loss in overweight and obesity, however, the protein percentage to achieve a better efficacy and acceptability has not been established.

Objective: To assess the effect of three energy-reduced diets with different high-amount of protein (20, 27 and 35% of whom around 50% coming from animal source) on weight loss and lipid metabolism. Secondary outcome involved acceptability, compliance and palatability.

Methods: Three-months randomized controlled study including women meeting the following criteria: aged ≥ 18 and < 80 years, body mass index (BMI) ≥ 27.5 and < 40 kg/m², steady weight in previous 3 months and not taking lipid-lowering drugs and/or sterols supplements. We randomly assigned 91 women to one of three calorie-reduced diets with the following distribution of calories from protein, carbohydrates and fat, respectively: 20%, 50% and 30%; 27%, 43%, and 30%; 35%, 35%, and 30%. Each participant’s caloric prescription represented a deficit of 600 kcal/day as calculated from energy expenditure. Individual visits with a nutritionist were performed every 2 weeks. Clinical, biochemical and anthropometric outcomes were assessed at baseline and at the end of dietary intervention.

Results: 80 women with a mean (±SD) age of 44.0±9.08 years and a BMI of 37.7±3.39 kg/m² completed the study. Weight loss was of -8.16±4.18, -9.66±5.28 and -10.7±4.28 kg in 20%, 27% and 35% protein-diets groups respectively (P = 0.164 among groups and P = 0.041 comparing 20 vs. 35% diets). Significant decreases were observed in triglycerides, total cholesterol and LDL cholesterol in all groups although they were higher in the 35% than in 20% group (P<0.05 in all of them). HDL cholesterol increased especially with the highest protein-diet (P=0.028 comparing 20 vs. 35% diets). Lipid profile improvement was not correlated to weigh loss. Dietary compliance was higher and exercise change was homogeneous in all groups. Acceptance, palatability and saciety questionnaire showed similar results among groups.

Conclusions: A high-protein, energy-restricted diet confers weight-loss benefit. Lipid profile improved specially in those women following 35%-protein diet regardless of weight loss.
Acceptability, palatability and compliance assessed by participants were similar in all diets.

Subdivision 5. Not applicable. Abstract matches with track d

Presentation Preference Oral presentation
Additional information
Rare APOE gene mutations in primary hyperlipidemias

Abstract nr. 132
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Topic Dyslipidemia; Lipids, Lipoproteins and Apolipoproteins
Keywords Dyslipidemia, Genetics

Apolipoprotein E has an important role in the cellular uptake of lipoproteins. APOE ε2/ε2 genotype produces dysbetalipoproteinemia, but other rare APOE mutations have been associated with other types of dyslipidemias. The objective was to identify rare APOE variants and to establish their contribution in the pathogenesis of primary hyperlipidemias.

Methods: A total of 1,112 unrelated subjects were recruited in the Lipid Unit at Hospital Universitario Miguel Servet, Zaragoza (Spain): 509 with isolated hypercholesterolemia (LDL cholesterol >95th percentile), 505 with mixed hyperlipidemia (total cholesterol and triglycerides >90th percentile) and 98 with isolated hypertriglyceridemia (triglycerides >95th percentile and total cholesterol <90th percentile). In addition, 183 normolipemic subjects were analyzed as control group. Exclusion criteria were: body mass index >30 Kg/m², diabetes, renal or liver disease and ε2/ε2 APOE genotype. Exon 4 of APOE was sequenced in all subjects and in all available family members when a rare variant was found in the index patient.

Results: The following APOE rare variants have been identified: p.Gly145Asp (rs267606662) in two subjects with mixed hyperlipidemia; p.Arg163Cys (rs769455) in 3 subjects, one in each hyperlipidemia group; p.Leu167del in 5 subjects with mixed hyperlipidemia and in 2 subjects with isolated hypercholesterolemia; p.Arg154Ser (rs121918393) in 2 subjects with mixed hyperlipidemia. Moreover, p.Ala217Ala variant (rs72654468) was found in 2 controls, one subject with isolated hypercholesterolemia and one subject with mixed hyperlipidemia. It has also been identified 2 non previously described variants: p.Met82Ile in 1 subject with isolated hypertriglyceridemia, and p.Gly191Cys in one subject with isolated hypercholesterolemia. Family studies confirmed co-segregation of the rare APOE variants with hyperlipidemia, except for p.Ala217Ala.

Conclusions: We have found five different APOE variants in 16 subjects with different hyperlipidemias that were not found in controls. Our results support an important role of APOE gene rare mutations in the etiology of several hyperlipidemias other than dysbetalipoproteinemia.
Subdivision 1. Basic Science

Presentation Preference Electronic poster presentation
Additional information
Direct atherogenic effects of sodium: Molecular mechanisms and shear stress pattern dependency in vitro and in vivo.

Abstract nr. 133
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Topic The Pathogenesis of Atherosclerosis; Immunity, Inflammation, and the Endothelium
Keywords Atherosclerosis, Endothelium, Hypertension, Pathogenesis

Background: Increased consumption of sodium is a risk factor for hypertension and cardiovascular diseases. In vivo studies indicated that high dietary sodium may have a negative influence on endothelium. We investigated the direct effect of high sodium on endothelial-monocytic cell interactions in the regions of non-uniform shear stress both in vitro and in vivo.

Methods: Human umbilical vein endothelial cells grown in a model of arterial bifurcations were exposed to shear stress for 18h in the presence of normal or high (+ 30 mmol/L) sodium, followed by stimulation with TNF-α for 2h and a dynamic adhesion assay. Adherent THP-1 cells and the adhesion molecule expression were quantified. Sodium channel blockers, pathways’ inhibitors, and siRNA against tonicity-responsive enhancer binding protein (TonEBP) were used to identify the mechanisms of sodium effects. ApoE-deficient mice on low-fat diet received water containing normal or high salt (8% w/v) for four weeks, followed by intravital microscopy and serum cytokine/chemokine analysis using magnetic bead-based multiplexing technology.

Results: In vitro, high sodium dramatically increased the endothelial responsiveness to TNF-α under non-uniform shear stress, reflected by a significant enhancement of adhesion molecules expression and monocytic cell recruitment. This effect was prevented by the laminar flow, and was slightly reversed in the static conditions. The blockade of sodium-calcium exchanger using NiCl₂ abolished the stimulatory effect of sodium under non-uniform shear stress, whereas blocking epithelial sodium channel with amiloride had no effect. Sodium-induced increase in monocytic cell adhesion was mediated by reactive oxygen species and the endothelial NO-synthase, and was sensitive to the knockdown of TonEBP.

The direct sodium effects on endothelium were subsequently confirmed in the ApoE-deficient mice. As compared with normal-salt group, high salt intake significantly enhanced the adhesion of circulating CD11b⁺ cells to carotid bifurcations, but not to the straight segment of common carotid artery. No significant effects of high salt intake on the blood cell counts, lipid levels, or cytokine profile were observed.

Conclusions: Elevated sodium has a direct effect on endothelial activation under atherogenic shear-stress in vitro and in vivo, and promotes the endothelial-leukocyte interactions even in the absence of increased lipid concentrations.
Subdivision 1. Basic Science

Presentation Preference Oral presentation
Additional information
Longer receptor residence times improve the effectiveness of CCR2 antagonists in the prevention of atherosclerosis

Abstract nr. 134
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Topic The Pathogenesis of Atherosclerosis; Immunity, Inflammation, and the Endothelium
Keywords Atherosclerosis, Inflammation, Therapy

Background: The chemokine receptor CCR2 is known to be critically involved in atherosclerosis development, rendering blockade of the CCL2-CCR2 interaction of therapeutic interest. CCR2 receptor antagonists have, however, limited clinical success. Interestingly, it was shown for other drug targets that a measure for the dissociation of the drug-receptor complex, the so-called residence time (RT), can have a crucial impact on a drug’s efficacy. In this study, we thus aimed to determine whether an increased RT improves the therapeutic effectiveness of CCR2 antagonists.

Methods: Carotid artery atherosclerosis was induced by perivascular collar placement in apoE−/− mice, followed by daily treatment with the short RT CCR2 antagonist 15a (RT=15 min, 150 µg/day), the long RT CCR2 antagonist 15b (RT=714 min, 150 µg/day) or vehicle control. After four weeks, atherosclerotic plaques were analyzed for size and composition.

Results: During the study, treatment with the CCR2 receptor antagonists did not affect total body weight or plasma total cholesterol levels compared to the controls. At sacrifice, numbers of circulating CCR2+ monocytes were only significantly reduced in the long RT 15b-treated mice (controls: 14.9±3.2*10³, 15a: 9.1±3.3*10³ and 15b: 4.5±1.0*10³ cells/mL, *P<0.05). Atherosclerotic plaque size was reduced from 64.4±11.8*10³ µm² in control mice to 33.2±6.8*10³ µm² in 15a-treated mice (-49%, *P<0.05), and even up to 17.6±4.1*10³ µm² in 15b-treated mice (-73%, **P<0.01). Interestingly, relative plaque macrophage content was only decreased in 15b-treated mice compared to both control and 15a-treated mice (controls: 46±4%, 15a: 45±6%, 15b: 25±8%, *P<0.05). In the aortic root, 15a did not significantly affect plaque size (controls: 252±25*10³ µm² versus 15a: 196±17*10³ µm²), while the long RT CCR2 antagonist 15b inhibited plaque development to 157±15*10³ µm² (-38%, **P<0.01). Furthermore, also at that site of lesion development, macrophage area was only significantly reduced in the 15b treated mice (controls: 35±4%, 15a: 32±3%, 15b: 23±4%, *P<0.05 compared to controls).

Conclusion: Our data demonstrate that the CCR2 antagonist with a long residence time was more
effective in inhibiting atherosclerotic plaque development compared to the short RT antagonist, which implies that receptor residence time is an important parameter in drug development.

Subdivision 1. Basic Science

Presentation Preference Oral presentation
Additional information
Accumulation of circulating superparamagnetic iron oxide nanoparticles (SPIONs) in endothelial cells: Effects on endothelial viability and monocytic cell adhesion.

Abstract nr. 135
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Topic Primary & Secondary prevention of CVD; Lifestyle Measures and Pharmacological Intervention
Keywords Atherosclerosis, Endothelium, Therapy

Background: Magnetic drug targeting is considered a promising method to accumulate drug-carrying nanoparticles at the atherosclerotic lesions. However, little is known about the biological effects of magnetic nanoparticles on the vascular cells. In this study, we analysed the endothelial accumulation of circulating SPIONs (superparamagnetic iron oxide nanoparticles), without or with external magnetic force. Moreover, the effects of SPION uptake on endothelial morphology, resistance to physiologic levels of shear stress, and TNF-α-induced monocytic cell adhesion were investigated.

Methods: Human umbilical vein endothelial cells (ECs) were grown in the bifurcating flow-through slides. Subsequently, the cells were perfused at 10 dyne/cm² for 18 h with medium containing SPIONs at a concentration of 30 µg/mL (without magnet), or 3 µg/mL (with magnet). The iron content of ECs was estimated using Prussian blue stain. In further experiments, the effects of SPION uptake on monocytic cell recruitment in response to TNF-α were analysed. EC morphology and resistance to physiologic levels of shear stress were investigated by extending the exposure to shear stress in the absence of SPIONs for up to 96 h, following the initial 18 h perfusion with SPION-containing media.

Results: In the absence of magnetic force, endothelial SPION uptake was independent of hemodynamic conditions, indicating that no increased accumulation of SPIONs occurs at non-uniform shear stress region at the outer walls of bifurcation. Application of external magnet allowed enhanced accumulation of SPIONs at the regions of non-uniform shear stress even at 10-fold decreased nanoparticle concentrations, accompanied by a reduced endothelial uptake in laminar shear stress regions. Increased uptake of SPIONs at non-uniform shear stress region was well tolerated by ECs and did not affect endothelial cell viability or resistance to prolonged shear stress exposure. At the tested concentrations, SPIONs were largely metabolized within 3 days post-application. Importantly, no significant differences in TNF-α-induced monocytic cell recruitment were detected between controls and SPION-treated ECs.

Conclusions: Magnetic targeting allows localized accumulation of increased amounts of SPION at the region of interest under physiologic-like flow conditions. These findings indicate that magnetic
targeting can constitute a suitable technique for the delivery of imaging and therapeutic nanoparticles to atherosclerotic lesions.

Accumulation of circulating SPIONs by external magnetic force in the region of interest.

Subdivision 2. Translational Research

Presentation Preference Electronic poster presentation

Additional information
Circadian activity of cholesterol 7α-hydroxylase is determined by -203A/C polymorphism of CYP7A1 gene

Abstract nr. 137
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Topic Dyslipidemia; Lipids, Lipoproteins and Apolipoproteins
Keywords Genetics, Lipids, Metabolism

The -203A/C polymorphism of CYP7A1 gene encoding cholesterol 7α-hydroxylase (CYP7A1) plays an important role in determination of cholesterolemia responsiveness to the diet. Importantly, the CYP7A1 activity displays a considerable diurnal variation. Therefore, we analyzed whether -203A/C polymorphism is involved in circadian regulation of CYP7A1 activity.

The three experiments lasting 15 hours were carried out in 16 healthy male volunteers, 8 homozygous for -203A and 8 homozygous for -203C variant. First of these experiments was carried out after one day treatment with bile acid sequestrant (Questran®), the second after one day treatment with chenodeoxycholic acid (Chenofalk®) and the third one without any treatment (control). The concentration of 7α-hydroxy-4-cholesten-3-one (C4), a serum marker of CYP7A1 activity, was measured from 7 AM to 10 PM in 90min intervals. The experiments were carried out in at least three weeks intervals and their order was randomized.

The treatment with bile acid sequestrant resulted in fourfold and eightfold increase of CYP7A1 activity during the day in A and C allele homozygous carriers, respectively. The treatment with chenodeoxycholic acid resulted in a pronounced decrease in CYP7A1 activity in carriers of both variants. Importantly, the homozygous carriers of -203A allele manifested a noticeable peak of enzyme activity around 1 PM whereas no such peak could be observed in -203C allele carriers.
It can be concluded that -203A/C polymorphism of CYP7A1 has a substantial impact on diurnal variation of enzyme activity. The mechanism behind such an effect and its possible role in determination of cholesterolemia responsiveness to the dietary fat and cholesterol remains to be determined.

Supported by grant No. NT 13151-4/2012 from IGA MH CR.

Subdivision 1. Basic Science

Presentation Preference Electronic poster presentation
Additional information
Carriers of the PCSK9 R46L variant are characterized by an anti-atherogenic lipoprotein profile assessed by nuclear magnetic resonance spectroscopy

Abstract nr. 138
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Topic Epidemiology of CVD; The Risk Factor Concept
Keywords Inflammation, Lipoproteins, PCSK9

Background — Carriers of the PCSK9 R46L genetic variant are characterized by low levels of low-density lipoprotein (LDL) cholesterol and a decreased risk of cardiovascular disease (CVD). Whether these individuals are characterized by other features of a more beneficial lipoprotein-lipid profile is unknown.

Methods and Results — We measured the lipoprotein-lipid profile of 2373 participants of the European Prospective Investigation into Cancer and Nutrition (EPIC)-Norfolk study by nuclear magnetic resonance spectroscopy. Among them, 77 participants carried at least one allele of the R46L genetic variant. Carriers and non-carriers had comparable clinical characteristics (age, body mass index, blood pressure, smoking and diabetes prevalence). As expected, carriers had lower LDL cholesterol levels compared to non-carriers (3.75±0.99 vs. 4.16±1.01 mmol/L, p<0.001 in carriers vs. non-carriers, respectively). Carriers were characterized by a lower very low-density lipoprotein (85.8±26.2 vs. 99.0±33.3 nmol/L, p<0.001 in carriers vs. non-carriers, respectively) particle concentration and a lower LDL particle concentration of any size (1479.7±396.8 vs. 1662.9±458.3 nmol/L, p<0.001 in carriers vs. non-carriers, respectively). Total high-density lipoprotein (HDL) particle concentration was not different in carriers vs. non-carriers. However, carriers had a higher concentration of large HDL particles (6.4±3.3 vs. 5.5±3.5 nmol/L, p=0.04 in carriers vs. non-carriers, respectively) and a higher mean HDL particle size (9.0±0.4 vs. 8.9±0.5 nm, p=0.04 in carriers vs. non-carriers, respectively). We also found that carriers were characterized by a lower secretory phospholipase A2 (sPLA2) activity (4.21±0.88 vs. 4.61±1.26 nmol/ml/min p=0.004 in carriers vs. non-carriers, respectively) and a lower lipoprotein-associated phospholipase A2 (Lp-PLA2) activity (47.5±14.1 vs. 52.4±16.2 nmol/ml/min, p=0.008 in carriers vs. non-carriers, respectively).

Conclusions — Results of this study suggest that on top of having low LDL cholesterol levels, carriers of the PCSK9 R46L genetic variant have a lower VLDL and LDL particle concentration, a higher concentration of large HDL particles and lower sPLA2 and Lp-PLA2 activity. This anti-atherogenic profile may explain to a certain extent the reduced CVD risk observed in carriers of the PCSK9 R46L genetic variant.
Subdivision 4. Not applicable. Abstract matches with track c

Presentation Preference Oral presentation
Additional information
Severe childhood infection is associated with adverse adult cardiovascular and metabolic risk phenotypes: The Cardiovascular risk in Young Finns Study

Abstract nr. 139
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Topic Epidemiology of CVD; The Risk Factor Concept
Keywords Cardiovascular Disease,Epidemiology,Inflammation,Obesity

**Background:** Childhood infections are ubiquitous and elicit repeated inflammatory responses. The relationships between the severity and timing of infection and later cardiometabolic risks are largely unknown.

**Methods:** Using fully adjusted multiple regression models, we investigated associations between infection-related hospitalisation (IRH, a marker of the severity of infection) and anthropometric, metabolic, and cardiovascular parameters in childhood and adulthood in 1376 participants from the Young Finns Study who had lifetime IRH data available. We also examined whether socio-economic status (SES) influenced the relationship between childhood infection and adult cardiometabolic outcomes.

**Findings:** By a mean age of 35.1 years, 597 (43·4%) individuals had ≥ 1 IRH, of which 181 (30·3%) occurred before 5 years of age. Early childhood IRH correlated with adverse adult (but not childhood) metabolic parameters; increased body mass index (BMI) (P=0·02) and metabolic syndrome (odds ratio 1·56, 95% CI 1·03-2·35, P=0·03), adjusting for age, sex, childhood BMI, and family income. Brachial flow-mediated dilatation (FMD) was significantly lower in those with early child IRH (mean±SEM 8.15±0.37 vs. 9.10±0.16%, P=0.03). These individuals had a 1.84% (95% CI 0.64-3.04, P=0.002) greater decrease in FMD between adult follow-ups at mean ages of 27 and 33 years. Childhood IRH was associated with increased asymmetrical dimethylarginine in adulthood (0.62±0.01 vs 0.59±0.01 μmol/l, P=0.04), adjusted for age, sex, adult BMI, and creatinine. Early childhood IRH was associated with lower carotid distensibility (1.95±0.06 vs. 2.09±0.02 %/10 mmHg, P=0.02), but not with carotid intima-media thickness (0.601±0.006 vs. 0.596±0.003 mm). The frequency of childhood IRH did not differ significantly between those of low and high SES. However there were significant interactions between childhood IRH & low SES, and adverse adult cardiometabolic parameters.
Conclusions: Childhood infections may contribute to causal pathways leading to adult cardiometabolic diseases. Childhood infection may be one mechanism underpinning the social gradients observed in cardiometabolic non-communicable diseases.

Subdivision 4. Not applicable. Abstract matches with track c

Presentation Preference Oral presentation
Additional information
Validation of the Pooled Cohort Equations in a Hong Kong Chinese Cohort

Abstract nr. 140
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Topic Epidemiology of CVD; The Risk Factor Concept
Keywords Cardiovascular Disease, Risk stratification

Objective: The 2013 American College of Cardiology and the American Heart Association guidelines recommended the Pooled Cohort equations for evaluation of atherosclerotic cardiovascular disease risk of individuals. We investigated the usefulness of the Pooled Cohort equations in Chinese by validating this risk prediction model using the Hong Kong Cardiovascular Risk Factor Prevalence Study (CRISPS) cohort.

Methods: The Hong Kong CRISPS is a population-based prospective cohort study of cardiovascular risk factors among 2895 Chinese men and women (aged 25-74 years) initiated in 1994. Cardiovascular (CV) events were ascertained until December 2013. The discrimination and calibration of the Pooled Cohort equations was evaluated and compared with the Framingham risk equation. A Hosmer-Lemeshow Chi-square statistic ($X^2$) < 20 indicated good calibration.

Results: The discrimination power of the 2 models in both men and women was moderate (C-statistic > 0.7). However, the calibration score of both models was unacceptable in men (Pooled Cohort $X^2$ = 24.1, Framingham $X^2$ = 20.1). Since the Framingham model systematically overestimated CV risk [average predicted risk 18.3% (95% CI 15.5-21.0) versus average observed risk 13.4% (95% CI 11.0-15.8)], this can be corrected by recalibration of the model using the CRISPS data [average predicted risk 11.5% (95% CI 9.2-13.7) versus average observed risk 11.8% (95% CI 9.6-14.1)]. Recalibration cannot be applied to the Pooled Cohort model because the degree of miscalibration varied across the different risk categories. In women, although calibration of Pooled Cohort ($X^2$ = 10.1) and Framingham model ($X^2$ = 12.1) appeared similar, the accuracy of the Framingham model was better [average predicted risk 6.2% (95% CI 4.6-7.7) versus average observed risk 6.3% (95% CI 4.8-7.9)] than the Pooled Cohort model [average predicted risk 4.8% (95% CI 3.3-6.3) vs average observed risk 6.9% (95% CI 5.1-8.7)].

Conclusions: Risk prediction models should be able to discriminate between individuals with and without disease, and also well-calibrated so that predicted risk estimates matches as closely as possible the observed risk in the population. The Pooled Cohort equations provide poor calibration and moderate discrimination in Hong Kong Chinese, especially in men. The Framingham risk equation can be applied to the Hong Kong population but requires recalibration in men.
Subdivision 4. Not applicable. Abstract matches with track c

Presentation Preference Mini-oral presentation
Additional information
The effect of simvastatin treatment in hypercholesterolemic patients: a prospective study using lipidomic profiling

Abstract nr. 141
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Topic Dyslipidemia; Lipids, Lipoproteins and Apolipoproteins
Keywords Cardiovascular Disease, Dyslipidemia, Lipids

Background: Statins are potent cholesterol-lowering drugs, widely prescribed to reduce cardiovascular risk reduction. While reduction of mevalonate pathway metabolites, including coenzyme Q10 (CoQ10) have been well-documented, the effect of statins on other lipid-related metabolites included sphingolipids and phospholipids is less well-studied. We hypothesize that statins significantly affect levels of lipid-related metabolites, beyond cholesterol, and these effects are independent of their reduction in CoQ10.

Aim: To investigate the effects of simvastatin, with/without CoQ10 (ubiquinol) supplementation, on serum lipidomic profiles in patients with hypercholesterolemia.

Methods: In this prospective double-blind study, serum lipidomic profiles were compared between baseline and after 12-week treatment of simvastatin (20mg daily), in 40 patients randomized to receive either supplementation of ubiquinol (Gp-A) or placebo (Gp-B). Lipidomic profiling was performed using UPLC and mass spectrometry and analysis using SIMCA 13.0 software, including principal component analysis (PCA), and orthogonal partial least-squares discriminant analysis (OPLS-DA). Univariate statistical tests (Paired t-test and Man-Whitney U test) were performed on SPSS software. The p values less than 0.05 were considered significant.

Results: Mean age (1SD) of patients in this study was 46.2 (12.0) years. All patients received simvastatin 20mg daily, and there was no significant differences, in terms of age, weight, baseline lipid profiles) between the groups receiving ubiquinol or ubiquinol-placebo. Baseline low-density-lipoprotein-cholesterol (LDL-C) was 4.35 (0.92) mmol/l, reducing by 30% with simvastatin treatment, with no attenuation of LDL-C lowering with ubiquinol supplementation. CoQ10 levels were significantly lowered with simvastatin treatment (Gp-B) and but not Gp-A who received supplementation of ubiquinol. Simvastatin treatment resulted in significant lowering of glycerolipids, sphingomyelins and phospholipids, and increase in lysophophotidylcholine (20:4), lysophophotidylethanolamine (20:4/0:0) and lysophophotidylethanolamine (22:6/0:0). Although the levels of some glycerolipids and ceramides were higher in Gp-A at 12-weeks compared to those in
Gp-B, ubiquinol supplementation had relatively small effect on simvastatin-induced reduction of these lipids.

**Conclusion:** In patients with hypercholesterolemia, simvastatin significantly lowers serum phospholipids and sphingolipids, and this was independent of CoQ10 supplementation for majority of lipid-related metabolites. Future molecular studies are required to study the functional significance of these changes at the cellular and tissue levels.

Subdivision 2. Translational Research

Presentation Preference Electronic poster presentation
Additional information
Statin-fenofibrate combination therapy for hypertriglyceridemia in statin-treated patients at high cardiovascular risk

Abstract nr. 142
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Topic Dyslipidemia; Lipids, Lipoproteins and Apolipoproteins
Keywords Dyslipidemia, Hypolipidemic Drugs, Triglycerides

Background: Statin-fibrate combination therapy was recommended by several lipid guidelines as an option for patients with hypertriglyceridemia after statin monotherapy to reduce the residual CV risk related to hypertriglyceridemia. However, clinical experience about the efficacy and safety of statin-fibrate combination therapy in China is insufficient due to concern about the safety profile.

Method: 506 subjects were enrolled in 28 sites in 14 cities of China. After at least 2-month statin monotherapy (including 7 types of statins) with standard dose, patients with coronary heart disease (CHD) or CHD risk equivalent and TG≥1.7mmol/L were enrolled and given fenofibrate 200mg daily on top of statins for 8 weeks. Lipid and safety parameters were compared between baseline and after treatment.

Results: After 8 weeks of fenofibrate add-on treatment, mean TG level decreased from 3.00mmol/L at baseline to 1.77mmol/L (-38.1%), mean VLDL-C level decreased from 0.95mmol/L to 0.63mmol/L (-22.7%) and mean HDL-C was increased from 1.07mmol/L to 1.22mmol/L (17.4%). Neither creatine kinase (CK) increased to ≥ 5 times of upper limit of normal (ULN) nor cases of rhabdomyolysis were reported. 6 subjects (1.22%) were reported with ALT and/or AST elevated to ≥ 3 times of ULN, all of them recovered shortly after discontinuation of statins and fenofibrate.

Conclusion: In patients at high CV risk with hypertriglyceridemia after standard statin therapy, add-on fenofibrate therapy effectively further improved lipid profile with acceptable safety profile.

Subdivision 3. Clinical Studies

Presentation Preference Electronic poster presentation
Additional information
Low levels of apoB-100 autoantibodies are associated with increased risk of coronary events

Abstract nr. 144
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Topic The Pathogenesis of Atherosclerosis; Immunity, Inflammation, and the Endothelium
Keywords Apolipoproteins, Cardiovascular Disease, Immunity, LDL

Aim: Immune responses against oxidized low density lipoproteins (LDL) play a key role in atherosclerosis development. Previous studies have indicated inverse associations between autoantibodies to oxidized LDL epitopes and cardiovascular disease (CVD). The purpose of this study was to investigate associations between autoantibodies against the apolipoprotein B-100 (apoB-100) peptides p45 and p210 and risk of CVD.

Methods and Results: In a prospective study, including 5400 individuals belonging to the cardiovascular arm of the Malmö Diet and Cancer cohort, apoB-100 autoantibodies were analyzed by ELISA. The analysis revealed significantly lower levels of IgM autoantibodies recognizing the native and malondialdehyde (MDA) apoB-100 peptides p45 and p210 and also lower IgG levels recognizing native p210 in individuals with a later incidence of CVD compared to controls. The autoantibodies were further analyzed in relation to coronary and stroke events. The same pattern was detected for coronary events, whereas the differences disappeared for incidence of stroke. No significant correlations between the autoantibodies and common and bulb carotid intima-media thickness were detected after adjustment for common risk factors (age, sex, LDL/HDL ratio, triglycerides, systolic blood pressure, smoking and diabetes). On the other hand, in a logistic regression model a significant association was found between high levels of IgG-p210_{native} (OR = 0.811, 95% CI 0.69-0.94, P=0.007) and occurrence of carotid plaques after adjustment for the risk factors. When tertiles of autoantibody levels were entered into a Cox proportional hazard regression model, a significant association was identified between high levels of IgM-p45_{MDA} (Hazard ratio (HR) [95%CI]: 0.73 [0.56, 0.96], P =0.022) or IgG-p210_{native} (Hazard ratio (HR) [95%CI]: 0.74 [0.56, 0.97], P =0.030) and a lower risk of incidence of coronary events after adjustment for the risk factors.

Conclusion: Taken together, the present findings suggest that high levels of apoB-100 autoantibodies protect against incidence of coronary events.

Subdivision 3. Clinical Studies

Presentation Preference Oral presentation
Additional information
Salsalate attenuates diet induced non-alcoholic steatohepatitis by decreasing lipogenic and inflammatory processes.

Abstract nr. 145
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Topic Dyslipidemia; Lipids, Lipoproteins and Apolipoproteins
Keywords Inflammation, Metabolism, Prevention

Background and aims. Salsalate is an anti-inflammatory drug that was recently found to exhibit beneficial metabolic effects on glucose and lipid metabolism. Although its utility in the prevention and management of a wide range of vascular disorders as well as of type 2 diabetes and metabolic syndrome has been suggested before, the potential of salsalate to protect against non-alcoholic steatohepatitis (NASH) remains unclear. The aim of the present study was therefore to ascertain the effects of salsalate in the development of NASH.

Methods. Transgenic APOE*3Leiden.CETP mice were fed a high fat high cholesterol diet with or without salsalate for 12 and 20 weeks. The effects on body weight, plasma parameters, liver histology and hepatic gene expression were assessed.

Results. Salsalate prevented weight gain, improved dyslipidemia and insulin resistance and ameliorated diet-induced non-alcoholic steatohepatitis, as shown by decreased hepatic micro- and macrovesicular steatosis, reduced hepatic inflammation and reduced development of fibrosis. Salsalate affected lipid metabolism by increasing β-oxidation and decreasing lipogenesis, as shown by the activation of PPAR-α, PGC1-β, RXR-α and inhibition of MLXIPL/ChREBP controlled genes, respectively. Inflammation was reduced by down-regulation of the NFκB pathway and fibrosis development was prevented by down-regulation of TGF-β signaling.

Conclusions. Salsalate was shown to exert a preventive effect on the development of NASH and progression to fibrosis. These data suggest a clinical application of salsalate in preventing NASH.

Subdivision 1. Basic Science

Presentation Preference Oral presentation
Additional information
Clinical relevance of morphological features of intracranial atherosclerosis in high resolution MRI vessel wall imaging

Abstract nr. 146
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Topic The Pathogenesis of Atherosclerosis; Immunity, Inflammation, and the Endothelium
Keywords Atherosclerosis, Imaging, Vulnerable Plaque

Introduction: Stroke in Chinese and other Asian populations is unique, in which intracranial arterial disease (ICAD), rather than extracranial carotid stenosis, accounts for the pathophysiology. The study aimed to explore the clinical relevance of morphological features of intracranial atherosclerosis evaluated by High resolution magnetic resonance imaging (HRMRI) vessel wall imaging in Chinese stroke patients.

Subjects and Methods: International Review Board approval was obtained for this retrospective study. All patients gave written informed consent. Imaging was performed on a 3 teslar Achieva MR system (Philips Healthcare, Cleveland, OH, USA) with an 8-channel SENSE head coil. The protocol included a T1-weighted (T1w) volumetric isotropic turbo spin-echo acquisition (VISTA) vessel wall sequence, before and after (83% of patients) contrast administration, and a Time-Of-Flight Magnetic Resonance Angiography (TOF-MRA) sequence. Before acquisition of the contrast enhanced T1w VISTA sequence, 0.1 mL/kg of a gadolinium-containing contrast agent (Gadobutrol, Gadovist 1.0 mmol/mL, Bayer Schering Pharma, Newbury, UK) was administered to the patient.

Results: Nineteen patients (7 females; mean age 67 years, range 47-81 years) with an MCA stenosis were recruited. Different degrees of intracranial vessel wall lesions were identified in 18 patients, totaling 57 lesions (12%, 57/494). The morphological comparison between symptomatic and asymptomatic lesions was demonstrated in Table 1. The rate of luminal stenosis of intracranial large arteries detected by MRA was higher in symptomatic lesions than those in asymptomatic lesions (36.9% vs. 10.5%, P=0.001). There was a trend that diffuse lesions along the arterial longitudinal axis was more frequent in symptomatic lesions than those in asymptomatic lesions (42.1% vs. 18.4%, P=0.062). The enhancement of lesions after contrast administration was similar between symptomatic and asymptomatic lesions (47.4% vs. 42.1%, p=0.781).
Conclusions: Intracranial vessel wall imaging using a 3D T1w VISTA vessel wall sequence could provide detailed morphological assessment of plaque features. The findings based on this pilot study suggest that both luminal stenosis and morphological features of individual lesions may play a synergetic effect on stroke occurrence.

Subdivision 3. Clinical Studies

Presentation Preference Oral presentation

Additional information
PBMC gene expression of inflammatory markers after an acute bout of resistance exercise in young and elderly subjects

Abstract nr. 147
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Topic Primary & Secondary prevention of CVD; Lifestyle Measures and Pharmacological Intervention
Keywords Atherosclerosis,Inflammation,Prevention

Regular physical activity promotes an anti-inflammatory response in the body. This may be one of the explanations why exercise protects against several diseases. In contrast, an acute bout of resistance exercise temporarily increases the levels of inflammatory cytokines in the muscle. How exercise influences peripheral mononuclear blood cells (PBMCs) is less clear. We wanted to investigate how an acute bout of resistance exercise affects the inflammatory gene expression in PBMCs.

Twenty-two young (25.0 ± 3.4 yrs) and fifteen elderly (74.2 ± 3.8 yrs) healthy men and women performed an acute bout of resistance exercise – 4x8 repetition maximum (RM) of leg press and knee extension, with a new set starting every third minute. Based on RNA isolated from PBMCs, 48 genes were analysed using RT-qPCR.
We will present data from the study, and discuss the possible impact of these, related to the development of chronic low grade inflammation, at the meeting.
Funding and conflict of interest: The project is funded by the Norwegian Research Council and the involved institutions.

Subdivision 5. Not applicable. Abstract matches with track d

Presentation Preference Oral presentation
Additional information
Intracranial atherosclerotic lesion characteristics correlate with cerebrovascular lesion load after TIA or ischemic stroke: a 7.0 tesla MRI study

Abstract nr. 148
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Topic The Pathogenesis of Atherosclerosis; Immunity, Inflammation, and the Endothelium
Keywords Atherosclerosis, Cardiovascular Disease, Imaging

Introduction. Intracranial atherosclerosis (ICAS) is denoted as one of the most prevalent cause of stroke worldwide. Assessing both macroinfarcts and cortical microinfarcts (CMI) in patients with a history of cerebrovascular disease may provide additional information on the spectrum of parenchymal brain injury caused by ICAS. In this study we investigated the presence of CMI at 7T MRI in patients with TIA or ischemic stroke of the anterior circulation and explored the relationship between ICAS, CMI and macroinfarcts.

Methods. Eighteen patients presenting with ischemic stroke (n=12) or TIA (n=6) underwent 7T MR imaging; the protocol included a FLAIR- and the MPIR-TSE intracranial vessel wall sequence. ICAS lesions and their characteristics, as well as infarcts (CMI and macroinfarcts), were scored by two raters (Fig.1). The relationship between ICAS lesions, calculated ratios of characteristics and infarcts were examined using linear regression analyses.

Results. A total number of 101 CMI (78% of patients), 31 macroinfarcts (67%) and 75 ICAS lesions (100%) were found. Seventy-six and sixty-five percent of CMI and macroinfarcts, respectively, were found in the same vascular territory as the ICAS lesions. A positive correlation existed between the number of macroinfarcts and CMI (p<0.05) and between a concentric configuration and macroinfarcts (p<0.01); for CMI no correlation was found. A diffuse thickening pattern was positively correlated to macroinfarcts (p<0.05); a weak trend was found for CMI (p=0.09).

Conclusion. This study shows that in patients with TIA or ischemic stroke CMI represent a relevant portion of the total cerebrovascular lesion load and coexist with macroinfarcts. These results demonstrate that the spectrum of parenchymal damage caused by ICAS is not restricted to macroinfarcts alone but also include CMI.

Fig1.(A) FLAIR shows infarct and CMI's; zoomed view(B). Vessel wall images show thickening(C+D) and enhancement(E) of the right M1(C) and M2(D) segments

Subdivision 3. Clinical Studies

Presentation Preference Oral presentation

Additional information
Discriminating host defense to fungal and bacterial infections by genome-scale metabolic modeling of human PBMCs

Abstract nr. 150
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Topic The Pathogenesis of Atherosclerosis; Immunity, Inflammation, and the Endothelium
Keywords Inflammation, Metabolism

This study aims at discriminating the metabolic pathways induced during induction of host immune responses by the fungal pathogen Candida albicans or the bacterial stimuli Escherichia coli-derived LPS, Borrelia burgdorferi, and Mycobacterium tuberculosis (MTB). We have developed PBMC (Peripheral Blood Mononuclear Cell) -specific Genome-scale Metabolic models (GEMs) for all immune challenges mentioned above. PBMC-specific GEM describes PBMC’s metabolic physiology with appropriate biochemical, genetic and genomic knowledge of PBMC. In this study, a PBMC-specific GEM was reconstructed for each immune challenge by applying the tINIT algorithm (Agren et al. 2014) based on proteomics and RNA sequencing data of unstimulated PBMCs together with PBMC microarray data stimulated by Borrelia, LPS, MTB or Candida. Within each metabolic network, the “hot regions” where significant gene expression changes occurred were identified. Through comparing such “hot metabolic regions” between fungal and bacterial stimulation, we identified de novo purine synthesis and cholesterol biosynthesis as the metabolic signatures of Candida-induced inflammation. We also propose that squalene 2,3-oxide and 5-aminoimidazole ribonucleotide (AIR), the intermediary metabolites in de novo purine synthesis and cholesterol biosynthesis can be used as biomarkers for diagnosing a Candida-induced inflammatory response. All the predictions are currently being validated using metabolomics-based approaches.

Keywords: Candida albicans, host defense, PBMCs, genome-scale metabolic models, biomarkers

Subdivision 1. Basic Science

Presentation Preference Oral presentation
Additional information
Assessment of Lipoprotein Particle Number by High-Performance Gel Permeation Chromatography in Patients with Cholesteryl Ester Transfer Protein Deficiency

Abstract nr. 151
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Topic Dyslipidemia; Lipids, Lipoproteins and Apolipoproteins
Keywords Dyslipidemia, HDL, Lipoproteins, Metabolism

Background: Recent studies showed that elevated plasma HDL-cholesterol (HDL-C) levels treated by CETP inhibitors were not associated with incidence of cardiovascular events. Therefore, we should take other parameters other than HDL-C levels into account.

Methods and Results: In this study, 9 CETP-deficient (CETP-D) patients, whose serum CETP mass was <0.1μg/mL, were compared with 9 normolipidemic controls. Free cholesterol, cholesteryl ester, triglyceride and phospholipid levels in each 20 lipoprotein subclass were determined by computer-assisted high-performance gel permeation chromatography (HPLC). Furthermore, we calculated the particle number of each subclass by using HPLC data, serum lipids and apolipoproteins, which is newly-developed LipoSEARCH® system (Skylight Biotech Inc, Akita). As we reported previously, serum HDL-C levels were markedly elevated in CETP-D patients compared with controls. The number of very large and large HDL particles in CETP-D patients was markedly higher than that in controls (4237.3±2353.4nM vs 213.4±55.7nM, 7672.2±1368.3nM vs 1720.2±536.6nM, respectively; p<0.001), while the number of small and very small HDL, which have anti-atherogenic function, was significantly lower (4339.1±937.4nM vs 5690.3±467.8nM, 1999.4±514.8nM vs 3256.5±294.0nM, respectively; p<0.001). The number of large and medium LDL was significantly lower in CETP-D patients than that in controls (158.3±36.4nM vs 240.6±51.1nM, 349.1±69.9nM vs 557.3±94.8nM, respectively; p<0.001), whereas the number of very small LDL, which is known to be atherogenic, was significantly higher (233.2±64.8nM vs 171.4±22.1nM, p=0.016).

Conclusion: The lipoprotein particle numbers calculated by this newly-developed HPLC method are dramatically changed in CETP-D patients, suggesting a proatherogenic lipoprotein profile by CETP deficiency.
Subdivision 3. Clinical Studies

Presentation Preference Electronic poster presentation
Additional information
Heritability Associated with Lp(a) and Apo(a) Differ Across Apo(a) Allele/Isoform Sizes and Ethnicity

Abstract nr. 153
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Topic Dyslipidemia; Lipids, Lipoproteins and Apolipoproteins
Keywords Apolipoproteins, Genetics, Lp(a)

**Background:** Levels of lipoprotein(a), Lp(a), an independent cardiovascular risk factor, are under strong genetic regulation through the apolipoprotein(a), apo(a), gene. However, the degree of heritability of Lp(a) level and apo(a) allele/isof orm within and across families of different ethnic background is not well understood. The goal of this study was to investigate the heritability of Lp(a) level and apo(a) allele/isof orm in a family-based cohort, consisting of Caucasians and African-Americans, where a substantial difference in the distributions of Lp(a) levels and apo(a) sizes exists.

**Methods:** Families with two parents and two biological children were recruited from the general population (239 Caucasians, 88 African-Americans, 6-74 years). We determined 1) Lp(a) level [apo(a)-size insensitive ELISA], 2) apo(a) allele sizes (pulsed field electrophoresis), 3) apo(a) isoforms (Western blotting), and 4) allele-specific apo(a) level (ASL), the amount of Lp(a) carried by individual apo(a) isoform. Heritability of these traits was estimated by measuring the relative contribution of the genetic component of variance responsible for parent-offspring resemblance.

**Findings:** For the entire study population, the estimated heritability (h²) of Lp(a) level, adjusted for ethnicity, was 0.95 ± 0.07. We then assessed heritability of smaller and larger apo(a) sizes for given allele pairs. The heritability estimates of ASL for the smaller apo(a) allele was greater than those of the larger allele (0.91 vs. 0.59, p=0.0173). Similarly, although not statistically significant, heritability estimates of apo(a) isoforms (0.90 vs. 0.70) and alleles (0.98 vs. 0.82) for the smaller apo(a) were higher than those of the larger apo(a). When analyzed by ethnicity separately, an overall lower heritability estimate was observed in African-Americans vs. Caucasians for all traits. Notably, the heritability estimate for the larger apo(a) allele was lower in African-Americans vs. Caucasians (0.28 vs. 0.95, p=0.0012).

**Conclusions:** Overall, Lp(a) level as well as all traits associated with the smaller apo(a) allele were more strongly determined by genetic factors, although with a varying degree of ethnic influence. Ethnic differences in heritability attributed to genetic variation of the larger apo(a) allele warrants further investigations.
Subdivision 3. Clinical Studies

Presentation Preference Oral presentation
Additional information
The expression of FceR receptors for IgE in human endothelial cells and its possible role in the endothelial integrity regulation

Abstract nr. 154
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Topic The Pathogenesis of Atherosclerosis; Immunity, Inflammation, and the Endothelium
Keywords Endothelium, Immunity, Inflammation

Background and aims: The presence of IgE and its FceR receptors in human atherosclerotic plaques suggests the potential involvement of IgE in the pathogenesis of atherosclerosis. The aim of the study was to assess the FceRs mRNA expression in human endothelial cells (EC) and their functional effect on the endothelial integrity.

Material and methods: FccR mRNA presence in EC was evidenced by the sequencing and mRNA expression in real-time PCR. To increase the FccRs mRNA expression, EC were induced with IL-4 (1, 10 and 100 ng/ml) for 48 hours. In the next step, the involvement of FccRs in the regulation of the endothelial integrity was assessed upon pre-stimulation of EC with, IL-4, and following induction, firstly, with anti-DNP-BSA IgE (250ng/ml) which is supposed to bind to FccRs and, secondly, with the specific antigen DNP–BSA (100, 250, 500ng/ml) binding to IgE in the Real-time Cell Electric Impedance Sensing (RTCA-DP) system.

Results: Our results revealed the presence of FcεRI and FcεRII mRNA expression in EC both in sequencing and real-time pcr. IL-4 (1 and 10 ng/ml) induced 2-fold increase of FcεRI mRNA expression as compared to the unstimulated control (p<0.001 and p<0.05, respectively) and 3-fold increase of FcεRII mRNA expression (p<0.05). In EC pre-induced with IL-4, linking of IgE with DNP-BSA caused the significant 20% increase of endothelial integrity observed in RTCA-DP system as compared to the unstimulated control (p<0.01).

Conclusion: FcεRI and FcεRII mRNA expression in endothelial cells suggests the existence of a potential mechanism of IgE-mediated response of endothelium to allergenic antigens.
Fig. 1 Cell-electrode impedance detection of the endothelial cells
Subdivision 1. Basic Science

Presentation Preference Mini-oral presentation
Additional information
Cholesterol Efflux Capacity in Patients with Familial Hypercholesterolemia

Abstract nr. 155
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Topic Epidemiology of CVD; The Risk Factor Concept
Keywords Familial Hypercholesterolemia, HDL, Reverse Cholesterol Transport, Risk Factor

Cholesterol efflux capacity from macrophages has been found to have a strong inverse association with carotid intima-media thickness (cIMT) and the likelihood of cardiovascular disease (CVD) independent of the high-density lipoprotein cholesterol (HDL-C) levels, supporting the importance of HDL function over the simple measurement of HDL-C levels. Familial hypercholesterolemia (FH) is a prevalent inherited disorder characterized by marked elevation of plasma low-density lipoprotein cholesterol concentrations and premature CVD. To date, residual risks in statin-treated FH have been rarely assessed. Accordingly, the present study was performed to investigate the relationships between cholesterol efflux capacity and clinical features including Achilles tendon thickness, subclinical atherosclerosis, and the presence of CVD in FH patients treated with statins. The subjects were 148 ethnic Japanese with clinically or genetically diagnosed as heterozygous FH previously treated with statins. Age ranged from 22 to 85 years with a mean age of 61 years [standard deviation ± 15], and 56 (37.8%) patients were known to have CVD. Serum cholesterol efflux capacity was measured in 3H-cholesterol-labeled J774.1 cells and incubated with 2.8% apolipoprotein B-depleted serum. Significant inverse relationships between cholesterol efflux capacity and Achilles tendon thickness as well as cIMT were observed after adjustment for age, sex and traditional cardiovascular risk factors (the presence of diabetes, hypertension, and/or obesity, low-density lipoprotein cholesterol levels, smoking history). However, subsequent adjustment for HDL-C attenuated these relationships. In a logistic-regression analysis adjusted for age, sex, and traditional cardiovascular risk factors, an increased cholesterol efflux capacity was associated with a decreased risk of CVD even after the addition of HDL-C level as a covariate (odds ratio per 1% increase, 0.94; 95% CI, 0.88 to 0.99; P < 0.05). The results were similar when the apolipoprotein A-I level was substituted for the HDL cholesterol level (odds ratio per 1% increase, 0.94; 95% CI, 0.88 to 1.00; P < 0.05). Among known cardiovascular risk factors, the presence of hypertension was also associated with the presence of CVD. These results suggest that cholesterol efflux capacity might be a novel biomarker as well as a therapeutic target for atherosclerosis in statin-treated FH patients.

Subdivision 3. Clinical Studies

Presentation Preference Oral presentation
Additional information
Estimation of Vasodilatory Effect of Hydrogen sulfide (H2S) using ultrasound on Rat Abdominal aorta

Abstract nr. 158
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Topic The Pathogenesis of Atherosclerosis; Immunity, Inflammation, and the Endothelium
Keywords Atherosclerosis, Cardiovascular Disease

Although hydrogen sulfide (H2S), a colorless gas with a strong odor of rotten eggs, has been recognized as a toxic gas affecting living organisms for nearly 300 years, it is now considered the third member of a family of endogenous biologically active gaseous transmitters, termed gasotransmitter or gasomediator family, along with nitric oxide (NO) and carbon monoxide (CO). H2S plays important protective roles in regulatory mechanisms of multiple systems, including cardiovascular, nervous, and immune systems. It causes relaxation of vascular smooth muscle, which results in increased organ blood flow, and hence lowers the systemic blood pressure. In addition, it has been shown to be involved in angiogenesis, energy metabolism and inflammation by acting specifically on ATP-sensitive K+ channels. Thus, abnormality in metabolism of hydrogen sulfide could lead to several diseases. The present study describes the effects of exogenous hydrogen sulfide on abdominal aorta of adult rats by using ultrasound machine. The H2S donor NaHS (5 mg/kg for 10 min) was injected in an infusion rate of (0.5 mg/kg/min), and the luminal aortic diameter during and after injection for about 60 min was measured by using ultrasound machine with assistance of computer software. It was found that the maximum dilatation was achieved after full dose injection as a concentration response curve and after 45 min from injection as a time response curve, suggesting the blood vessels are significantly dilated when exposed to H2S. As H2S is required for the physiological control of vascular function, it may be used therapeutically in hypertension and coronary heart disease.

Subdivision 1. Basic Science

Presentation Preference Electronic poster presentation
Additional information
Relationship of fibroblast growth factor 21 with microvascular disease in the Fenofibrate Intervention and Event Lowering in Diabetes Study

Abstract nr. 159
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Topic Primary & Secondary prevention of CVD; Lifestyle Measures and Pharmacological Intervention
Keywords Diabetes, Epidemiology, Metabolism, Risk Factor

Baseline fibroblast growth factor 21 (FGF21) levels can predict total cardiovascular disease events in the Fenofibrate Intervention and Event Lowering in Diabetes (FIELD) Study. This study investigated the relationship of plasma FGF21 levels with baseline and on-study microvascular disease in patients with type 2 diabetes from the FIELD study. Plasma FGF21 levels were measured by enzyme-linked immunosorbent assay in 9,697 study participants at baseline. Total microvascular disease was defined as the presence of any nephropathy, retinopathy, neuropathy, and/or microvascular amputation. We assessed the association of FGF21 levels with both baseline and the development of new on-study total microvascular disease during the 5-year follow-up. Higher baseline FGF21 levels were found in patients with baseline total microvascular disease (P<0.001). The associations remained significant after further adjusting for confounding factors (OR [95% CI] = 1.13 [1.08-1.19] per SD increase in ln-transformed FGF21 levels, P <0.001). Among 6,465 patients without baseline microvascular disease, 1,517 patients developed on-study total microvascular disease over 5 years of follow-up. Higher baseline ln-transformed FGF21 levels were associated with a higher risk of new on-study total microvascular disease after adjusting for confounding factors (OR [95% CI] = 1.09 [1.02-1.16] per SD increase in ln-transformed FGF21 levels, P=0.01). The addition of FGF21 levels in a model of new on-study total microvascular disease with established risk factors significantly increased the integrated discrimination improvement and the net reclassification improvement (both P<0.01). Higher baseline plasma FGF21 levels are seen in patients with type 2 diabetes and established microvascular disease, and predict the future development of new microvascular disease over 5 years of follow-up, suggesting a potential role of FGF21 in microvascular disease. FGF21 may be...
useful as a potential biomarker for monitoring the progress of microvascular disease in high risk patients. The measurement of FGF21 levels was supported by a Grant-in-Aid (G 12S 6681) from the National Heart Foundation of Australia. K.L.O. was supported by Program grants (482800 & 1037903) from the National Health and Medical Research Council (NHMRC) of Australia, and a Vice-Chancellor’s Postdoctoral Fellowship from the University of New South Wales. A.C.K. was supported by NHMRC Program grant (1037786) and Fellowship grant (1024105).

Subdivision 3. Clinical Studies

Presentation Preference Oral presentation

Additional information
Are intracranial arteries athero-protected?

Abstract nr. 162
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Topic The Pathogenesis of Atherosclerosis; Immunity, Inflammation, and the Endothelium
Keywords Atherosclerosis

Atherosclerosis of the intracranial arteries is a major but underestimated cause of ischemic stroke and has been related to dementia. Whereas most literature focuses on the epidemiology and therapy of intracranial atherosclerosis, we provide a literature review focusing on disease etiology. Based on this review and the documented observation that intracranial atherosclerosis develops 20 years later than extracranial atherosclerosis we hypothesize that intracranial arteries are athero-protected and developed the following working model: Intracranial arteries and especially the small circle of Willis arteries have a specific constitution. They are muscular type arteries that contain only few medial elastic fibers, a thick and dense internal elastic lamina, few adventitial vasa vasorum and lack an external elastic lamina. A low endothelial permeability, a special glycocalyx and enhanced protective mechanisms against oxidative stress suggest the presence of a barrier function. Early in life, the compliance of the aorta and carotid arteries maintains a low pulse pressure in the intracranial arteries retarding the development of intracranial atherosclerosis. With increasing age and accelerated by hypertension, diabetes and an enhanced stiffness of aorta and carotid arteries the protective effect of a low pulse pressure is lost and the enhanced pulse wave propagation may become a major driver of intracranial atherosclerosis and explain the exponential increase in its incidence. Intracranial atherosclerotic lesions show special features such as fibrosis, small lipid pools, and a low grade of inflammation. This so-called stable plaque morphology may also explain the relatively low numbers of ruptured or eroded plaques in intracranial arteries. The underlying mechanisms remain largely unknown, but may be related to the above mentioned characteristics of the intracranial arteries such as the sparsity of vasa vasorum, a high antioxidant capacity, low inflammatory activity and response and protective effects of the cerebrospinal fluid. These characteristics suggest that the effect of specific atherogenic stimuli, but also of specific drug therapies may differ between extra- and intracranial arteries and is suggestive of divergent disease etiologies.

Subdivision 5. Not applicable. Abstract matches with track d

Presentation Preference Oral presentation
Additional information
Glucocorticoid-mediated immunosuppression underlies the cholestasis-induced atherosclerosis resistance

Abstract nr. 163
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Topic The Pathogenesis of Atherosclerosis; Immunity, Inflammation, and the Endothelium
Keywords Atherosclerosis

Background & Aims: Hypercholesterolemia is an established risk factor for atherosclerosis and cardiovascular disease in the general population. Interestingly, cholestatic liver disease pathology in humans is associated with marked hypercholesterolemia but not an increased susceptibility to atherosclerosis or associated cardiovascular events. Here we aimed to provide mechanistic insight in the apparent resistance of cholestasis patients to hyperlipidemia-associated atherogenesis.

Methods: Hyperlipidemic apolipoprotein E knockout mice were fed a chow diet with or without alpha-naphthylisothiocyanate (ANIT; 0.025%) for 8 weeks to induce cholestasis.

Results: ANIT-fed mice exhibited extensive liver fibrosis, compensatory cholangiocyte proliferation, and marked increases in established plasma cholestatic indices, i.e. taurocholic acid levels (24-fold; p<0.01), alanine transaminase activity (2.7-fold; p<0.05) and bilirubin levels (+60%; p<0.01). Cholestatic mice displayed a reduced atherosclerotic lesion size (-28%; P<0.05) despite a marked rise in the free cholesterol (+31%; p<0.01) and cholesterol ester (+42%; p<0.001) levels associated with pro-atherogenic very-low-density lipoproteins and low-density lipoproteins. Macrophage and collagen contents of lesions were similar. In contrast, lesional T cell numbers were 47% (p<0.05) lower upon ANIT treatment. Importantly, cholestatic mice displayed a 72% increase (p<0.01) in plasma levels of the immunosuppressive molecule corticosterone, which could explain the concomitant 50% decrease (p<0.001) in circulating lymphocyte numbers (correlation coefficient R=-0.66; P<0.01).

Conclusions: We have shown that cholestasis is associated with elevated glucocorticoid levels, lymphocytopenia, and reduced atherosclerosis susceptibility in mice. Our findings for the first time highlight that an enhanced endogenous glucocorticoid function may contribute to the atherosclerosis resistance observed in cholestatic subjects.

Subdivision 1. Basic Science

Presentation Preference Oral presentation
Additional information
Haloperidol inhibits the development of atherosclerotic lesions in LDL receptor knockout mice

Background and Purpose: Antipsychotic drugs have been shown to modulate the expression of ATP-binding cassette transporter A1 (ABCA1), a key factor in the anti-atherogenic reverse cholesterol transport process, in vitro. Here we evaluated the potential of the typical antipsychotic drug haloperidol to modulate the macrophage cholesterol efflux function in vitro and susceptibility to atherosclerosis in vivo.

Experimental Approach: Thioglycollate-elicited peritoneal macrophages were used for in vitro studies. Hyperlipidemic low-density lipoprotein (LDL) receptor knockout mice were implanted with a haloperidol-containing pellet and subsequently fed a Western-type diet for 5 weeks to induce the development of atherosclerotic lesions in vivo.

Key Results: Haloperidol induced a 54% decrease (P=0.043) in the mRNA expression of ABCA1 in peritoneal macrophages. This coincided with a 30% (P<0.001) decrease in the capacity of macrophages to efflux cholesterol to apolipoprotein A1. Haloperidol treatment stimulated the expression of ABCA1 (+51%; P=0.021) and other genes involved in reverse cholesterol transport, i.e. CYP7A1 (+98%; P=0.004) in livers of LDL receptor knockout mice. No change in splenic ABCA1 expression was noted. However, the average atherosclerotic lesion size was significantly smaller (-31%; P=0.039) in the context of a mildly more atherogenic metabolic phenotype upon haloperidol treatment. Importantly, haloperidol markedly lowered MCP-1 expression (-70%; P<0.001) and secretion (-28%; P=0.018) by peritoneal macrophages.

Conclusions and Implications: These studies show that haloperidol treatment lowers the susceptibility for atherosclerotic lesion development in hyperlipidemic LDL receptor knockout mice. Our findings suggest that the beneficial effect on atherosclerosis susceptibility can be attributed to a haloperidol-induced inhibition of macrophage chemotaxis.
High Density Lipoproteins exert pro-inflammatory effects on macrophages via passive cholesterol depletion and PKC-dependent NF-κB/STAT1 activation

Abstract nr. 166
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Topic Dyslipidemia; Lipids, Lipoproteins and Apolipoproteins
Keywords Apolipoproteins, HDL, Immunity, Inflammation

Membrane cholesterol is known to modulate a variety of cell signaling pathways and functions. While cholesterol depletion by High-Density Lipoproteins (HDL) has potent anti-inflammatory effects in various cell types, its effects on inflammatory responses in macrophages remain ill defined.

Pre-incubation of human and murine macrophages in vitro with human reconstituted (apolipoproteinA-I/phosphatidylcholine) or native HDL significantly decreased LPS-induced anti-inflammatory IL-10 production, while the opposite was observed for the pro-inflammatory mediators IL-12 and TNF-α. We show that these effects are mediated by passive cholesterol depletion and lipid raft disruption, without involvement of ABCA1, ABCG1, SR-BI or CD36. These pro-inflammatory effects are confirmed in vivo in peritoneal macrophages from ApoA-I transgenic mice, which have high circulating HDL levels. Native and reconstituted HDL enhances Toll Like Receptor-induced signaling by activating protein kinase C (PKC), since inhibition of PKC ablated the observed HDL effects. Using macrophages from NF-κB luciferase mice, we observed that HDL induces NF-κB activation. Western blot analyses showed that in particular the p65 subunit was activated. Using specific knock-out mice for the upstream activation pathways, we show that the observed HDL effects are IKK, NIK and CKII independent. Furthermore, using STAT1 knock-out mice we observed that also STAT1 is involved in the pro-inflammatory HDL effects on IL-10 and IL-12 secretion. On the other hand, using pharmacological inhibitors, we show that HDL enhances ADAM protease activity, thereby mediating TNF-α release.

Such pro-inflammatory activities on macrophages could at least partly underlie the disappointing therapeutic potential of HDL raising therapy in current cardiovascular clinical trials.
Subdivision 1. Basic Science

Presentation Preference Oral presentation
Additional information
Autophagy dysfunction correlated with low cystatin C levels in atheroma is associated with plaque progression in human atheroma

Abstract nr. 167
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Topic The Pathogenesis of Atherosclerosis; Immunity, Inflammation, and the Endothelium
Keywords Atherosclerosis, Pathogenesis, Vulnerable Plaque

Autophagy dysfunction in mouse atherosclerosis models has been associated with increased lipid accumulation, apoptosis and inflammation. Expression of cystatin C (CysC) is decreased in human atheroma and CysC deficiency enhances atherosclerosis in mice. Here we first investigated the association of autophagy and CysC expression levels with atheroma plaque severity in human Atheros atherosclerotic lesions is decreased while dysfunctional markers of autophagy p62/SQSTM1 and ubiquitin are increased together with elevated levels of lipid accumulation and apoptosis. The expression of LC3β and Atg5 were positively associated with CysC expression. We next investigated whether CysC expression is involved in autophagy in atherosclerotic apoE deficient mice, demonstrating that CysC deficiency (CysC−/−) in these mice results in reduction of Atg5 and LC3β levels and induction of apoptosis. Thirdly, macrophages isolated from CysC−/− mice displayed increased levels of p62/SQSTM1 and higher sensitivity to 7-oxysterol-mediated lysosomal membrane destabilization and apoptosis. Finally, CysC treatment minimized oxysterol-mediated cellular lipid accumulation. We conclude that autophagy dysfunction is a characteristic of the progression of human atherosclerotic lesions and associated with reduced levels of CysC. The deficiency of CysC causes autophagy dysfunction and apoptosis in macrophages and apoE deficient mice. The results indicate that CysC plays an important regulatory role in combating cell death induced by oxysterols via the autophagic pathway.

Subdivision 1. Basic Science

Presentation Preference Oral presentation
Additional information
Pro-inflammatory cytokine IFNg modulates hepatic Sortilin expression and hepatocyte uptake capacity.

Abstract nr. 168
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Topic Dyslipidemia; Lipids, Lipoproteins and Apolipoproteins
Keywords Atherosclerosis,Inflammation,Lipoproteins,Metabolism

Aim: Dysregulation of lipid metabolism and immunity are the two major risk factors for atherosclerosis. Yet, we reported recently increased atherosclerosis upon Treg (regulatory T lymphocytes) depletion or induced death. The effect was associated with elevated circulating VLDL (very low density lipoprotein) particles and decreased expression of hepatic Sortilin. At the same time, the Sortilin inhibitor, Atf3 mRNA was increased. The specific objective is to define how immunity, especially Treg, can regulate Sortilin and lipid metabolism.

Methods: To reproduce the inflammatory milieu, in vitro cytokine treated hepatocytes (mouse hepatocyte cell line AML-12) are used. qPCR and western blotting are used to follow expression of Sortilin Atf3 and Stat1. In silico method is used to find conserved binding sites of Stat1 on Sortilin between humans and mice, confirmed by Chip (chromatin immune precipitation) assays. Radioactive lipoprotein cultured hepatocytes are used to assess the lipid uptake capacity in inflammatory conditions.

Results: While anti-inflammatory cytokine treatments (IL-10, TGFb) don’t have any effects on Sortilin, pro inflammatory cytokine IFNg (which can be released upon cell death or induced by the absence of Treg) decreases Sortilin mRNA and protein level when added to the culture of hepatocytes. At the same time, Atf3 is upregulated. Sortilin is decreased only after 12h of culture. Thus suggesting that IFNg can regulated Sortilin at a transcriptional level. In hepatocyte cultures, STAT1 is phosphorylated only after IFNg treatment. In silico experiment reveals 4 putative binding sites for STAT1 on Sortilin between humans and mice, confirmed by Chip assays. Upon IFNg treatment, hepatocytes have decreased uptake capacity for VLDL and LDL particles.

Conclusion: these first results suggest that IFNg can reduce Sortilin which is described to modulate VLDL secretion. Treg by reducing inflammation may inhibit IFNg effects on Sortilin.

Key words: Inflammation, lipid metabolism.

Subdivision 1. Basic Science

Presentation Preference Electronic poster presentation
Additional information
Distinctive proteomic profiles among different regions of human carotid plaques

Abstract nr. 169
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Topic The Pathogenesis of Atherosclerosis; Immunity, Inflammation, and the Endothelium
Keywords Atherosclerosis, Cardiovascular Disease, Pathogenesis, Vulnerable Plaque

Purpose: Revealing the mechanisms leading to plaque vulnerability, different regions of human carotid plaques may have differential roles in development of atherosclerotic plaques. The aims of this investigation were to create a comprehensive proteomic profile from different regions of the human carotid atherosclerotic plaque, and to establish a protein reference map that could help identify functional roles of different plaque regions in plaque development.

Experimental Design: Two-dimensional gel electrophoresis was used to separate extractable proteins from five different regions of the human carotid endarterectomy samples; internal control, fatty streak, plaque shoulder, plaque centre and fibrous cap. Identification of proteins was made using matrix-assisted laser desorption/ionisation-time of flight mass spectrometry, confirmed by nano-liquid chromatography tandem-mass spectrometry.

Results: Protein mapping resulted in the successful identification of 52 unique proteins, including 15 previously unmapped proteins with regards to atherosclerosis. Expression levels of 13 proteins in atherosclerotic lesions significantly differ from the expression in internal control tissue, including overexpression of apolipoprotein A-IV in plaque centre and of fibrinogen β chain fragment in all three plaque regions. In addition, reduced levels of 9 proteins implicated in remodeling of the extracellular matrix and functions of smooth muscle cells were found in plaque regions.

Conclusions and clinical relevance: The unique sampling method of the atherosclerotic plaque was found to be successful in revealing newly mapped proteins and significant differential expression among different regions of human carotid plaques. The protein profiles with distinct functional implications are of importance for understanding and modulation of plaque biology in atherosclerosis.

Subdivision 4. Not applicable. Abstract matches with track c

Presentation Preference Electronic poster presentation
Additional information
Atherogenic shifts in lipoprotein profile: the relationship with biological and chronological vessel aging

Abstract nr. 170
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Topic Dyslipidemia; Lipids, Lipoproteins and Apolipoproteins
Keywords Atherosclerosis, Dyslipidemia, LDL, Lipoproteins

Aim: to explore the relationship between atherogenic shifts in lipoprotein profile and vessel aging.

Materials and methods. Totally 202 subjects of both sexes aged 30-75 years without clinical manifestations of atherosclerosis-related diseases which didn't receive regular cardiovascular therapy were included into the study. Depending on biological age of vessels (flexible or stiff) and chronological age (years) patients were divided into 4 groups. Pulse wave velocity (PWV) > 10 m/s was used as a measure of arterial stiffness. Lipid levels were determined by routine laboratory methods. LDL subfractional distribution was analyzed using Lipoprint LDL System (Quantrimetrix, USA).

Results. In more younger subjects (≤ 45 years) with stiff vessels in comparison with younger ones with flexible vessels higher levels of total C and LDL-C were found. In older subjects (> 45 years) TG concentration was higher and that of Lp(a) - lower in those with stiff than with flexible vessels. The subfractional LDL analysis revealed elevated VLDL portion in subjects with stiff arteries irrespectively on age. In older subjects with stiff vessels the portion of the largest particles within IDL range was the lowest as compared to all other groups. Older subjects with elevated arterial stiffness had significantly more small particles of IDL-B and, especially IDL-A subfractions.

Conclusion. The increased vessel stiffness as a marker of biologically old vessels in chronologically old patients was associated with elevated portion of small dense IDL particles, by the size close to potentially atherogenic LDL.

Subdivision 1. Basic Science

Presentation Preference Electronic poster presentation

Additional information
"LRP1 and human HDL metabolism: from gene to function"

Abstract nr. 171
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Topic Dyslipidemia; Lipids, Lipoproteins and Apolipoproteins
Keywords Dyslipidemia, Genetics, Lipoproteins, Metabolism

**Aim:** The LDL-receptor related protein 1 (LRP1) is the largest member of the LDL receptor gene family and has been shown to play a key role in the hepatic clearance of apoE-containing lipoproteins. Surprisingly, recent studies in liver-specific LRP1 knock-out mice have indicated that LRP1 has a direct role in HDL biogenesis and cholesterol levels. We questioned whether this also holds true in humans.

**Methods:** Targeted-sequencing in individuals with extremely low HDL-C levels identified the first 3 non-synonymous variations in the LRP1 gene, i.e. c.3644G>A (p.Gly1215Glu), c.11949G>T (p.Glu3983Asp) and c.9730G>A (p.Val3244Ile). To evaluate the functional importance of these variations they were introduced in LRP1 GFP-tagged expression constructs in HEK293/Huh7 cells for mRNA/protein and cellular localization studies through fluorescence microscopy. Efflux studies using respectively, fibroblasts isolated from index cases and knock-out/in hepatic cells engineered by CRISPR-Cas9 were carried out to assess the effect of these mutations on HDL metabolism.

**Results:** All variants involve highly-conserved nucleotides and are predicted to be deleterious to protein structure/function. Mutant LRP1 protein levels are significantly decreased by 40-60% when compared to wild-type whilst mRNA levels are not affected. In addition, measurements of LRP1 stability and localization studies have shown that mutants are less stable and co-localizing with early-endosomes.

**Conclusion:** Three LRP1 variants that are likely to be of functional importance have been identified in individuals with low HDL-C levels. A comprehensive approach is currently used to test for functionality and elucidate how LRP1 affects HDL metabolism in humans.

Subdivision 1. Basic Science

Presentation Preference Oral presentation

Additional information
Effect of a Chronic High Cholesterol Diet on Arterial Atherosclerotic Burden in Nonhuman Primates with Advancing Age

Abstract nr. 172
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Topic The Pathogenesis of Atherosclerosis; Immunity, Inflammation, and the Endothelium
Keywords Animal model, Atherosclerosis, Inflammation, Lipids

Background
Both aging and a high cholesterol diet (HCD) remodel inflammatory signaling pathways, predisposing the arterial wall to metabolic vulnerability, facilitating the pathogenesis of atherosclerosis. However, synergic interactions of age and HCD remain to be clarified.

Main findings
A 2-year chronic HCD in rhesus monkeys (n=16) markedly (~2-fold, p<0.001) increases plasma cholesterol by the 6th month in both young (≤ 15 yrs) and old (>15 yrs) groups compared to a standard diet (SD, n=10). HCD dramatically increases atherosclerotic burden (a percentage of the cap perimeter to corresponding arterial circumference) along the direction of blood flow, in particular, from thoracic and abdominal aorta to iliac artery (Figure). HCD significantly increases atherosclerotic burden to a greater extent in the old vs young group (Figure) (Two-way ANOVA p<0.001). The increased plaque burden in old monkeys appears as a significant increase in plaque area, enriched with an abundant inflammatory lipid deposition of intra-and-extra macrophages.

Conclusions
HCD increases the atherosclerosis burden in both young and old groups. However, the effects of HCD and aging are additive on inflammatory responses and subsequently synergistically amplify the atherosclerotic burden with aging. Thus, targeting age/diet-associated arterial remodeling is an evidence-based approach to curb an increased prevalence of atherosclerotic burden in the elderly.
Atherosclerosis Burden
Subdivision 2. Translational Research

Presentation Preference Oral presentation
Additional information
FUNCTIONAL MUTATION IN ABCA1, PLASMA LEVELS OF APOLIPOPROTEIN E AND RISK OF ALZHEIMER DISEASE AND CEREBROVASCULAR DISEASE

Abstract nr. 173
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Topic Dyslipidemia; Lipids, Lipoproteins and Apolipoproteins
Keywords Apolipoproteins, Dyslipidemia, Genetics, HDL

Aim and background: The ATP Binding Cassette Transporter A1 (ABCA1) is a major cholesterol transporter highly expressed in liver and brain. In brain, ABCA1 lipidates apolipoprotein E (apoE) and thus facilitates clearance of β-amyloid and maintenance of the blood-brain-barrier via apoE mediated pathways. Whether functional mutations in ABCA1 are associated with decreased levels of plasma apoE and increased risk of Alzheimer disease and cerebrovascular disease in the general population is unknown. We tested this hypothesis.

Methods: In a prospective study of the general population (N=92,726), we tested whether a functional mutation in ABCA1, N1800H, was associated with plasma levels of apoE and with increased risk of Alzheimer disease and cerebrovascular disease.

Results: N1800H AC versus AA was associated with a 13% decrease in plasma levels of apoE (p=1·10^-11). Multifactorially adjusted hazard ratios (HRs) for N1800H AC versus AA were 4.13 (1.32-12.9) and 2.46 (1.10-5.50) for Alzheimer disease and cerebrovascular disease, respectively. For subtypes of cerebrovascular disease, multifactorially adjusted HRs for N1800H AC versus AA were 8.28 (2.03-33.7) and 1.81 (0.67-4.84) for hemorrhagic stroke and ischemic stroke, respectively. Multifactorially adjusted HR for N1800H AC versus AA was 0.33 (0.05-2.33) for myocardial infarction.

Conclusions: A functional mutation in ABCA1, presenting with a frequency of 2:1,000, is associated with decreased plasma levels of apoE, and increased risk of Alzheimer disease and cerebrovascular disease. N1800H is not associated with increased risk of myocardial infarction, suggesting that the present observations between N1800H and Alzheimer disease and cerebrovascular disease are not due to atherosclerosis but rather may be attributed to brain and blood-brain-barrier specific effects.

Subdivision 2. Translational Research

Presentation Preference Oral presentation
Additional information
**Metformin lowers plasma triglycerides by promoting VLDL-triglyceride clearance by brown adipose tissue in mice**

Abstract nr. 174  
Author Geerling, Janine, Leiden Academic Center for Drug Research, Leiden, Netherlands  
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Co-author(s) - Hoek, Anita van den  
Co-author(s) - Lombès, Marc  
Co-author(s) - Princen, Hans  
Co-author(s) - Havekes, Louis  
Co-author(s) - Rensen, Patrick  
Co-author(s) - Guigas, Bruno  
Topic Dyslipidemia; Lipids, Lipoproteins and Apolipoproteins  
Keywords Diabetes, Dyslipidemia, Therapy, Triglycerides

**BACKGROUND AND AIM**  
Metformin, a member of the biguanides family of antidiabetic drugs, is currently considered as the first-line drug treatment for type 2 diabetes. Metformin is well-known for its antihyperglycemic properties, which mainly involve the suppression of hepatic gluconeogenesis and subsequent lowering of hepatic glucose production. Importantly, metformin has also been shown to lower plasma very low-density lipoprotein (VLDL) triglyceride (TG) levels, via a yet unknown mechanism. Therefore, the current study was aimed at unraveling the mechanism underlying the lipid-lowering effect of metformin using APOE*3-Leiden.CETP mice, a well-established model for human-like lipoprotein metabolism.

**METHODS AND RESULTS**  
Twelve-week old female APOE*3-Leiden.CETP mice were fed a Western-type diet for 4 weeks, followed by a Western-type diet with or without metformin (200 mg/kg BW/day) for another 4 weeks. We show that metformin markedly lowered plasma total cholesterol (-36%, P<0.05) and TG (-38%, P<0.05) levels. Importantly, metformin did not affect hepatic VLDL-TG production, VLDL particle composition, and hepatic lipid content. Metformin did, however, selectively enhance clearance of glycerol tri[3H]oleate-labeled VLDL-like emulsion particles into brown adipose tissue (BAT) (+58%, P<0.05). Importantly, BAT mass and lipid droplet content were reduced in metformin-treated mice, pointing to increased BAT activation. Both AMP-activated protein kinase (AMPK) α1 expression and activity (+38% and +19% respectively) were increased in BAT, as was the expression of hormone-sensitive lipase (HSL) and various subunits of the mitochondrial electron transport chain complex. Finally, therapeutic concentrations of metformin increased AMPK and HSL activities and promoted lipolysis in T37i differentiated brown adipocytes *in vitro.*

**CONCLUSION**
To our knowledge, this study is the first to identify BAT as a new important player in the lipid-lowering effect of metformin, by enhancing VLDL-TG uptake, intracellular TG lipolysis, and subsequent mitochondrial fatty acid oxidation. Targeting BAT might therefore be considered as a future therapeutic strategy for the treatment of dyslipidemia.

Note: This study was conducted at the Leiden University Medical Center. The presenting author (Janine Geerling) is currently employed at the Leiden Academic Center for Drug Research.

Subdivision 1. Basic Science

Presentation Preference Oral presentation
Additional information
RELATIONSHIPS BETWEEN POLYMORPHISM OF PARAOXONASE 1 AND
APOLIPOPROTEIN A1 GENES IN PATIENTS WITH CORONARY ATHEROSCLEROSIS

Abstract nr. 175
Author Urazgildeeva, Soreya, Saint-Petersburg State University, Medical Faculty, Saint-Petersburg, Russian Federation
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Co-author(s) - Gurevich, Victor
Topic Dyslipidemia; Lipids, Lipoproteins and Apolipoproteins
Keywords Apolipoproteins, Genetics, HDL

Background. Apolipoprotein A₁ (ApoA₁) is an essential part of high density lipoproteins (HDL) responsible for the reverse cholesterol transport. Antiatherogenic action of HDL is implemented also due to antioxidative effect which is attributed to its paraoxonase 1 (PON1) enzymatic activity. Purpose. The aim of this research was to study the common genetic variation in the PON1 and APOA1 genes in patients with coronary artery disease (CHD).

Methods. Blood samples of 177 patients with clinical and instrumental signs of CHD were examined in this study. PON1 activity was determined towards substrate – paraoxon. Polymorphisms in the PON1 and ApoA1 were analyzed by means of polymerase chain reaction assay.

Results. PON₁ activity was considerably higher in patients with 192RR/QR and 55LL genotypes of PON1 and (-75)AA/AG genotypes of ApoA1. In patients with CHD a modified genetic variant (192RR or 192QR) of PON1 gene was revealed. Earlier manifestation of CHD was also typical for the patients with genotype (-75)AA/AG of ApoA1. More pronounced atherosclerotic lesions verified by the coronary angiography were associated with the presence of allele R in 192QR genes PON1, as well as allele A in (-75)GA and allele C in 83CT gene ApoA1. The ApoA1 (-75)AG polymorphism was connected with 192QR and 54LM PON1 polymorphism; genotype 192RR and 54MM was significantly more commonly detected in patients with genotype (-75)AG/AA of ApoA1.

Conclusions. The obtained findings prove the association of the PON1 192RR/QR and the Apo A1 (-75)AG/AA polymorphisms in patient with coronary atherosclerosis.

Subdivision 3. Clinical Studies

Presentation Preference Electronic poster presentation
Additional information
Molecular genetics of familial hypercholesterolemia in Israel – revisited

Abstract nr. 176
Author Durst, Ronen, Hadassah Hebrew University Medical Center, Jerusalem, Israel
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Co-author(s) - Futema, Marta
Co-author(s) - Whittall, Ros
Co-author(s) - Humphries, Steve E
Co-author(s) - Leitersdorf, Eran
Topic Dyslipidemia; Lipids, Lipoproteins and Apolipoproteins
Keywords Familial Hypercholesterolemia, Genetics, Metabolism

Background
In 1996, the first summary of molecular genetics of familial hypercholesterolemia (FH) in Israel was published (Reshef A, Hum Gen, 1996). Since then, new technology for mutation screening became available making genetic diagnosis easier more accurate, and more comprehensive. We performed systematic mutation screening of index cases of 68 pedigrees to reanalyze the profile of mutations among Israeli FH patients.

Methods and results
In 68 individuals the entire coding region, promoter and intron-exon junctions of the LDLR and part of exon 26 of the APOB gene were screened for variants using High Resolution Melting, with Sanger sequencing of any identified melt shifts. Mutations of the LDLR gene were found in twenty-three patients (34% of the total) with seventeen different mutations. The most common mutation was p.(V827I) (47% of the detected mutations), not previously reported in Refech et al but reported to occur in patients from Russia. Three variants, two in exon 4 and one in the promoter region were not reported before; p.(C121S), p.(E140A) and c.-191 C>A. One patient carried the common APOBp.(R3527Q) mutation. Two families from Druze ancestry carried a novel deletion of exons 7 to 14. Seventy percent of the cohort were negative for an LDLR or APOB mutation. It was hypothesized that FH can be caused by an accumulation of LDL-C raising alleles each having a small contributive effect (Talmud et al., 2013). Using this published gene score method derived from twelve common LDL-C raising SNPs in eleven genes, the mean polygene score was significantly higher (p=0.03) among mutation negative Israeli FH patients compared with a European control population.

Conclusion
We identified mutations in 30% of a new Israeli FH cohort. In these we found 3 novel LDLR mutations. The high prevalence of p.(V827I) likely reflects the change in demographics of the
Israeli population since 1996. In the remaining mutation free cohort, there is likely to be a polygenic cause of their elevated LDL-C and FH diagnosis. These data can help design a future strategy for early screening for FH in our population.

Subdivision 1. Basic Science

Presentation Preference Electronic poster presentation
Additional information
Insulin-like growth factor type 1 in children and adolescents with hypertension and prehypertension

Abstract nr. 177
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Co-author(s) - Tóhátyová, Alžbeta
Co-author(s) - Fatulová, Nina
Topic The Pathogenesis of Atherosclerosis; Immunity, Inflammation, and the Endothelium
Keywords Atherosclerosis,Hypertension,Obesity

Background: The insulin-like growth factor type 1 (IGF-1) system is associated with growth, differentiation and tissue development, and non-physiological activation of this system plays a role in atherogenesis. Decreased levels of IGF-1 in adults are independently associated with glucose intolerance, 2nd type diabetes mellitus, abdominal obesity and atherogenic dyslipidemia.

Material and methods: The study sample consisted of 84 patients (49 boys) with a mean age of 14 years. The analyzed outcomes were plasma levels of IGF-1, growth hormone, uric acid, insulin, glucose, total cholesterol, HDL, LDL, triglycerides, and systolic and diastolic blood pressure measured at rest. Blood pressure levels were divided into groups - normotensive, prehypertensive and hypertensive according to height percentile for age and sex.

Results: The values of circulating IGF-1 in the study group of children were positively correlated with age (p<0.001) and negatively with BMI percentile (p=0.039) and percentile for both systolic (p=0.004) and diastolic blood pressure (p=0.024). In the comparison of the groups of normotensive children (systolic blood pressure <95 percentile, n=38) and children with systolic blood pressure in the range of prehypertension to hypertension (≥95percentile, n=28) we found a statistically significant difference in mean IGF-1 between the groups: 400.05±129.31ng/ml versus 299.29±148.97 ng/ml (p=0.005).

Conclusion: Low IGF-1 may represent a potential marker for the presence of cardiometabolic risk factors in the pediatric population.

Subdivision 3. Clinical Studies

Presentation Preference Electronic poster presentation

Additional information
Apolipoprotein A-I restores endothelial function in rats with arthritis

Abstract nr. 178
Author Wu, Ben, The University of New South Wales, Sydney, Australia
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Co-author(s) - Rye, Kerry-Anne
Topic The Pathogenesis of Atherosclerosis; Immunity, Inflammation, and the Endothelium
Keywords Apolipoproteins, Endothelium, HDL, Inflammation

Endothelial dysfunction is a key event in the development of atherosclerosis and has been identified in patients with rheumatoid arthritis and in rats with experimental arthritis. We have recently shown that apolipoprotein A-I (apoA-I), the most abundant apolipoprotein in high density lipoproteins (HDL), and reconstituted HDL [(A-I)rHDL] consisting of apoA-I complexed with phosphatidylcholine inhibit streptococcal cell wall peptidoglycan-polysaccharide (PG-PS)-induced arthritis in female Lewis rats. This study asks if apoA-I also improves endothelial dysfunction in rats with arthritis. A single intraperitoneal injection of PG-PS (15 mg/kg) or an equivalent volume of saline (control) was administered to female Lewis rats. After four days the PG-PS-treated animals had acute joint inflammation, elevated circulating inflammatory cytokine levels, and had aortic endothelial dysfunction. Intravenous infusions of lipid-free apoA-I (8 mg/kg) 24 h pre- and 24 h post-PG-PS administration decreased the acute joint inflammation, reduced plasma TNF-α, IL-6 and IL-1β levels, and restored aortic endothelial function with a 39±9.2% improvement in aortic vasorelaxation and a 53±17% increase in guanosine 3’,5’-cyclic monophosphate (cGMP) production at day 4 post-PG-PS injection. In ex vivo studies, incubation of aortic rings from control female Lewis rats with TNF-α (10 ng/mL) for 6 h impaired aortic vasorelaxation by 82±2.2% and decreased cGMP production by 81±5.5%. Pre-incubation of the aortic rings for 16 h with (A-I)rHDL (final apoA-I concentration 0.5 and 1.0 mg/mL) improved the TNF-α-induced impaired aortic vasorelaxation by 1.9±0.3- and 3.2±0.9-fold, cGMP production by 2.1±0.4- and 3.4±0.4-fold, respectively. In addition, (A-I)rHDL induced endothelial nitric oxide synthase (eNOS) expression in human coronary artery endothelial cells (HCAECs) in a time- and dose-dependent manner. This effect was abolished by knockdown of scavenger receptor-B1. Incubation of HCAECs with TNF-α (1 ng/mL) for 6 h reduced HCAEC eNOS expression by 67±9.9%. Pre-incubation of the HCAECs for 16 h with (A-I)rHDL (final apoA-I concentration 0.5 and 1.0 mg/mL) restored the TNF-α reduced HCAEC eNOS expression by 2.2±0.2- and 2.7±0.2-fold, respectively. These findings establish that apoA-I improves endothelial dysfunction in rats with arthritis by, at least partly, inhibiting inflammatory cytokine induced endothelial dysfunction. This work was supported by National Health and Medical Research Council of Australia.
Subdivision 1. Basic Science

Presentation Preference Oral presentation
Additional information
Validation for risk assessment chart of Japanese Atherosclerosis Society by a large external population: EPOCH-JAPAN

Abstract nr. 179
Author Nakai, Michikazu, Suita, Japan
Topic Epidemiology of CVD; The Risk Factor Concept
Keywords Atherosclerosis, Cardiovascular Disease, Epidemiology, Risk Factor

Some assessment tools for future individual risk for atherosclerotic diseases had been constructed and applied in developed countries, which should be originally established because the absolute risk of atherosclerotic diseases varies among different ethnic groups. However, there exists a time lag between baseline surveys of cohort studies that provided coefficients of risk assessment and the time when the relevant risk assessment tools are utilized. Consequently, it is important to validate the risk assessment tools by external cohort with more recent baseline surveys than the original ones.

In Japan Atherosclerosis Society guideline 2012 (JAS2012), NIPPON DATA80 risk assessment chart (ND80RAC) was adopted to estimate 10-year probability of coronary artery disease (CAD) mortality for the adequate management for dyslipidemia. In order to validate this chart, we used one of the largest pooled cohorts in Japan, the Evidence for Cardiovascular Prevention from Observational Cohorts in Japan (EPOCH-JAPAN), as an external population of which baseline survey was almost 10 years newer than that of ND80RAC. We analyzed the dataset of 15,091 men and 18,589 women aged 40-74 years without a history of cardiovascular disease. The probability of 10-year risk for CAD/stroke mortality was estimated using ND80RAC. The participants were divided into decile according to the estimated mortality and the mean estimated 10-year risk and the actual cumulative mortality for CAD/stroke were compared, respectively. The mean estimated 10-year risk of CAD/stroke mortality was higher than the actual mortality in higher risk group, however, which was concordant with the actual mortality in low/moderate risk group in both sexes.

The causes of overestimating the mortality in ND80RAC could be explained as followings: i) decreased morality in the high-risk elderly during last decade, ii) remarkable medical cure progress, iii) high concern of one’s prevention and control, especially in higher risk individuals.

ND80RAC is useful tool to predict mortality for CAD/stroke although it overestimates mortality in high-risk individuals.

Subdivision 4. Not applicable. Abstract matches with track c

Presentation Preference Electronic poster presentation

Additional information
Deletion of progranulin exacerbates atherosclerosis in ApoE knockout mice.

Abstract nr. 180
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Topic The Pathogenesis of Atherosclerosis; Immunity, Inflammation, and the Endothelium
Keywords Atherosclerosis, Inflammation

Progranulin (PGRN) is a multifunctional glycoprotein involved in cellular proliferation, survival, migration and wound repair. Moreover, some mutations in the PGRN gene have been reported to result in frontotemporal lobar degeneration. We previously reported that progranulin (PGRN), which is secreted from human monocyte-derived macrophages, is bound to apolipoprotein A-I (apoA-I), a major component of HDL. Although PGRN is also known to be involved in inflammation, there is no information available on the direct effect of PGRN expression on atherosclerosis. Therefore, we generated PGRN-/-ApoE-/- (double knockout, DKO) mice to explore the role of PGRN in atherogenesis. DKO mice that were fed high fat diet for 12 weeks developed severe atherosclerosis compared to ApoE KO mice fed the same diet, suggesting that PGRN has an atheroprotective role in the development of atherosclerosis. The increase in atherosclerotic lesions in DKO mice was in part due to the enhanced expression of adhesion molecules, as well as the decreased expression of endothelial nitric oxide synthase (eNOS) in the aortic lesions. Moreover, lack of PGRN leads to accumulate excessive cholesterol in the macrophages and alter HDL-associated proteins. Recently, PGRN has been reported to bind directly to TNF receptors and suppress inflammation by disrupting TNF-alpha signaling. PGRN has a variety of atheroprotective functions, therefore PGRN can be a promising therapeutic target for atherosclerosis.

Subdivision 1. Basic Science

Presentation Preference Electronic poster presentation
Additional information
ASSOCIATION BETWEEN SMALL DENSE LDL-CHOLESTEROL AND CORONARY ARTERY DISEASE IN NORTH INDIAN POPULATION- A CASE CONTROL STUDY

Abstract nr. 181
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Topic Dyslipidemia; Lipids, Lipoproteins and Apolipoproteins
Keywords Cardiovascular Disease,Dyslipidemia,LDL,Risk Factor

Background –Indian population studies with established CAD often show LDL levels within normal range in patients with proven CAD. We hypothesized that Small dense LDL-cholesterol (sd-LDL-c) being more atherogenic might correlate to occurrence and severity of CAD.

Objective- The aim of the study was to evaluate the association between sd-LDL-c and severity of coronary artery disease.

Method- 125 patients with coronary stenosis on angiography, 25 patients without coronary stenosis and 40 healthy controls were studied. Direct quantitative measurement of sd-LDL-c was done by standard method.

Results- There was no significant difference between triglyceride (TG) levels and HDL-c levels among the three groups. Mean sd-LDL-c levels were higher in patients with coronary stenosis than patients without and also healthy individuals viz (16.3 + 6.8 mg/dl vs 12.7 + 7.1mg/dl vs 8.5 + 3.9 mg/dL respectively, (p<0.0001). There was a linear relation between mean sdLDL and severity of CAD with mean sd LDL in single vessel disease, double vessel disease and triple vessel disease being 14.3 + 5.8 mg/dL, 16.1 + 6.7 mg/dl and 18.2 + 7.3 mg/dl respectively ( p value <0.0001). A cut off value of 10.02 mg/l was associated with presence of CAD.(95% CI 0.82-0.93, p< 0.001).

Conclusion- Indian patients with established CAD have higher sd-LDL-c levels compared to individuals without CAD despite having comparable LDL-c levels.Beyond traditional lipid profile estimation of sd-LDL-c in Indian patients as a routine which may assist in identifying a higher risk population even treated with statin.

Subdivision 3. Clinical Studies

Presentation Preference Oral presentation
Additional information
Cholesterol in remnant-lipoproteins as measured by different methods

Abstract nr. 182
Author Toth, Peter, Peoria, United States of America
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Co-author(s) - Tomassini, Joanne E.
Co-author(s) - Wang, Colin
Co-author(s) - Polis, Adam B.
Co-author(s) - Tershakovec, Andrew
Topic Dyslipidemia; Lipids, Lipoproteins and Apolipoproteins
Keywords LDL, Lipids, Lipoproteins, Risk Factor

Background: Elevated remnant-lipoprotein cholesterol (RLP-C) levels increase the risk of ischemic heart disease (IHD). The concurrence of RLP-C assessment by different separation methods is not well described. This analysis examined RLP-C assessed by immunoseparation (IM) and vertical auto profile (VAP [IDL+VLDL-3]) methods using samples from a previously reported randomized, clinical trial.

Methods: This analysis assessed fasting RLP-C in hyperlipidemic patients (n=2,382) treated with ezetimibe/simvastatin (E/S) 10/20 mg, E/S + niacin (N) 2g and N 2 g during 24 weeks, and E/S 10/20 mg and E/S + N 2 g during 64 weeks. Pearson correlation and Bland-Altman plots were used to evaluate the degree of similarity between the 2 methods used to measure RLP-C levels, and change and % change from baseline across treatments.

Results: Cholesterol mass at baseline measured by RLP-C VAP was ~4X higher than by IM; both declined with treatment by 24 weeks with little further reduction at 64 weeks. RLP-C change and % reduction from baseline were larger when measured by VAP vs IM. Although the 2 methods were moderately correlated (r=0.54 - 0.59) for RLP-C levels and changes, Bland-Altman plots showed little agreement between the methods for RLP-C levels but slightly better agreement for RLP-C changes.

Conclusion: RLP-C defined by IM and VAP methods differs in mass and response to pharmacologic intervention. Given the relationship between RLP-C and IHD risk, standardization of methods is needed for RLP-C use in risk assessment.
## Subdivision 3. Clinical Studies

**Presentation Preference** Oral presentation

**Additional information**

<table>
<thead>
<tr>
<th>Parameter</th>
<th>RLP-C IM</th>
<th>RLP-C VAP</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N</td>
<td>Mean (SD)</td>
</tr>
<tr>
<td><strong>RLP-C [mg/dL]</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline</td>
<td>1212</td>
<td>11.3 (6.0)</td>
</tr>
<tr>
<td>Week 24</td>
<td>774</td>
<td>6.9 (4.5)</td>
</tr>
<tr>
<td>Week 64</td>
<td>637</td>
<td>6.6 (4.2)</td>
</tr>
<tr>
<td><strong>Change from baseline in RLP-C (mg/dL)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Week 24</td>
<td>772</td>
<td>-4.3 (6.6)</td>
</tr>
<tr>
<td>Week 64</td>
<td>635</td>
<td>-4.8 (6.2)</td>
</tr>
<tr>
<td><strong>% Change from baseline in RLP-C (%)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Week 24</td>
<td>772</td>
<td>-30.2 (50.5)</td>
</tr>
<tr>
<td>Week 64</td>
<td>635</td>
<td>-35.7 (45.5)</td>
</tr>
</tbody>
</table>

IM=immunoseparation method; RLP-C=remnant lipoprotein cholesterol; VAP=vertical auto profile (IDL+VLDL) method
Ezetimibe does not increase fasting glucose levels more than statins alone in non-diabetic, hypercholesterolemic patients

Abstract nr. 183
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Co-author(s) - Tomassini, Joanne E.
Co-author(s) - Jensen, Erin
Co-author(s) - Polis, Adam B.
Co-author(s) - Musliner, Thomas
Co-author(s) - Tershakovec, Andrew M.
Topic Dyslipidemia; Lipids, Lipoproteins and Apolipoproteins
Keywords Cardiovascular Disease, Diabetes, LDL

Background: Statin (St) therapy can be associated with a slightly increased risk of diabetes mellitus (DM) and insulin resistance in nonDM patients. In prior studies, ezetimibe (Eze)+St did not increase fasting serum glucose (FSG) more than St alone in St naïve, nonDM, hypercholesterolemic (HC) patients for up to 96 wks. This analysis assessed the effects of Eze on FSG changes when given to nonDM, HC patients on stable St therapy.

Methods: Data was pooled from 2 randomized, double blind, add on‡ (Eze added to stable St [n=1506] vs placebo [n=851] studies) for 8 wks in nonDM patients at baseline (BL). Mean FSG changes from BL were estimated for each treatment group (LDA model¶) and between treatment differences calculated. Numbers of patients with FSG ≥126 mg/dl and effect of BL cofactors were also assessed.

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

Conclusion: In HC patients on stable St therapy, addition of Eze did not increase FSG levels more than St therapy, consistent with Eze+St therapy effects in St naïve patients.
Subdivision 3. Clinical Studies

Presentation Preference Oral presentation

Additional information

†1st line: 7 studies in St-naive/drug wash-out HC patients treated with Eze 10 mg + St vs St (10 to 80 mg of simvastatin and atorvastatin, 10 to 40 mg lovastatin and pravastatin) during 12 weeks; ‡2nd line Add-on: 2 studies in HC patients on St therapy (10 to 80 mg of atorvastatin, simvastatin, pravastatin, fluvastatin and lovastatin, 0.2 to 0.8 mg cerivastatin) ≥6 weeks prior to study entry, randomized to Eze 10 mg vs placebo; ns=not statistically significant at the 0.05 alpha level; **p<0.01. Change from baseline assessed using longitudinal data analysis (LDA) model with terms for treatment and trial."
Introduction: Statins effectively reduce LDL-C and cardiovascular (CVD) morbidity and mortality. However, studies indicate 5 to 15% of patients are unable to tolerate statins due to muscle-related complaints, with no similarly effective LDL-C reducing agent available. Evolocumab (AMG 145), a PCSK9 monoclonal antibody, results in large reductions in LDL-C, and has been assessed in phase 2 and 3 trials in patients with statin intolerance (GAUSS-1 and GAUSS-2). We report the characteristics of these patients from a pooled analysis of 464 patients from these two trials (Table).

Methods: GAUSS-1 and GAUSS-2 enrolled patients who were intolerant of at least one and two statin(s), respectively, who also had LDL-C above their NCEP ATP III risk levels.

Results: Baseline characteristics are reported below (Table). Mean (SD) LDL-C was 5.0 (1.5) mmol/L at entry, a majority was <65 yrs old, and there was no gender imbalance. The reasons for statin intolerance were: myalgia (84%), myositis (15%), and rhabdomyolysis (2%). Baseline median (Q1, Q3) CK was 105 (71, 170) IU/L; 100% of patients were intolerant of ≥1 statin, 92% of ≥2 statins, 46% of ≥3 statins, and 17% of ≥4 statins.

Conclusion: In this analysis of statin-intolerant patients from GAUSS-1 and GAUSS-2, most patients had existing CVD, diabetes, were considered high risk by NCEP ATP III, could not tolerate ≥2 statins, and had extremely high baseline LDL-C. These patients constitute a significant unmet need for effective and tolerable LDL-C lowering therapy.
Table. Baseline Patient Characteristics

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>N = 464</th>
</tr>
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<tbody>
<tr>
<td>Demographics</td>
<td></td>
</tr>
<tr>
<td>Age, years</td>
<td>62 (9)</td>
</tr>
<tr>
<td>Male sex, n (%)</td>
<td>223 (48)</td>
</tr>
<tr>
<td>Lipid parameters</td>
<td></td>
</tr>
<tr>
<td>Ultracentrifugation LDLC-C, mmol/L</td>
<td>5.0 (1.5)</td>
</tr>
<tr>
<td>LDL-C, mmol/L, calculated</td>
<td>5.0 (1.4)</td>
</tr>
<tr>
<td>Total cholesterol, mmol/L</td>
<td>7.2 (1.5)</td>
</tr>
<tr>
<td>HDL-C, mmol/L</td>
<td>1.4 (0.4)</td>
</tr>
<tr>
<td>Triglycerides, mmol/L</td>
<td>1.7 (1.2, 2.4)</td>
</tr>
<tr>
<td>Lp(a), nmol/L</td>
<td>36 (11, 133)</td>
</tr>
<tr>
<td>Worst muscle-related side effect in statin intolerance history, n (%)</td>
<td></td>
</tr>
<tr>
<td>Myalgia</td>
<td>388 (84)</td>
</tr>
<tr>
<td>Myositis</td>
<td>68 (15)</td>
</tr>
<tr>
<td>Rhabdomyolysis</td>
<td>7 (2)</td>
</tr>
<tr>
<td>Cardiac risk factors</td>
<td></td>
</tr>
<tr>
<td>Type 2 diabetes mellitus</td>
<td>83 (18)</td>
</tr>
<tr>
<td>Hypertension</td>
<td>255 (55)</td>
</tr>
<tr>
<td>Current smoking</td>
<td>46 (10)</td>
</tr>
<tr>
<td>Metabolic syndrome</td>
<td>188 (41)</td>
</tr>
<tr>
<td>BMI, kg/m²</td>
<td>29 (5)</td>
</tr>
<tr>
<td>NCEP risk categories</td>
<td></td>
</tr>
<tr>
<td>High</td>
<td>208 (45)</td>
</tr>
<tr>
<td>Moderately high</td>
<td>136 (29)</td>
</tr>
<tr>
<td>Moderate</td>
<td>99 (21)</td>
</tr>
<tr>
<td>Lower</td>
<td>21 (7)</td>
</tr>
</tbody>
</table>

* All values are mean (SD). Triglycerides and Lp(a) are median (Q1, Q3)
* In GAUSS-1, LDL-C was measured by preparative ultracentrifugation method; in GAUSS-2, LDL-C was determined by the Friedewald formula with reflexive testing via preparative ultracentrifugation when calculated LDL-C was <1.0 mmol/L or triglyceride levels were >3.9 mmol/L.
* Muscle symptoms with marked CK elevation
* Muscle symptoms with increased CK levels
* Risk category definitions: high, diagnosed coronary heart disease(CHD) or risk equivalent; moderately high, 2 or more risk factors and Framingham risk score 10%-20%; moderate, 2 or more risk factors and Framingham risk score <10%; lower, 0 or 1 risk factor.

This study was funded by Amgen Inc.

Subdivision 3. Clinical Studies

Presentation Preference Oral presentation

Additional information
Multicenter Evaluation of new LDL-Cholesterol Generation 3 assay on Roche Clinical Chemistry Analyzers

Abstract nr. 185
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Topic Dyslipidemia; Lipids, Lipoproteins and Apolipoproteins
Keywords Atherosclerosis,LDL,Risk Factor

Medical Background: Low Density Lipoprotein (LDL) is produced in the circulation from its heptic precursor, VLDL (Very Low Density Lipoproteins). Elevated LDL concentrations in blood results in the destruction of the endothelial function and a higher LDL-cholesterol (LDL-C) uptake in the monocyte/macrophage system as well as by smooth muscle cells in vessel walls. The LDL-C concentration is the most powerful clinical predictor with respect to coronary atherosclerosis, and, therefore, it is used for coronary heart disease (CHD) risk assessment and monitoring of lipid lowering therapies.

Methods and Results: The analytical performance of the new LDL-Cholesterol Gen.3 (LDLC3) assay was evaluated in four different laboratories using cobas c 702, cobas c 502 and cobas c 501 instruments. LDL cholesterol esters and free cholesterol in LDL are directly measured using cholesterol esterase and cholesterol oxidase in the presence of surfactants which selectively solubilizes only LDL.
Repeatability and intermediate precision was measured in the concentration range from 1.5 to 5.1 mmol/L according to the CLSI EP5 protocol using two Roche controls and three human serum pools. For the repeatability the coefficients of variation (CVs) were determined to be less than 1.5 % and for intermediate precision yielded CVs ranging between 1.3 and 3.7 % (two runs/day, 21 days). The recovery of four controls (Roche Diagnostics) was determined in three independent runs. The recovery of LDL-C target values ranged from 96.7 to 107.4 %.
Method comparison experiments were designed in compliance with CLSI EP09-A3, using > 250 serum samples. Statistical Passing-Bablok analysis of method comparisons against the Roche LDL-C Gen.2 yielded correlation coefficients r > 0.992 (p < 0.0001), slopes between 0.99 and 1.01 (95 % confidence interval: 0.98 - 1.04) and intercepts from -0.05 to 0.01 (-0.09 – 0.04) mmol/L.
The reactivity against VLDL's was tested as well as the interference of chylomicrons appearing in non-fasting samples (up to 2000 mg/dL triglyceride). Fasting and non-fasting samples can be used.

**Conclusions:** The MCE of the LDL-Cholesterol Gen.3 assay from Roche Diagnostics proved excellent analytical performance with regard to precision, recovery, method correlations, and specificity. The assay is well-suited for routine use.

Subdivision 3. Clinical Studies

Presentation Preference Electronic poster presentation

Additional information
Different profiles of intracranial atherosclerotic plaque compositions between anterior and posterior circulation

Abstract nr. 186
Author Yang , Wenjie, Chinese University of Hong Kong, Hong Kong, Hong Kong
Co-author(s) - Niu , Chunbo
Co-author(s) - Zhao , Hailu
Co-author(s) - Wong , Kasing
Co-author(s) - Ng , Hokeung
Co-author(s) - Chen , Xiangyan
Topic The Pathogenesis of Atherosclerosis; Immunity, Inflammation, and the Endothelium
Keywords Atherosclerosis,Pathogenesis

**Background:** Intracranial atherosclerotic disease (ICAD) is reaching greater clinical prominence as the most common cause of ischemic stroke, especially in Asian patients. Current understanding of ICAD has been advanced by high-resolution magnetic resonance imaging (HRMRI), but the clinical application of HRMRI is limited by insufficient pathological evidence about intracranial atherosclerosis. Based on a cohort of Chinese adult autopsy cases, the aim of the study was to investigate the distribution of intracranial atherosclerosis, the plaque compositions and to explore whether variations existed between anterior and posterior circulation in plaque features.

**Methods:** It was a hospital cohort based study collecting a series of consecutive Chinese adult autopsy cases (88 cases). Intracranial large arteries including 164 middle cerebral arteries (MCA), 25 internal carotid arteries (ICA), 35 vertebral arteries (VA) and 36 basilar arteries (BA) were collected. H&E staining, Victoria Blue staining and immunostaining for inflammatory cells were performed. The phenotype of atherosclerotic plaques, the involvement of the entire intima or not and the occurrence of complications (intraplaque hemorrhage, neovasculature, thrombus and calcification) were evaluated and compared between anterior and posterior circulation.

**Results:** A total of 88 cases were included, with a median age of 74 years old (range 23-99 years), 55.7% men. Compared with the plaques in anterior circulation, the more plaques in posterior circulation were categorized to lower level of revised AHA classification with a higher rate of adaptive intima thickening (26.8% vs. 7.9%) but lower proportion of pathological intima thickening (8.5% vs. 15.9%) and fibrocalcific atheroma (12.7% vs.21.7%, p = 0.025). As for the involvement of the intima for individual plaques, the rate of plaques involving the entire intima circumferential was higher than that in anterior circulation (66.2% vs. 26.5%; p < 0.001). Thrombi was more frequently detected in plaques of posterior circulation than those of anterior circulation (21.1% vs. 7.4%; p = 0.03).

**Conclusions:** Intracranial atherosclerotic plaques presented with different phenotypes and compositions between anterior and posterior circulation. Plaques of the posterior circulation were less atheromatous but more involvement of the entire intima and complicated with higher percentages of thrombi than those of anterior circulation.
### Table 1 Plaque histological differences between anterior and posterior circulation groups

<table>
<thead>
<tr>
<th>Plaque Phenotype</th>
<th>Total cerebral arteries (N=260)</th>
<th>Anterior circulation (n=180)</th>
<th>Posterior circulation (n=71)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal</td>
<td>12 (3.2%)</td>
<td>6 (8.5%)</td>
<td>6 (8.5%)</td>
<td>0.095</td>
</tr>
<tr>
<td>Intima xanthoma</td>
<td>15 (5.9%)</td>
<td>13 (6.9%)</td>
<td>2 (2.8%)</td>
<td>0.369</td>
</tr>
<tr>
<td>Adaptive intima thickening</td>
<td>34 (13.0%)</td>
<td>15 (8.3%)</td>
<td>19 (26.8%)</td>
<td>&lt;0.001*</td>
</tr>
<tr>
<td>Pathological intima thickening</td>
<td>30 (11.5%)</td>
<td>30 (16.6%)</td>
<td>5 (7.0%)</td>
<td>0.222</td>
</tr>
<tr>
<td>Fibrous cap atheroma</td>
<td>30 (11.5%)</td>
<td>25 (13.2%)</td>
<td>5 (7.0%)</td>
<td>0.196</td>
</tr>
<tr>
<td>Thin fibrous cap atheroma</td>
<td>83 (31.2%)</td>
<td>59 (32.8%)</td>
<td>24 (33.8%)</td>
<td>0.766</td>
</tr>
<tr>
<td>Fibrocalcific atheroma</td>
<td>59 (21.5%)</td>
<td>41 (22.7%)</td>
<td>9 (12.7%)</td>
<td>0.194</td>
</tr>
<tr>
<td>Involvement of the entire intima</td>
<td>97 (36.5%)</td>
<td>50 (26.9%)</td>
<td>47 (65.2%)</td>
<td>&lt;0.001*</td>
</tr>
<tr>
<td>Thrombi</td>
<td>20 (7.4%)</td>
<td>13 (7.2%)</td>
<td>15 (21.1%)</td>
<td>0.03</td>
</tr>
<tr>
<td>Calcification</td>
<td>70 (26.5%)</td>
<td>54 (29.5%)</td>
<td>25 (35.2%)</td>
<td>0.564</td>
</tr>
<tr>
<td>Hemorrhage</td>
<td>48 (18.1%)</td>
<td>20 (10.6%)</td>
<td>8 (11.3%)</td>
<td>1.00</td>
</tr>
<tr>
<td>Neovascularization</td>
<td>81 (30.2%)</td>
<td>24 (12.7%)</td>
<td>7 (9.9%)</td>
<td>0.669</td>
</tr>
<tr>
<td>Inflammatory cells</td>
<td>60 (22.2%)</td>
<td>42 (22.2%)</td>
<td>18 (25.4%)</td>
<td>0.622</td>
</tr>
</tbody>
</table>

*p < 0.05

**Fig. 1 Comparison of histological phenotype between anterior circulation plaques and posterior circulation plaques**

Subdivision 2. Translational Research

Presentation Preference Oral presentation

Additional information
Plaque components of intracranial atherosclerosis is co-existent with aorta or coronary artery atherosclerosis

Abstract nr. 187
Author Yang, Wenjie, Chinese University of Hong Kong, Hong Kong, Hong Kong
Co-author(s) - Niu, Chunbo
Co-author(s) - Zhao, Hailu
Co-author(s) - Wong, Kasing
Co-author(s) - Ng, Hokeung
Co-author(s) - Chen, Xiangyan
Topic The Pathogenesis of Atherosclerosis; Immunity, Inflammation, and the Endothelium
Keywords Atherosclerosis, Pathogenesis

**Background:** Atherosclerosis is a systemic disease that affects the entire body, involving aorta, coronary artery, renal artery and cerebral artery. Intracranial atherosclerotic disease (ICAD) was known as one of the most common subtype of strokes worldwide, especially in Asians. However, its pathophysiology has long been understudied due to the inaccessibility of intracranial vessel specimen. Based on our intracranial atherosclerotic plaque biobank, we aimed to explore the potential correlation between intracranial atherosclerosis and the severity of generalized atherosclerosis in a series of Chinese adult autopsy cases.

**Methods:** We histologically examined the pathological feature of cerebral artery atherosclerosis from 88 consecutive autopsy cases (median age, 74 years; 55.7% men). The autopsy reports were retrieved to get information about the severity of atherosclerosis in aorta, coronary arteries and renal arteries. Totally 260 intracranial large arteries were collected and H&E staining and Victoria Blue staining were examined. The atherosclerotic plaque phenotypes and components were evaluated.

**Results:** Compared with cases without pathological brain infarctions, cases with brain infarctions exhibited severer atherosclerosis of the coronary arteries ($p = 0.006$), but not aorta or renal arteries (Table 1). The phenotypes of intracranial atherosclerosis were correlated with the severity of generalized atherosclerosis (table 2): with the severity aggravation of coronary and aorta atherosclerosis, the phenotypes of intracranial atherosclerosis increased from I to VI (Spearman correlation coefficients $= 0.310$ and $0.296$, respectively, all $p < 0.05$); for benign nephrosclerosis, its frequency increased gradually with increase of intracranial atherosclerosis phenotype from I to VI (Spearman correlation coefficients $= 0.183$, $p < 0.05$). As for plaque compositions, intraplaque hemorrhage, neovasculature and calcification were more frequently detected in cases with aorta atherosclerosis than those without aorta disease (14.8% vs. 3.4%, $p < 0.01$; 16.6% vs. 3.4%, $p < 0.01$; and 34.9% vs. 21.3%, $p < 0.05$, respectively), and in cases with coronary artery atherosclerosis than those without (15.1% vs. 1.3%, $p < 0.01$; 15.1% vs. 5.1%, $p < 0.05$; and 35.2% vs. 19.0%, $p < 0.05$, respectively).

**Conclusions:** Among Chinese populations, stroke patients due to intracranial atherosclerosis often
present with co-existent coronary artery atherosclerosis.

Table 2 Correlations between intracranial vasculature changes and generalized atherosclerosis

Table 1 Comparison of generalized atherosclerosis between the cases with and without brain infarctions due to intracranial atherosclerosis

Subdivision 2. Translational Research

Presentation Preference Oral presentation
Additional information
Analyses of Serum and Thrombus Fatty Acid Composition at the onset of Acute Coronary Syndrome in Japan

Abstract nr. 188
Author Yasuda, Tomoyuki, Kakogawa East City Hospital, Kakogawa, Japan
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Co-author(s) - Mori, Kenta
Co-author(s) - Toh, Ryuji
Co-author(s) - Ishida, Tatsuro
Co-author(s) - Hirata, Ken-ichi
Co-author(s) - Ohnishi, Yoshio

Topic Primary & Secondary prevention of CVD; Lifestyle Measures and Pharmacological Intervention
Keywords ACS, Lipids, Nutrition, Thrombosis

Background:
Fatty acids (FAs) can affect the pathogenesis of acute coronary syndrome (ACS). However, serum FA levels and thrombus FA composition at ACS onset have not been evaluated. In Japan, it is not mandatory to state the trans FA (TFA) content in the food. TFA has some pro-atherogenic (which are solid) and pro-inflammatory properties. The ratio of omega-3 polyunsaturated fatty acids eicosapentaenoic acid (EPA)/arachidonic acid (AA) has been an established predictor of ACS. In this study, we hypothesized that the levels of these FAs may change at ACS onset, possibly contributing to the pathogenesis of ACS.

Methods:
Forty-four subjects with ACS were enrolled in this study. Serum and thrombus aspirated from occluded coronary arteries were collected from patients with ACS onset and subjected to gas chromatographic analysis. Thrombus FA ratio was calculated from the specific FA content per total FA content.

Results:
Similar to previous reports with a general population, age was positively correlated with serum EPA/AA ratio and negatively correlated with serum TFA concentrations. Serum triglyceride levels were strongly correlated with serum AA and TFA levels. Patients with high serum TFA levels exhibited the presence of coronary thrombi that contained a high TFA thrombus ratio. The thrombus/serum ratio of TFA was greater than that of EPA and AA, indicating that solid TFA was highly concentrated in the coronary thrombus.

Conclusions:
The results indicate that solid TFAs formed a part of the components of coronary thrombi, revealing their possible role in the pathogenesis of ACS. Young patients with ACS had a high TFA
and low EPA/AA ratio. Therefore, banning the intake of TFA should be considered in Japan and all over the world to prevent the onset of ACS, particularly in the younger generation.

Subdivision 5. Not applicable. Abstract matches with track d

Presentation Preference Oral presentation
Additional information
Prevention of ethanol induced steatosis in experimental rats by naringenin and rutin

Abstract nr. 189
Author Nalini, Nalini, Chidambaram, India
Topic Dyslipidemia; Lipids, Lipoproteins and Apolipoproteins
Keywords Apolipoproteins, LDL, Pharmacology, Prevention

Alcohol is the most frequently abused psychomotor drug throughout the world and has been known in all civilizations since ancient times. The World Health Organization reports about two billion alcohol consumers worldwide and 76.3 million people with diagnosable alcohol use disorders. Chronic consumption of alcohol leads to lipid accumulation and inflammation which are early manifestations of steatosis/atherosclerosis in turn poses serious health problems. Our present investigation was aimed to evaluate the modulatory mechanism of the natural products, naringenin and rutin against ethanol induced alterations in lipids and inflammatory markers of control and experimental rats. Male albino wistar rats were randomized into four groups. Groups 1, 2 and 3 received 40% isocaloric glucose. Liver injury/steatosis was induced in groups 4, 5 and 6 by administering 20% ethanol (equivalent to 6g/kg/b.wt.,) via intragastric intubation for 60 days. In addition, groups 2 and 4 were given naringenin at the dose of 50mg/kg/b.wt., suspended in 0.5% CMC for the last 30 days of the experiment. Group 3 and 6 were given rutin at the dose of 100mg/kg/b.wt., suspended in 0.5% CMC for the last 30 days of the experiment. Ethanol administered rats showed significantly increased levels of lipids (total cholesterol, triglycerides, free fatty acids, phospholipids, HDL, LDL and VLDL), increased expression of inflammatory markers (TNF-, IL-6, NF-κB, COX-2 and iNOS) and fibrosis markers (TGF- and collagen). Supplementation with naringenin and rutin restored the ethanol induced changes. Thus, naringenin and rutin showed a protective effect against lipids and inflammatory markers mediated steatosis in alcohol induced liver injury.

Subdivision 3. Clinical Studies

Presentation Preference Oral presentation
Additional information
Deficiency of the co-stimulatory molecule CD27 impairs regulatory T cell survival and exacerbates atherosclerosis.

Abstract nr. 190
Author Winkels, Holger, Ludwig-Maximilian University, Munich, Germany
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Co-author(s) - Bürger, Christina
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Co-author(s) - Lutgens, Esther
Co-author(s) - Gerdes, Norbert
Topic The Pathogenesis of Atherosclerosis; Immunity, Inflammation, and the Endothelium
Keywords Atherosclerosis, Immunity

Atherosclerosis, an inflammatory disease of large arteries, is – through its clinical manifestations stroke and myocardial infarction – the leading cause of morbidity and mortality in the industrialized world. Adaptive immunity and co-stimulatory signals play a pivotal role during all stages of the disease. Recently, regulatory T cells “Treg” were attributed an anti-inflammatory and anti-atherogenic role. The interaction of CD70, a member of the tumor necrosis factor super family “TNFSF” with its receptor CD27 modulates Treg development but also affects T cell proliferation, differentiation, and activation at the sites of antigen priming and at effector function. We hypothesized an increased atherosclerotic burden and an exacerbation of disease upon CD27 deficiency.

Cd27-/- mice were crossed with Apoe-/- mice. Cd27-/-Apoe-/- and littermate controls (Cd27+/+ Apoe-/-) were sacrificed at the age of 18 and 28 weeks. Cryosections of the aortic sinus were prepared and analyzed for atherosclerotic lesion size, histology and cellular composition. 18 week-old Cd27-/-Apoe-/- mice have a trend towards bigger atherosclerotic lesions displaying a 2.5-fold higher macrophage content. Flow cytometry revealed a significant decrease in the abundance of splenic (26%) and aortic (27%) Tregs and increased apoptosis of Treg in the thymus (60%) of Cd27-/-Apoe-/- mice. In contrast, 28 week-old Cd27-/-Apoe-/- mice did not differ in splenic Treg content and had similar atherosclerotic plaque size and phenotype compared to their littermate controls. Furthermore, bone marrow transplantation of Cd27-/-Apoe-/- and littermate controls into Apoe-/- recipient mice revealed a 2.3-fold increase in atherosclerotic plaque size and a pronounced pro-inflammatory plaque phenotype accompanied by reduced frequency of aortic (54.1%) and splenic (17.7%) Tregs. Cd27-/-Apoe-/- Tregs showed the same suppressive and migratory capacity as those isolated from controls.

Taken together, our data reveal that deficiency for CD27 impairs thymic Treg development thereby...
exacerbating early atherogenesis and increasing the macrophage content of atherosclerotic lesions. However, later stages of atherosclerosis were not affected by a CD27 deficiency.

Funding resources
Deutsche Forschungsgemeinschaft (DFG), SFB1054 and SFB1123
The Netherlands Organization for Scientific Research, Vidi and Vici grant
The Netherlands Heart Foundation, Dr. E. Dekker Established Investigator grant

Subdivision 1. Basic Science

Presentation Preference Oral presentation
Additional information
REPLACING SATURATED FAT WITH POLYUNSATURATED FAT REDUCES TOTAL CHOLESTEROL AND LDL CHOLESTEROL IN HEALTHY SUBJECTS WITH MODERATE HYPERCHOLESTEROLAEMIA

Abstract nr. 191
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Co-author(s) - Telle-Hansen, Vibeke
Co-author(s) - Raael, Ellen
Co-author(s) - Granlund, Linda
Co-author(s) - Andersen, Lene
Co-author(s) - Holven, Kirsten
Topic Primary & Secondary prevention of CVD; Lifestyle Measures and Pharmacological Intervention
Keywords Intervention, LDL, Nutrition

Background and aim: Reduced intake of saturated fatty acids (SFAs) combined with increased intake of polyunsaturated fatty acids (PUFAs) is the main focus of dietary recommendations to reduce plasma cholesterol and subsequently the risk of cardiovascular disease (CVD). The objective of the present study was to investigate the effect of replacing food items with different fat quality (replacing SFAs with PUFAs) on plasma total cholesterol and LDL cholesterol among healthy subjects with moderate hypercholesterolemia.

Methods: An eight-week double-blinded randomized, controlled parallel designed trial with two groups including healthy adults aged 25-70 y with serum total cholesterol within the normal range and LDL cholesterol ≥ 3.5 mmol/L was performed. The intervention group received commercially available food items in which saturated fat was replaced by vegetable sunflower and rapeseed oil. The control group received similar commercially food items with a higher content of SFAs and lower content of PUFAs, and were chosen based on sales statistics and were among the most sold products within each food category. In both groups, the minimum daily intake of each food item was according to data from the National dietary survey in Norway assessed in men and women aged 18-70 y. Before the baseline visit, all subjects (n=99) performed a run-in period where the control food items were consumed daily for two weeks.

Results and conclusion: Preliminary data shows that daily intake of food items with improved fatty acid composition for eight weeks caused significant lowered plasma total cholesterol and LDL cholesterol levels in healthy adults with moderate hypercholesterolemia compared to the control group.
Subdivision 5. Not applicable. Abstract matches with track d

Presentation Preference Oral presentation
Additional information
Development of new LDL-Cholesterol Generation 3 assay on Roche Clinical Chemistry Analyzers

Abstract nr. 192
Author Dr. Klima, Horst, Roche Diagnostics GmbH, Penzberg, Germany
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Co-author(s) - Sobczak, Georg
Co-author(s) - Pelloli, Jolanda
Co-author(s) - Loehr, Bernd
Topic Dyslipidemia; Lipids, Lipoproteins and Apolipoproteins
Keywords Cardiovascular Disease, Dyslipidemia, LDL, Lipids

Medical background:
LDL-C is the primary target of lipid lowering therapy, because low density lipoproteins are the most arteriosclerotic particles. LDL-C possesses the highest predictive value in the diagnosis of atherosclerosis and CHD risk. It is the leading parameter in monitoring of lipid lowering therapies.

Test principle
In the colorimetric direct assay for LDL cholesterol esters and free cholesterol in LDL are measured on the basis of a cholesterol enzymatic method using cholesterol esterase and cholesterol oxidase in the presence of surfactants which selectively solubilizes only LDL.

Development Goals LDL-Cholesterol Gen.3:
- Good correlation to reference method (BQ)
- Improvement of specificity for LDL-C
- Reduction of interference of remnants and of VLDL fractions
- Improvement of interference of turbidity (L-Index 1000)

Results
Measuring range and Lower limits of measurement
The linear assay range of the LDLC3 assay from 0.10 to 14.20 mmol/L. The LoB, LoQ and LoD are 0.10 mmol/L.

Traceability
LDLC3 assay has been standardized against the beta quantification method.

Limitations and interferences
No interference of bilirubin (conjugated and non-conjugated) up to 60 mg/dL (1026 μmol/L), L-Index of 60, no interference of lipaemia (Intralipid) up to a L-Index of 1000, no interference of hemoglobin up to 1000 mg/dL (1026 μmol/L), H-Index of 1000, and no interference by lipid lowering drugs (statin, fibrates, nicotinic acid).

Fasting / Non-fasting study: Non-fasting samples can be used in the LDLC3 assay.

Precision - CLSI EP5 – 21 days
Repeatability ≤ 1.2% and Intermediate precision ≤ 2.1%.

Conclusions
The development goals for the new LDLC3 assay were met. The use of LDLC3 method in
laboratory routine will improve quality of test results for LDL-C.

Subdivision 4. Not applicable. Abstract matches with track c

Presentation Preference Electronic poster presentation
Additional information
Intracranial arterial calcification is a risk factor of new onset non-cardioembolic stroke but fails to predict long-term stroke recurrence

Abstract nr. 193
Author Wu, Xiaohong, Chinese University of Hong Kong, Hong Kong, China
Co-author(s) - Chen, Xiang Yan
Co-author(s) - Leung, Thomas Wai Hong
Co-author(s) - Wong, Ka Sing
Topic Epidemiology of CVD; The Risk Factor Concept
Keywords Atherosclerosis, Risk Factor

Introduction: Intracranial arterial calcification (IAC) is frequently observed on computed tomography of the brain (CT brain). However, its clinical relevance to vascular events has been understudied. Based a hospital-based cohort, the objective of this study was to investigate the effects of IAC on first time non-cardioembolic stroke and long term stroke recurrence in Chinese adults.

Subjects and methods: The cohort included consecutive men and women referred for brain CT during December 2004 in Prince of Wales Hospital. The severity of IAC on 16-slice brain MDCT (multi-detector-row computed tomography) was assessed at baseline among 85 first time non-cardioembolic ischemic stroke patients and 144 age-gender-matched non-ischemic stroke patients. Traditional risk factors of atherosclerosis were recorded at baseline. Regular follow up was performed to record stroke recurrence in stroke patients till October 2014. Patients with atrial fibrillation or valvular heart disease were excluded. Patients with tumor or other disease causing mortality within one year were excluded.

Results: Logistic regression showed that diabetes (OR 2.203; 95% CI, 1.098-4.418; P=0.026), smoking (OR 2.693; 95% CI, 1.334-5.437; P=0.006), hyperlipidemia (OR 2.331; 95% CI, 1.034-5.259; P=0.041), mild calcification in intracranial internal carotid artery (IICA) (OR 2.711; 95% CI, 1.226-5.999; P=0.014) and moderate calcification in IICA (OR 5.404; 95% CI, 1.546-18.888; P =0.008) were risk factors of new onset non-cardioembolic stroke. During a follow up of mean 7.13 years, stroke recurrence was recorded in 16 patients (18.82%). The vascular risk factors and severity of IAC were compared between patients with and without stroke recurrence during follow up, which showed that diabetes (OR 3.909; 95% CI, 1.166-13.103; P=0.027) and ischemic heart diseases (IHD) (OR 6.202; 95% CI, 1.443-26.658; P=0.014) could predict recurrent non-cardioembolic stroke, while severity of IAC in patients with and without recurrent stroke was similar.

Conclusions: Intracranial arterial calcification is a risk factor of new onset non-cardioembolic stroke but fails to predict long-term stroke recurrent in Chinese adults. Diabetes and ischemic heart diseases could predict long term recurrent non-cardioembolic stroke.
<table>
<thead>
<tr>
<th>variable</th>
<th>overall N=85</th>
<th>recurrent stroke N=16</th>
<th>no recurrent stroke N=69</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>age (mean SD)</td>
<td>69.97(13.01)</td>
<td>68.19(12.57)</td>
<td>70.39(13.16)</td>
<td>0.335</td>
</tr>
<tr>
<td>gender male</td>
<td>43(52.9%)</td>
<td>8(50.0%)</td>
<td>35(53.6%)</td>
<td>0.704</td>
</tr>
<tr>
<td>hypertension</td>
<td>53(62.4%)</td>
<td>13(75.0%)</td>
<td>40(59.4%)</td>
<td>0.247</td>
</tr>
<tr>
<td>diabetes</td>
<td>29(34.1%)</td>
<td>9(56.3%)</td>
<td>20(29.0%)</td>
<td>0.038</td>
</tr>
<tr>
<td>renal failure</td>
<td>4(4.7%)</td>
<td>1(6.3%)</td>
<td>3(4.3%)</td>
<td>0.573</td>
</tr>
<tr>
<td>smoking</td>
<td>27(31.8%)</td>
<td>4(25.0%)</td>
<td>23(33.3%)</td>
<td>0.766</td>
</tr>
<tr>
<td>hyperlipidemia</td>
<td>22(25.9%)</td>
<td>6(37.5%)</td>
<td>16(23.2%)</td>
<td>0.239</td>
</tr>
<tr>
<td>IHD</td>
<td>11(12.9%)</td>
<td>5(31.3%)</td>
<td>6(8.7%)</td>
<td>0.015</td>
</tr>
<tr>
<td>TIA</td>
<td>12(14.1%)</td>
<td>3(18.8%)</td>
<td>9(13.0%)</td>
<td>0.698</td>
</tr>
<tr>
<td>ICA (mean rank)</td>
<td></td>
<td></td>
<td></td>
<td>0.550</td>
</tr>
<tr>
<td>mild/moderate/severe</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>noncalcified/minimal</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>VA (mean rank)</td>
<td>45.66</td>
<td>42.38</td>
<td>43.74</td>
<td>0.315</td>
</tr>
<tr>
<td>MCA (mean rank)</td>
<td>39.83</td>
<td>43.78</td>
<td>39.12</td>
<td>0.368</td>
</tr>
<tr>
<td>BA (mean rank)</td>
<td>44.19</td>
<td>41.48</td>
<td>42.72</td>
<td>0.368</td>
</tr>
<tr>
<td>ACA (mean rank)</td>
<td>43.16</td>
<td>42.96</td>
<td>41.34</td>
<td>0.945</td>
</tr>
<tr>
<td>PCA (mean rank)</td>
<td>43.00</td>
<td>43.00</td>
<td>42.89</td>
<td>1.000</td>
</tr>
<tr>
<td>Intracranial artery (mean rank)</td>
<td>44.41</td>
<td>42.67</td>
<td>0.742</td>
<td></td>
</tr>
<tr>
<td>mild/moderate/severe</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>noncalcified/minimal</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Table 2. Patients with and without recurrent non-cardioembolic stroke in 10-year follow up (mean 7.13 ys/person)**
Table 1. Comparisons of baseline characteristics and intracranial arterial calcification scores between patients with non-cardioembolic stroke and controls

<table>
<thead>
<tr>
<th>Variable</th>
<th>Overall (N=229)</th>
<th>Ischemic Stroke (N=85)</th>
<th>Controls (N=144)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>age (mean/SD)</td>
<td>68.48(12.18)</td>
<td>69.97(13.01)</td>
<td>67.6(11.62)</td>
<td>0.450</td>
</tr>
<tr>
<td>gender (male)</td>
<td>117(51.1%)</td>
<td>45(52.9%)</td>
<td>72(50.0%)</td>
<td>0.667</td>
</tr>
<tr>
<td>hypertension</td>
<td>118(51.5%)</td>
<td>53(62.4%)</td>
<td>65(45.5%)</td>
<td>0.012</td>
</tr>
<tr>
<td>diabetes</td>
<td>53(23.1%)</td>
<td>29(34.1%)</td>
<td>24(16.7%)</td>
<td>0.002</td>
</tr>
<tr>
<td>renal failure</td>
<td>8(3.5%)</td>
<td>4(4.7%)</td>
<td>4(2.8%)</td>
<td>0.473</td>
</tr>
<tr>
<td>smoking</td>
<td>49(21.4%)</td>
<td>27(31.8%)</td>
<td>22(15.3%)</td>
<td>0.003</td>
</tr>
<tr>
<td>hyperlipidemia</td>
<td>37(16.2%)</td>
<td>22(25.9%)</td>
<td>15(10.4%)</td>
<td>0.002</td>
</tr>
<tr>
<td>IHD</td>
<td>17(7.4%)</td>
<td>12(14.1%)</td>
<td>5(3.5%)</td>
<td>0.003</td>
</tr>
<tr>
<td>TIA</td>
<td>19(8.3%)</td>
<td>12(14.1%)</td>
<td>7(4.9%)</td>
<td>0.014</td>
</tr>
<tr>
<td>ICA (mean rank)</td>
<td>131.97</td>
<td>104.98</td>
<td>&lt;0.001</td>
<td></td>
</tr>
<tr>
<td>noncalcified/ minimal/</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>mild: moderate/ severe</td>
<td>11/1:62/11:0</td>
<td>43/5:89/7:0</td>
<td></td>
<td></td>
</tr>
<tr>
<td>VA (mean rank)</td>
<td>126.66</td>
<td>108.11</td>
<td></td>
<td></td>
</tr>
<tr>
<td>noncalcified/ minimal/</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>mild: moderate/ severe</td>
<td>49/1:31/4:0</td>
<td>108/0:29/6:1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>MCA (mean rank)</td>
<td>120.25</td>
<td>111.90</td>
<td></td>
<td></td>
</tr>
<tr>
<td>noncalcified/ minimal/</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>mild: moderate/ severe</td>
<td>74/1:8/1:0</td>
<td>136/1:5/1:1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>BA (mean rank)</td>
<td>118.47</td>
<td>112.95</td>
<td>0.115</td>
<td></td>
</tr>
<tr>
<td>noncalcified/ minimal/</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>mild: moderate/ severe</td>
<td>78/0:7/0:0</td>
<td>139/1:4/0:0</td>
<td></td>
<td></td>
</tr>
<tr>
<td>ACA (mean rank)</td>
<td>118.71</td>
<td>112.81</td>
<td>0.019</td>
<td></td>
</tr>
<tr>
<td>noncalcified/ minimal/</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>mild: moderate/ severe</td>
<td>80/0:5/0:0</td>
<td>143/0:0/1:0</td>
<td></td>
<td></td>
</tr>
<tr>
<td>PCA (mean rank)</td>
<td>115.00</td>
<td>115.00</td>
<td>1.000</td>
<td></td>
</tr>
<tr>
<td>noncalcified/ minimal/</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>mild: moderate/ severe</td>
<td>85/0:0/0:0</td>
<td>144/0:0/0:0</td>
<td></td>
<td></td>
</tr>
<tr>
<td>intracranial artery (mean rank)</td>
<td>131.01</td>
<td>105.55</td>
<td>0.001</td>
<td></td>
</tr>
<tr>
<td>noncalcified/ minimal/</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>mild: moderate/ severe</td>
<td>9/1:63/12:0</td>
<td>39/6:88/10:1</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

TIA = transient ischemic attack; VA = vertebral artery; MCA = middle cerebral artery; BA = basilar artery; ACA = anterior cerebral artery; PCA = posterior cerebral artery; Intracranial artery = calcification in the most severe intracranial artery.

Table 1. Comparisons of baseline characteristics and IAC scores between patients with non-cardioembolic stroke and controls

Subdivision 4. Not applicable. Abstract matches with track c

Presentation Preference Oral presentation

Additional information
Framingham and PDAY Risk Scores Measured at 18-30 Years Predict Coronary Ischemia During the Next 25 Years: The CARDIA Study

Abstract nr. 195
Author Gidding, Samuel, A.I. duPont Hospital for Children, Wilmington, United States of America
Co-author(s) - Colangelo, Laura
Co-author(s) - Lewis, Cora E.
Co-author(s) - Jacobs, David
Co-author(s) - Liu, Kiang
Co-author(s) - Loria, Catherine
Topic Epidemiology of CVD; The Risk Factor Concept
Keywords Atherosclerosis, Epidemiology, Prevention, Risk Factor

Risk factors measured in adolescence and young adulthood predict future atherosclerosis but no studies assessing future cardiovascular events (CVD) later in life have been published. The Framingham risk score predicts CVD well in middle aged-adults. The PDAY (Pathobiological Determinants of Atherosclerosis in Youth Study) risk score, derived directly from correlations of measures of atherosclerosis in 15-35 year olds with post mortem risk factor measurement, predicts future coronary calcium accumulation. In the CARDIA (Cardiovascular Risk Development in Young Adults Study) study, we assessed the ability of the Framingham and PDAY risk scores, age adjusted and calculated at baseline, in 5016 black and white men and women aged 18 to 30 years to predict future ischemic heart disease (myocardial infarction, sudden death, angina, coronary revascularization procedure). There were 97 ischemic events during 25 years of follow up. Outcomes are presented in the Table. Both scores had high predictive values of future events with large increases in risk for every standard deviation increase in score; Framingham performed slightly better but the difference was not statistically significant. When education level (above and below a high school education) and family history of cardiovascular disease were added to make a revised PDAY score, event prediction improved only slightly. Results were similar when total CVD (189 events) was the outcome variable. This study demonstrates that CVD risk as a young adult strongly predicts premature CVD and that risk estimated by likelihood of having atherosclerosis (PDAY) has a similar predictive value as a clinically based risk score (Framingham)
| Risk score                                      |
| (adjusted for age)                             |
| PDAY                                           |
| Revised PDAY                                   |
| Framingham                                     |
All participants (N=5016) with 97 CHD events:
Subdivision 3. Clinical Studies

Presentation Preference Oral presentation
Additional information
N-acetylcysteine Prevents Lipid Peroxidation, Inflammation and Insulin Resistance Induced by Advanced Glycated Albumin in Wistar Rats

Abstract nr. 196
Author Santana Silva, Karolline, Faculty of Medical Sciences University of Sao Paulo, Sao Paulo, Brazil
Co-author(s) - Takashima Fabre, Nelly
Co-author(s) - Catanozi, Sergio
Co-author(s) - Juvenal Gomes, Diego
Co-author(s) - Ramos Pinto, Paula
Co-author(s) - Massola Shimizu, Maria Heloísa
Co-author(s) - Mitiko Okamoto, Maristela
Co-author(s) - Correa Pinto Jr, Danilo
Co-author(s) - Fabres Machado, Ubiratan
Co-author(s) - C. Corrêa-Giannella, Maria Lúcia
Co-author(s) - Passarelli, Marisa
Topic Dyslipidemia; Lipids, Lipoproteins and Apolipoproteins
Keywords Animal model, Diabetes, Inflammation, Lipids

Advanced glycation end products (AGE) contribute to the pathogenesis of chronic complications in diabetes mellitus (DM) by increasing oxidative and inflammatory stress. We investigated the effect of chronic administration of homologous AGE-albumin in rats, associated or not with N-acetylcysteine (NAC) treatment in lipid peroxidation, mRNA expression of interleukins 6 (Il6) and 10 (Il10) in periepididimal adipose tissue and insulin sensitivity.

One-month old male Wistar rats (n=8/group) were randomized to four groups receiving daily intraperitoneal injections of control (C) or AGE-albumin (20 mg/kg/day) alone or together with NAC (600mg/L drinking water), for 90 days. AGE-albumin was prepared by incubating rat albumin with 10 mM glycolaldehyde for 4 days, 37 °C and C-albumin with PBS alone. Plasma total cholesterol, triglycerides, glucose and liver enzymes were determined by enzymatic techniques; thiobarbituric acid reactive substances (TBARS; nmol/24h) in urine samples by spectrophotometric assay; gene expression by real-time quantitative RT-PCR with TaqMan system and glucose disappearance constant by the insulin tolerance test (kITT; %/min). One-way ANOVA and Newman-Keuls post-test were utilized to compare groups (mean±SD).

Body weight, blood pressure, plasma lipids, glucose and liver enzymes were unchanged after AGE or AGE+NAC treatment as compared to their respective controls. NAC reduced TBARS concentration that was increased by AGE-albumin (AGE-albumin 247±45.6 vs AGE-albumin + NAC = 166±26.1; p<0.05). Compared to AGE-albumin, NAC diminished the mRNA of Il6 (respectively, 2.0±0.4 vs 0.3±0.02; p=0.01) and Il10 (respectively, 1.8±0.1 vs 0.4±0.02; p=0.0001). A worsening in insulin sensitivity by the ITT was observed in AGE-albumin when compared to C-albumin-treated animals (2.6±0.5 vs 3.4±0.6; p<0.05), which was prevented by NAC (AGE+NAC...
In conclusion, NAC reduces lipid peroxidation, inflammation in adipose tissue and improves insulin sensitivity that were adversely affect by chronic administration of AGE-albumin. These events can contribute to prevent chronic complications elicited by AGE in DM.

Subdivision 1. Basic Science

Presentation Preference Oral presentation
Additional information
The expression of genes involved in lipid flux and inflammation is downregulated by aerobic exercise training in mouse peritoneal macrophages

Abstract nr. 197
Author Ramos Pinto, Paula, Faculty of Medical Sciences University of Sao Paulo, Sao Paulo, Brazil
Co-author(s) - Santana Silva, Karolline
Co-author(s) - Juvenal Gomes, Diego
Co-author(s) - Machado-Lima, Adriana
Co-author(s) - Tallada Iborra, Rodrigo
Co-author(s) - C. Corrêa-Giannella, Maria Lúcia
Co-author(s) - Catanozi, Sergio
Co-author(s) - Passarelli, Marisa

Topic Dyslipidemia; Lipids, Lipoproteins and Apolipoproteins
Keywords Animal model, Atherosclerosis, Lipids, Lipoproteins

Regular physical exercise effects on atherosclerosis prevention and reduction are related to improvement on lipid metabolism, reverse cholesterol transport and oxidative and inflammatory stress. We aimed at investigating how aerobic exercise training modulates the expression of genes involved in lipid flux and inflammation in macrophages.

Three-month-old C57BL/6J male mice were trained on treadmill (15m/min; 30 min/day), during 6 weeks and a control group were kept sedentary. Immediately after the last exercise bout macrophages were harvested from peritoneal cavity and RT-PCR by Taqman assay was performed to access mRNA expression of Abca1, Abcg1, Nr1h3, Nr1h2, Scarb1, Olr1, Cd36, Pparg, Il10, Il6, Tnf. Actb was utilized as housekeeping. Plasma total cholesterol (TC), HDL cholesterol (HDLc), triglycerides (TG) and glucose were determined by enzymatic methods. Comparisons between groups were carried out by Student t test (mean±SE).

Exercise training did not change plasma levels of TC, HDLc, TG and glucose. Body weight was similar between sedentary and trained animals. In comparison to sedentary animals, exercise training reduced mRNA levels of genes involved in macrophage lipid influx: Olr1 (respectively, 1.0±0.01 vs 0.80±0.01; p=0.046) and Cd36 (1.0±0.03 vs 0.65±0.01; p=0.007). Genes related to cholesterol efflux were also diminished by exercise: Abca1 (1.0±0.01 vs 0.8±0.01; p=0.0006), Abcg1 (1.0±0.01 vs 0.87±0.01; p=0.038), Nr1h3 (1.0±0.02 vs 0.64±0.01; p=0.008), Nr1h2 (1.0±0.01 vs 0.81±0.01; p=0.009), while Scarb1 (1.0±0.02 vs 0.89±0.01; p=0.278) remained unchanged. In addition, there was a reduction in the expression Tnf (1.0±0.03 vs 0.76±0.01; p =0.021), Pparg (1.0±0.01 vs 0.69±0.01; p=0.016), Il10 (1.0±0.03 vs 0.62±0.01; p=0.016) and a trend for reduction in Il6 mRNA (1.0±0.01 vs 0.71±0.01; p=0.065).

In conclusion, aerobic exercise training in wild type mice reduces the mRNA levels of genes involved in the uptake of LDL-cholesterol by macrophages, which agrees with the reduction of those related to cholesterol efflux and inflammation. Our data points for a beneficial role of
physical exercise in the prevention of atherosclerosis that is reflected in peritoneal macrophages.

Subdivision 1. Basic Science

Presentation Preference Oral presentation
Additional information
PCSK9 increases Lp(a) secretion in primary human hepatocytes without modifying Lp(a) uptake

Abstract nr. 198
Author Villard, ELISE F., SANOFI, Chilly-mazarin, France
Co-author(s) - Poirier, Bruno
Co-author(s) - Guillot, Etienne
Co-author(s) - Le Bail, Jean-Christophe
Co-author(s) - Blankenstein, Jorg
Co-author(s) - Muslin, Anthony J.
Co-author(s) - Janiak, Philip
Topic Dyslipidemia; Lipids, Lipoproteins and Apolipoproteins
Keywords Dyslipidemia, LDL, Lp(a), PCSK9

PCSK9 inhibition by monoclonal antibody administration is a very effective therapeutic strategy to reduce circulating LDL-C. PCSK9 inhibition is associated with an unexpected reduction of lipoprotein (a) [Lp(a)] plasma levels in patients, but the mechanism responsible for this reduction remains to be elucidated. The objective of this study was to identify the underlying mechanism of Lp(a) regulation by PCSK9 in primary human hepatocytes. For this purpose, Lp(a) levels in cell media were quantified by ELISA after incubation with physiological concentrations of wild type or mutant forms of PCSK9. PCSK9 increased, in a concentration dependent manner, Lp(a) levels (67% at 20 nM, p<0.001). The gain of function D374Y-PCSK9 mutant was more efficient than wild type PCSK9 to increase Lp(a) levels, while the loss of function mutant R194A failed to modulate Lp(a) levels. We therefore aimed to determine whether this PCSK9-dependent increase in Lp(a) levels in hepatocyte media resulted from a modulation of Lp(a) expression or Lp(a) cellular uptake. APOA gene expression was up regulated by 1.6 fold (p=0.03) in the presence of 20 nM PCSK9. To explore Lp(a) uptake by hepatocytes, Lp(a) was purified from human plasma and labeled with BODIPY-FL. The contribution of LDL receptor [LDLR] in cellular Lp(a) uptake was evaluated by use of 3 different strategies to modulate LDLR activity. Atorvastatin, a potent inducer of LDLR expression, significantly increased LDL uptake (+40% at 1 µM, p<0.05) but did not modulate Lp(a) uptake. In addition, selective inhibition of LDLR with an anti-LDLR antibody impaired LDL uptake without modifying the uptake of Lp(a). Finally, PCSK9 failed to modulate Lp(a) uptake by human hepatocytes, while it reduced LDL uptake by 60% (p<0.05). Taken together, these results show that PCSK9 does not prevent Lp(a) uptake by human hepatocytes but instead promotes APOA expression and increased Lp(a) assembly and secretion. These findings provide new insights into the regulation of Lp(a) metabolism by PCSK9 in primary human hepatocytes and suggest that PCSK9 inhibition may reduce Lp(a) secretion.

Subdivision 1. Basic Science

Presentation Preference Oral presentation
Additional information
Nonalcoholic fatty liver disease induced by apolipoprotein CIII overexpression is associated with inflammation and cell death

Abstract nr. 199
Author Oliveira, Helena, State University of Campinas / Biology Institute, Campinas, Brazil
Co-author(s) - Paiva, Adriene
Co-author(s) - Raposo, Helena
Co-author(s) - Amarylis, Wanschel
Co-author(s) - Nardelli, Tarlliza
Topic Dyslipidemia; Lipids, Lipoproteins and Apolipoproteins
Keywords Apolipoproteins, Hypolipidemic Drugs, Inflammation, Triglyceride-Rich Proteins

Nonalcoholic fatty liver disease (NAFLD) is the principal liver manifestation in obesity and metabolic syndrome. The natural history of the disease involves steatosis, oxidative stress, inflammation and cell death. By comparing apolipoprotein (apo) CIII transgenic mice with control non-transgenic (NTg) littermates, we show here that the overexpression of apoCIII, independent of high fat diet (HFD), results in NAFLD features including increased liver lipid content, decreased antioxidant power, increased expression of TNFα, TNFα receptor, cleaved caspase-1 and interleukin-1β, decreased adiponectin receptor-2 and increased cell death. This phenotype is aggravated and additional NAFLD features are differentially induced by HFD in apoCIII mice. HFD induced glucose intolerance together with increased gluconeogenesis, evidencing hepatic insulin resistance. Marked increases in plasma TNFα (8-fold) and IL-6 (60%) were induced by HFD in apoCIII mice compared to NTg mice. Cell death signals (Bax/Bcl2), effectors (caspase-3) and apoptosis were augmented in both low and HFD apoCIII mice. Fenofibrate treatment reversed several of the diet and apoCIII effects, but did not normalize apoCIII inflammatory traits even under fully corrected liver lipid content. These results indicate that apoCIII overexpression plays a major role in liver inflammation and cell death, increasing the susceptibility to and the severity of diet induced NAFLD.

Subdivision 1. Basic Science

Presentation Preference Electronic poster presentation
Additional information
Physical Exercise Reduces Inflammatory State of Atherosclerotic Lesions in Hypercholesterolemic Mice Fed a High Fat Diet

Abstract nr. 200
Author Oliveira, Helena, State University of Campinas / Biology Institute, Campinas, Brazil
Co-author(s) - Rentz, Thiago
Co-author(s) - Amarylis, Wanschel
Co-author(s) - Salemo, Alessandro
Co-author(s) - Lorza-Gil, Estela
Co-author(s) - Paiva, Adriene
Co-author(s) - Souza, Jane

Topic The Pathogenesis of Atherosclerosis; Immunity, Inflammation, and the Endothelium
Keywords Atherosclerosis, Inflammation, LDL

Increased infiltration of LDL into the subendothelial space, oxidative stress and inflammation are early atherogenesis events. Physical exercise promotes beneficial effects in the prevention and progression of atherosclerosis. These exercise effects are related to improved endothelial function and lipid profile. The aim of this study was to evaluate the effects of chronic aerobic exercise on the inflammatory state of early atherosclerotic lesions in LDL receptor deficient mice (LDLr-/-) fed a high-fat diet. LDLr-/- male mice were submitted to exercise on a treadmill for 8 weeks or remained sedentary. Then, plasma was collected to determine biochemical parameters, bone marrow-derived macrophages were isolated for migration and chemotaxis assays and gene expression (RT-PCR), and the atherosclerotic lesions were analyzed in the aortic root. As expected, exercised mice had reduced lipid laden lesion areas and adipose tissue mass. Plasma levels of glucose, triglycerides and cholesterol were similar between sedentary and exercised mice; however, FPLC plasma lipoprotein fractionation showed lower IDL/LDL-cholesterol levels in the exercised mice. By immunohistochemistry, we verified a reduction in the inflammatory markers IL-1β and MCP-1 in the atherosclerotic plaque. Consistent with these findings, we also observed in macrophages significant reductions in the mRNA expression of IL-1β, MCP-1, IL-6 and TNF-α. In addition, we show that exercise reduces the expression of the endoplasmic reticulum stress related protein CHOP/GADD153 and the presence of the oxidative stress marker, nitrotyrosine, in the plaque. In macrophages, there was a significant decrease in the expression of CD36 mRNA, suggesting a reduced oxidized LDL uptake in these cells. The macrophage migration, evaluated in vitro either in the basal or stimulated conditions, was attenuated by the exercise intervention (50%). The cell motility phenotype of these cells, determined by the interaction of RAC-1 and F-actin, was repressed by the exercise. Besides the plaque and macrophages findings, we observed that exercise also reduced the plasma concentrations of proinflammatory cytokines IL-1β, IL-6 e TNF-α. Together, these data demonstrate that chronic aerobic exercise during the early development of atherosclerosis leads to rapid and beneficial changes in size, cellular composition and inflammatory status of the plaque, as well as reduces the systemic inflammation.
Subdivision 1. Basic Science

Presentation Preference Electronic poster presentation
Additional information
Foxp3 regulatory T cells and T regulatory type 1 cells would cooperatively suppress the development of atherosclerosis in mice.

Abstract nr. 201
Author Kasahara, Kazuyuki, Kobe University Graduate School of Medicine, Kobe, Japan
Topic The Pathogenesis of Atherosclerosis; Immunity, Inflammation, and the Endothelium
Keywords Atherosclerosis, Immunity, Inflammation

**Background:** Recent studies have shown that Foxp3+ regulatory T cells (Tregs) may inhibit atherosclerosis development through suppressing pathogenic immune responses. However, previous studies do not provide the direct evidence for the atheroprotective role of Tregs. The purpose of this research is to clarify the role of Tregs in the development of atherosclerosis.

**Methods and Results:** We employed DEREG (Depletion of regulatory T cells) mice, which carry a diphtheria toxin (DT) receptor under the control of the foxp3 gene locus, and crossed them with LDLR-deficient (LDLR−/−) mice to establish DEREG/LDLR−/− mice. In these mice, DT injection led to efficient depletion of Foxp3+ Tregs in spleens, lymph nodes and aortas. DEREG/LDLR−/− (n=20) or control LDLR−/− (n=22) mice fed a high-cholesterol diet were injected with DT (125ng/mouse) twice per week for 4 weeks and atherosclerosis was examined. No statistical differences in plasma lipid profiles were detected between the 2 groups. Unexpectedly, depletion of Foxp3+ Tregs did not aggravate atherosclerotic lesion formation in the aortic root, while increasing IFNγ producing inflammatory CD4 T cells and proliferative activity of T lymphocytes. Treg-depletion did not change the lipid content of the plaques and the accumulation of macrophages in the atherosclerotic plaques. Interestingly, we found that Foxp3+ Treg depletion resulted in a dramatic increase of T regulatory type 1 (Tr1) cells, which are known as IL-10 producing T cells with anti-atherogenic properties. We also found marked increased IL-10 secretion in splenic lymphocytes of Treg-depleted mice. Furthermore, blockade of IL-10 receptor (IL-10R) in vivo increased the exaggerated inflammatory response and the atherosclerotic lesion size in the Treg-depleted mice, raising an intriguing possibility that Foxp3+ Tregs and Tr1 cells represent alternative fates of T-cell differentiation under hypercholesterolemia, and that their anti-atherogenic function would be partially redundant.

**Conclusions:** Our data indicate that Foxp3+ Tregs and Tr1 cells would cooperatively inhibit atherosclerotic plaque formation in hypercholesterolemic mice. These findings suggest that modulating regulatory immune responses mediated by not only Foxp3+ Tregs but also Tr1 cells would be the promising strategies to prevent or cure atherosclerotic disease.

Subdivision 1. Basic Science

Presentation Preference Oral presentation
Additional information
Vascular PCSK9: a mediator for atherogenesis independent of LDL receptor

Abstract nr. 203

Author Teng, Ba-Bie, University of Texas Health Science Center at Houston, Houston, TX, U.S.A.
Co-author(s) - Sun, Hua
Co-author(s) - Tan, Michael

Topic Dyslipidemia; Lipids, Lipoproteins and Apolipoproteins
Keywords Animal model, Atherosclerosis, LDL, PCSK9

PCSK9 (Proprotein convertase subtilisin/kexin type 9) increases the LDL levels by binding to hepatocyte LDL receptors (LDLR) and subjects it to degradation. We show that PCSK9 regulates apolipoprotein B (apoB) production by inhibiting its degradation process via the autophagic pathway irrespective of the presence of LDLR. In addition to the role of PCSK9 in promoting hyperlipidemia, we propose that vascular-PCSK9 in endothelial cells (EC) plays a role in initiating atherogenesis, irrespective of the presence of LDL receptor.

Our laboratory has generated double knockout mice lacking both LDLR and Apobec1 (apoB mRNA editing enzyme), named LDb, Ldlr-/-Apobec1-/- . They develop atherosclerotic lesions spontaneous. To investigate the role of PCSK9 in atherogenesis, we deleted Pcsk9 gene from LDb mice to generate the triple knockout mice (named LTp, Ldlr-/-Apobec1-/-Pcsk9-/-). The LTp mice had significantly decreased levels of cholesterol (29%), triglyceride (33%) and apoB (34%), compared to parental LDb mice. However, despite their high cholesterol levels at over 300 mg/dl, the atherosclerotic lesions in LTp mice were significantly decreased in comparison to LDb mice (8.8%±3.5 vs. 24%±3.3, p=0.004). We hypothesized that vascular PCSK9 regulates the development of atherosclerosis. We incubated LDL containing PCSK9 (LDL/PCSK9) on primary aortic endothelial cells (EC) obtained from LDb or LTp to study the effects of LDL/PCSK9 on inflammation. We show that LDL/PCSK9 could not induce the expressions of Lox-1, TLR-2, or ICAM-1 in EC from LTp, resulting in absence responses on proinflammatory markers and autophagic molecules. Our results suggest that vascular PCSK9 play a role in atherogenesis.

Subdivision 1. Basic Science

Presentation Preference Oral presentation
Additional information
Triglyceride Rich Lipoprotein Cholesterol and Risk of Cardiovascular Events Among Patients Receiving Statin Therapy in the TNT Trial

Abstract nr. 204
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Co-author(s) - Kastelein, John
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Topic Primary & Secondary prevention of CVD; Lifestyle Measures and Pharmacological Intervention
Keywords Cardiovascular Disease, Risk Factor, Therapy, Triglyceride-Rich Proteins

Background: Mendelian randomization data suggest that lifetime higher triglyceride rich lipoprotein cholesterol (TRL-C) levels calculated as the difference between non-HDL-C and LDL-C are causally related to cardiovascular disease (CVD). We assessed the relationship between TRL-C and CVD risk, and whether this was modifiable in the Treat to New Targets (TNT) trial.

Methods: The effect of atorvastatin 10mg (AT10) on TRL-C was assessed during the open-label run-in phase and that of atorvastatin 80mg (AT80) vs AT10 assessed over 5 years (N=10001). The relationship between quintiles of baseline TRL-C and the primary endpoint (PEP) of the TNT trial was determined in the AT10 arm. The randomized effect of AT80 vs AT10 on the PEP was assessed across baseline quintiles of TLR-C. Finally the independent relationship between the % change in TRL-C levels at 3 months and subsequent risk of PEP was assessed using Cox regression models.

Results: AT10 reduced TRL-C from a median of 30mg/dl to 27mg/dl (p<0.0001), which was reduced further to 23mg/dl at 3 months by AT80 (p<0.0001) and maintained over time. Higher TRL-C levels were associated with higher rates of PEP, ranging from 9.72 % (Q1) at 5 years to 13.77% (Q5); hazard ratio (HR) Q5 vs Q1 1.49, 95%CI 1.15-1.92 (p trend <0.0001, AT10 arm). AT80 did not significantly alter risk of PEP in TRL-C Q1 and 2, but did reduce the PEP risk in Q3-Q5, with evidence of effect modification (p for homogeneity 0.0053) and greater absolute benefits observed in Q4 and Q5 of baseline TRL-C (Figure). Finally in multivariable models independent of reductions in LDL-C, a 1SD reduction in TRL-C was associated with lower risk (HR 0.93, CI 0.864-0.999) and of similar magnitude to that for 1SD lowering in LDL-C (HR 0.89, CI 0.831-0.953).

Conclusion: TRL-C levels are reduced by atorvastatin therapy in a dose dependent fashion. Higher TRL-C levels are associated with increased CVD risk which is significantly attenuated by intensive atorvastatin therapy. Independent of the reduction in LDL-C, the percentage reduction in TRL-C is associated with CVD suggesting that TRL-C is both a risk marker and a potential target for therapeutic intervention.
Subdivision 3. Clinical Studies

Presentation Preference Oral presentation

Additional information
Longer GT repeats and rs2071746T allele in the heme oxygenase-1 gene promoter are associated with abdominal aortic aneurysm

Abstract nr. 205
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Co-author(s) - Staniszewski, Ryszard
Co-author(s) - Oszkinis, Grzegorz
Co-author(s) - Słomski, Ryszard
Topic The Pathogenesis of Atherosclerosis; Immunity, Inflammation, and the Endothelium
Keywords Atherosclerosis, Genetics, Inflammation

Abdominal aortic aneurysm (AAA) is multi-factorial disease with life-threatening complications due to mainly asymptomatic course of development. Vascular inflammation induced by oxidative stress contribute to pathogenesis. Inter-individual differences in response to oxidative stress are partially under genetic control. In this study the associations between the functional SNPs and (GT)n repeat length polymorphisms in genes involved in the vascular response to hypoxia/ischemia: HIF1A (hypoxia inducible factor-1α) and HMOX1 (heme oxygenase-1) and the development of AAA were examined.

The study encompassed a series of 518 AAA patients, 345 patients with atherosclerotic aortoiliac occlusive disease (AOID) and 498 controls. The HIF1A rs11549465C>T, rs11549467G>A and HMOX1 rs2071746A>T SNP genotyping was performed by using predesigned TaqMan SNP-genotyping assays. For simultaneous assessment of the HIF1A and HMOX1 (GT)n polymorphisms, the method based on multiplex-PCR with fluorescent-labeled sense primers and fragment size analysis using DNA sequencer has been developed.

We found, that carriers of the HMOX1 (GT)n repeat long allele (n>27) had increased risk of developing AAA (OR=1.46 for dominant model, P=.034). The frequency of carriers of both HMOX1 risk alleles: rs2071746T and/or long (GT)n repeat in AAAs (58.5%) was higher as compared to AIOD (49.0%, P=.007). On the other hand, the frequency of noncarriers in AAAs was 0.0%, as compared to 1.3% in controls (P=.010) and 0.9% in AIOD (P=.066).

In conclusion, HMOX1 gene promoter long (GT)n repeat allele and rs2071746T, allele related to decreased anti-inflammatory and antioxidant capacity of heme oxygenase-1, are associated with abdominal aortic aneurysm. Supported by Polish Ministry of Sciences grant NN403_250440 and INNOMED.

Subdivision 3. Clinical Studies

Presentation Preference Mini-oral presentation

Additional information
KMUP-3 protects Cardiac Fibroblasts from apoptosis induced by hydrogen peroxide through the Adaptive Autophagy

Abstract nr. 206
Author Liou, Shu-Fen, Chia-Nan University of Pharmacy and Science, Tainan, Taiwan, Tainan, Taiwan
Co-author(s) - Chen, Chiu-Lan
Topic Primary & Secondary prevention of CVD; Lifestyle Measures and Pharmacological Intervention
Keywords Pharmacology

Autophagy is important for the turnover of organelles at low basal levels under normal conditions and it is up-regulated in response to stresses such as ischemia/reperfusion and in cardiovascular diseases such as heart failure. Apoptosis also plays important biological roles in the pathogenesis of many diseases. Oxidative stress induced by myocardial infarction is one of the major factors of heart failures. In our previous studies, 7-[2-[4-(4-nitrobenzene)piperazinyl]ethyl]-1,3-dimethylxanthine (KMUP-3) is a chemically synthetic xanthine-based derivative. It has been shown to induce autophagy in cardiac fibroblasts. The aim of this study was to investigate how KMUP-3 modulates hydrogen peroxide (H$_2$O$_2$)-induced apoptosis in neonatal rat cardiac fibroblasts and to elucidate the cellular and molecular mechanism. Preincubation of KMUP-3 significantly inhibited apoptosis and increased cell viability for neonatal rat cardiac fibroblasts under oxidative stress. Western blot showed that KMUP-3 enhanced p-eNOS, eNOS, PKG, LC3-II, Atg7 formation, and increased Bcl-2/Bax ratio in H$_2$O$_2$-treated neonatal rat cardiac fibroblasts under oxidative stress. Moreover, KMUP-3 attenuated H$_2$O$_2$-induced MMP-2, MMP-9 and cleaved caspase-3 protein expressions. These effects were blocked by both the L-NAME and L-NIO, indicating that eNOS plays a role in the modulation of KMUP-3 in H$_2$O$_2$-induced apoptosis. However, when cardiac fibroblasts treated with Atg7 siRNA, which blocked the autophagy in the cells and resulted in a further increase in cell apoptosis. These results showed that KMUP-3 may promote autophagy to decrease oxidative stress-induced apoptosis in cardiac fibroblasts. Therefore, KMUP-3 might exert cardioprotective effects in heart diseases through regulation of autophagy and apoptosis.

Subdivision 1. Basic Science

Presentation Preference Electronic poster presentation
Additional information
Influence of ranolazine and trimetazidine on inflammatory parameters in patients with chronic ischemic heart disease

Abstract nr. 207
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Topic The Pathogenesis of Atherosclerosis; Immunity, Inflammation, and the Endothelium
Keywords Inflammation, Intervention, Therapy

Levels of tumor necrosis factor α (TNF-α) and interleukin 6 (IL-6), that together with stimulates the synthesis of the acute-phase proteins, correlate closely with C-reactive protein (CRP) serum levels. They were all found to be independent predictors of future coronary artery events in apparently healthy males as well as in patients with coronary artery disease. The novel anti-ischemic drugs, ranolazine and trimetazidine, reduce the levels of some inflammatory parameters in patients with stable coronary artery disease.

The aim of this study was to compare the effects of ranolazine and trimetazidine on CRP, TNF-α, IL-6, interleukin 10 (IL-10) and vascular adhesion molecules (VCAM) in patients with stable coronary artery disease.

In a prospective, double blind study, 56 males aged between 32 to 65 years with chronic ischemic heart disease were randomised and submitted to 12 weeks treatment with either trimetazidine (35 mg twice daily) or ranolazine. Ranolazine was given in a dose of 375 mg twice daily for 4 weeks and was increased to 500 mg twice daily.

Ranolazine was found to lower the CRP concentration after 12 weeks from 4.5±6.26 to 1.93±3.11 mg/l (p=0.038), while no changes was observed in trimetazidine group (3.78±7.65 to 3.6±6.46 mg/l; p=0.831) (p=0.103 for comparison of interventions). Ranolazine lower IL-10 levels from 1.5±1.2 to 1.1±1.2 ng/l (p=0.031), with no changes in trimetazidine group (1.4±0.7 to 1.4±1.0 ng/l; p=0.817) with no difference between the groups (p=0.327). TNF-α decreased in ranolazine group from 18.8±28.9 to 11.7±20.5 ng/l (p=0.186) and from 27.4±34.0 to 22.6±31.1 ng/l (p=0.639) in trimetazidine group, with no difference between the groups (p=0.844). IL-6 changed in ranolazine group from 3.4±2.2 to 2.8±1.4 ng/l (p=0.109) and from 3.4±2.4 to 3.5±2.4 ng/l (p=0.631) in trimetazidine group, with no difference between the groups (p=0.116). VCAM changed in ranolazine group from 888±219 to 904±356 μg/l (p=0.688) and from 1002±345 to 993±386 ng/l (p=0.756) in trimetazidine group, with no difference between the groups (p=0.608).

Our study shows that ranolazine significantly lower the levels of CRP and IL-10 with no influence on IL-6, TNF-α and VCAM, while trimetazidine have no influence on measured parameters in patients with stable coronary artery disease.

Subdivision 3. Clinical Studies

Presentation Preference Oral presentation
Additional information
Renal and cardioprotective effects of irbesartan via reduction of serum sodium, uric acid, LDL-C, and microalbuminuria in hypertensive patients

Abstract nr. 208
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Topic Primary & Secondary prevention of CVD; Lifestyle Measures and Pharmacological Intervention
Keywords Blood pressure, Hypertension, Renal function, Risk Factor

Background Irbesartan, angiotensin II receptor blocker (ARB) is a well-established first-line treatment option for hypertension. We examined the long-term effects of irbesartan beyond lowering blood pressure. **Methods and results** In this study, 211 (97 male and 114 female, mean 66.1 years) hypertensive patients treated with irbesartan were enrolled. We observed blood pressure (BP), pulse rate (PR), serum levels of sodium, potassium, uric acid, microalbuminuria and lipid profile at baseline, 6 and 12 months after administration of irbesartan. Systolic and diastolic BP were significantly reduced (-23±3 mmHg and -10±2 mmHg, respectively), while there was no significant change in PR during the period. Serum sodium was significantly reduced (141 ± 2.2 mEq/l to 140 ± 2.4 mEq/l), while there was no significant changes in serum potassium. Furthermore, urinary albumin was significantly reduced at 12 months (167 ±686 mg/g Cr to 80 ± 237 mg/g Cr). In 35 patients with uric acid more than 7.0 mg/dl without medication for hyperuricemia, serum uric acid was significantly reduced (7.9 ±1.1 mg/dl to 6.7 ± 1.1, p<0.01). LDL cholesterol was also significantly reduced (115 ± 5 mg/dl to 107 ± 5 mg/dl, p<0.01) in patients with uric acid less than 7.0 mg/dl. **Conclusion** Irbesartan therapy significantly reduced not only BP, but also other metabolic factors in patients with hypertension. Furthermore, irbesartan had sodium excretion effect in addition to angiotensin receptor blocker for lowering blood pressure. This study suggested that irbesartan might have renal and cardioprotective effects in hypertensive patients.

Subdivision 3. Clinical Studies

Presentation Preference Electronic poster presentation
Additional information
Epicardial adipose tissue in overweight and obese children and its relationship to cardiometabolic risk factors, insulin resistance and hyperuricemia

Abstract nr. 209
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Topic Epidemiology of CVD; The Risk Factor Concept
Keywords Cardiovascular Disease, Obesity, Risk Factor, Visceral Fat

Background: Epicardial adipose tissue (EAT) is the visceral fat deposit around the heart and is commonly increased in obese subjects. EAT is related to cardiometabolic risk factors and non-alcoholic fatty liver disease (NAFLD) in adults, but this relationship is not well known in children.

Objectives: The aim of our study was to assess by echocardiography the EAT in overweight and obese children and its relationship to cardiometabolic risk factors, insulin resistance, NAFLD markers and hyperuricemia.

Study group and methods: In 25 (mean age 13.0 ± 2.3) overweight and obese subjects and 24 lean controls, blood pressure (BP), waist circumference (WC), fasting plasma glucose and insulin, lipids, uric acid and hepatic enzymes were established and EAT thickness measured by transthoracic echocardiography.

Results: In overweight and obese subjects, EAT was significantly higher compared to normal weight children. Overweight and obese children had significantly higher body mass index (BMI), WC, BP, triglycerides (TAG), low density lipoprotein and total cholesterol, hepatic enzymes alanine aminotransferases (ALT) and g-glutamyl transferase, and lower high density lipoprotein cholesterol (HDL-C). EAT correlated significantly with BP, TAG, uric acid, HDL-C, apolipoprotein B and ALT. Correlation coefficients were similar or better than for WC, but similar or lower then for BMI.

Conclusions: In conclusion EAT thickness in children is associated with an unfavourable cardiometabolic risk profile including biochemical signs of NAFLD and hyperuricemia but is not a stronger indicator than BMI.

Subdivision 3. Clinical Studies

Presentation Preference Electronic poster presentation

Additional information
Endothelial dysfunction, inflammation and body mass index in patients with coronary heart disease in combination with nonalcoholic hepatic steatosis

Abstract nr. 210
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Topic The Pathogenesis of Atherosclerosis; Immunity, Inflammation, and the Endothelium
Keywords Endothelium, Inflammation, Obesity

Objective: To compare the relationship of endothelial dysfunction, inflammation, serum levels of aminotransferases depend from body mass index (BMI) in patients with coronary heart disease in combination with nonalcoholic hepatic steatosis.

Methods: We studied 19 patients with coronary heart disease in combination with nonalcoholic hepatic steatosis. Allocated 2 groups according to BMI: one group consisted of 10 (52%) people with first degree of obesity (BMI 30,0 to 34,9 kg/m²) mean age 53,7±5,4, group 2 - 9 (40%) who are overweight (BMI 25 to 29,9 kg/m²) mean age 57,2±7,04. Patients with diabetes were excluded. All patients not taking statins. The reactive hyperemia test for assessment of endothelial dysfunction was consecutively performed in all patients. Brachial artery enlargement by less than 10% was considered as a sign of endothelial dysfunction. Studied biochemical parameters: the levels of C-reactive protein (CRP), alanine transaminase (ALT), aspartate transaminase (AST), gamma-glutamyl transpeptidase (GGT).

Results: Endothelial dysfunction was found in 9 patients (90%) in a group 1 and in 6 patients (66%) in a group 2, vasospastic response observed in 1 patient (10%) in a group 1. The mean level reactive hyperemia index changes did not significantly differ between the two groups (5,5±4,3 % and 5,4±1,4 %, p>0,05 ). The mean level CRP in a group 1 was higher (4,7±0,6mmol/l) than in group 2 (2,3±0,34mmol/l) (p<0,05); of ALT: 36,2±11,9mmol/l and 27,2±13,2mmol/l (p<0,05); of AST: 27,0±2,4mmol/l and 20,2±2,3mmol/l (p<0,05); of GGT: 60,2±9,03mmol/l and 47,2±3,7mmol/l (p<0,05). There was correlation between the endothelial dysfunction and level of AST (r=0,89; p<0,05) in a group 1 however in a group 2 such connection was not observed. The level of CRP in a group 1 associated with level gamma-glutamyl transpeptidase (GGT) (r=0,87; p<0,05) than in group 2.

Conclusion:
In patients with coronary heart disease in combination with NAFLD and first degree of obesity (BMI 30,0 to 34,5 kg/m²) inflammation were more expressed in those who had overweight (BMI 25,0 to 29,9). There was an association between endothelial dysfunction and level of AST, level of CRP and level GGT in a group 1 however in a group 2 such connection was not observed.

Subdivision 1. Basic Science
Prevalence of cardiovascular diseases among type 2 diabetic patients shifted to insulin therapy in Najaf Governorate, Iraq

Abstract nr. 212
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Topic Epidemiology of CVD; The Risk Factor Concept
Keywords Cardiovascular Disease,Diabetes,Epidemiology

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Background: Diabetes mellitus is a diseases of vascular complications particularly when it is associated with dyslipidemia .More than half of type two diabetic patients (51%) have being shifted to insulin therapy by their specialist physicians in Iraq . The prevalence of cardiovascular diseases from the start of disease exceed 30% of type two diabetic patients in Iraq. There is no local evidence about the role of insulin therapy on reducing risk of cardiovascular diseases .

Objective : To estimate the prevalence of cardiovascular diseases among patients with type 2 diabetes who are shifted to insulin treatment.

Design: A cross sectional study

Methods: From registered 7120 diabetic patients in the Popular Medical Clinics Directorate in Najaf governorate , 5248 patients diagnosed by Najaf Center of Diabetes and Endocrine Diseases, as Type 2 Diabetes Mellitus. A random sample of 2820 patients with Type 2 diabetes were selected during their attendance to Ninth popular medical clinic in Najaf from January 1st 2005 to 30 September 2014 for receiving their free prescribed treatments .The selected patients were interviewed for presence or absence of cardiovascular events regarding the duration of their started therapy .

Results: The prevalence of cardiovascular diseases in type 2 diabetic shifted to insulin in Najaf-Iraq was 34.6% after age of 60 years versus 48% of patients on oral hypoglycemic drugs . No significant difference in use of available statins ( Fluvastatin and Atorvastatin,) between diabetics with and without these disease. Conclusion : cardiovascular diseases were less prevalent among type 2 diabetic patients on insulin therapy regardless of their statin use.
Effect of Saroglitazar on HbA1c level in type 2 Diabetes Mellitus: A clinical experience data

Abstract nr. 214
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Co-author(s) - Chandarana , Hardik
Co-author(s) - Patel , Swati
Topic Dyslipidemia; Lipids, Lipoproteins and Apolipoproteins
Keywords Diabetes, Dyslipidemia

Background: Saroglitazar (ZYH1) is a novel peroxisome proliferator-activated receptor (PPAR) agonist with predominant PPARα and moderate PPARγ activity. It has been developed for the treatment of dyslipidemia and has favourable effects on glycaemic parameters in type 2 diabetes mellitus. Saroglitazar showed both anti-dyslipidemic and anti-diabetic effects mainly mediated via activation of PPARα and PPARγ respectively. It has also shown favorable glycaemic indices by reducing the fasting plasma glucose and glycosylated hemoglobin in diabetic patients.

Objective: To evaluate the clinical effectiveness of saroglitazar in terms of glycaemic control (HbA1c) in type 2 diabetic patients.

Method: An analysis of the clinical features and laboratory data of 200 (109 males, 91 females) patients of either gender, aged 18-70 years diagnosed with type 2 diabetes mellitus (glycosylated hemoglobin [HbA1c] > 7 to 9%) was collected. All the patients with type 2 Diabetes Mellitus treated with Saroglitazar were observed for a period of 6 months. Saroglitazar was recommended for once daily administration as 4 mg tablets. Outcome was assessed in terms of HbA1c level.

Result: Out of 200 patients, Eighty-three percentages (n=166) T2DM patients achieved significant reduction in glycemic level in terms of HbA1c level ≥0.5% from the baseline HbA1c level, whereas marked reduction of HbA1c level was not achieved in seventeen percentage (n=34) within 6 months of observation period.

Conclusion: Effects of Saroglitazar 4 mg, on HbA1c were significantly better than baseline, thus, Saroglitazar appeared to be an effective therapeutic option for improving glycemic control (HbA1c) in patients with type 2 diabetes mellitus.

Subdivision 3. Clinical Studies

Presentation Preference Mini-oral presentation
Additional information
Abstract nr. 215
Author Maciejewska, Dominika, Pomeranian Medical University, Poland, Szczecin, Poland
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Co-author(s) - Drozd, Arleta
Co-author(s) - Banaszczyk, Marcin
Co-author(s) - Ryterska, Karina
Co-author(s) - Milkiewicz, Małgorzata
Co-author(s) - Raszeja-Wyszymierska, Joanna
Co-author(s) - Milkiewicz, Piotr
Co-author(s) - Jeleń, Henryk

Topic Dyslipidemia; Lipids, Lipoproteins and Apolipoproteins
Keywords Apolipoproteins, Inflammation, Lipids, Risk Factor

Introduction: Apolipoprotein E (apoE) is an important element in the metabolism of cholesterol, lipoproteins and triglycerides. We can distinguish three types of apoE protein: apoE 2, apoE 3 and apoE 4. The fourth phenotype is associated with significantly increased risk of cardiovascular diseases, diabetes and Alzheimer's disease. The role of apoE 4 in patients with metabolic syndrome (MS) has been broadly discussed recently. MS is associated with serious lipid metabolism disorders as well as increased oxidative stress. The same pathological factors are also a cause of nonalcoholic fatty liver disease (NAFLD). There are no reports about lipids metabolism changes in apoE4 carriers with NAFLD.

Aim: The aim of the study was to compare fatty acids and their derivatives concentration in apoE 4 and the other apoE variants among patients with NAFLD.

Materials and methods: 22 patients with NAFLD were enrolled in the study. The study group included 11 apoE 4 carriers, as well as a control group, also consisting of 11 patients, with apoE 2 and apoE 3 phenotypes. The concentrations of fatty acids and their derivatives were measured in plasma. The extraction is based on solid phase extraction technique. The fatty acids analysis was performed using Agilent Technologies 7890Agas chromatography. Arachidonic and linoleic acid transformation products – Lipoxin A4 (LX A4), 16–hydroxyeicosatetraenoic (16-HETE), 13–hydroxyoctadecadienoicacid (13-HODE), 9–hydroxyoctadecadienoic acid (9-HODE), 15–hydroxyeicosatetraenoic acid (15-HETE), 12–hydroxyeicosatetraenoic acid (12-HETE), 5–oxoicosatetraenoic acid (5-oxoETE) – were analyzed using Agilent Technologies 12600 high-performance liquid chromatography. Statisticawas used for statistical analysis (Statsoft 2011).

Results: ApoE 4 carriers had significantly increased plasma concentration of several fatty acids (Table 1) as well as the concentration of arachidonic and linoleic transformation products (Table 2).

Discussion: ApoE 4 carriers showed increased concentration of monounsaturated fatty acids,
which is caused by increased activity of Δ 9 desaturase. Increased activity of this enzyme and significantly higher concentration of stearic acid seems to be a consequence of increased lipogenesis in patients with ApoE4 phenotype. In the other hand, ApoE 4 carries are more exposed to inflammation because of their higher concentration of inflammatory markers (5-HETE, 9-HODE, 3-HODE).

<table>
<thead>
<tr>
<th>Fatty acids derivatives</th>
<th>Median (IQR) apoE 4</th>
<th>Median (IQR) control</th>
<th>p.value</th>
</tr>
</thead>
<tbody>
<tr>
<td>LX A4</td>
<td>2.579 (3.197)</td>
<td>1.472 (3.627)</td>
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</tr>
<tr>
<td>16 - HETE</td>
<td>4.837 (7.103)</td>
<td>1.235 (0.256)</td>
<td>NS</td>
</tr>
<tr>
<td>13 - HODE</td>
<td>4.053 (5.919)</td>
<td>1.860 (0.190)</td>
<td>p&lt;0.05</td>
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<tr>
<td>9 - HODE</td>
<td>8.273 (8.794)</td>
<td>1.896 (0.693)</td>
<td>p&lt;0.05</td>
</tr>
<tr>
<td>15 - HETE</td>
<td>1.233 (1.187)</td>
<td>0.506 (0.300)</td>
<td>NS</td>
</tr>
<tr>
<td>12 - HETE</td>
<td>16.960 (2.232)</td>
<td>13.524 (8.804)</td>
<td>NS</td>
</tr>
<tr>
<td>5-oxoETE</td>
<td>0.0134 (0.009)</td>
<td>0.0192 (0.089)</td>
<td>NS</td>
</tr>
<tr>
<td>5 - HETE</td>
<td>0.902 (1.057)</td>
<td>0.151 (0.124)</td>
<td>p&lt;0.05</td>
</tr>
</tbody>
</table>

Fatty acids derivatives concentrations

<table>
<thead>
<tr>
<th>Fatty acids</th>
<th>Median (IQR) apoE 4</th>
<th>Median (IQR) control</th>
<th>p.value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Palmitic acid (C16:0)</td>
<td>0.0326</td>
<td>0.0531</td>
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<tr>
<td>Palmitoleic acid (C16:1)</td>
<td>0.0132</td>
<td>0.0144</td>
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<td>Stearic acid (C18:0)</td>
<td>0.0652</td>
<td>0.0944</td>
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<td>Oleic acid(C18:1 n9)</td>
<td>0.3834</td>
<td>0.0800</td>
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<td>Vaccenic acid (18:1 n7)</td>
<td>0.0137</td>
<td>0.0933</td>
<td>p&lt;0.05</td>
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<td>Linoleic acid (C18:2 n6)</td>
<td>0.2505</td>
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<td>NS</td>
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<tr>
<td>α-Linolenic (18:3 n3)</td>
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<td>0.0243</td>
<td>NS</td>
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<td>Arachidonic acid (C20:4 n6)</td>
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<td>0.1423</td>
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<tr>
<td>Eicosapentaenoic acid (20:5 n3)</td>
<td>0.0357</td>
<td>0.0270</td>
<td>NS</td>
</tr>
<tr>
<td>Docosapentaenoic acid (22:5 n3)</td>
<td>0.1029</td>
<td>0.0651</td>
<td>p&lt;0.05</td>
</tr>
<tr>
<td>Docosahexaenoic acid (22:6 n3)</td>
<td>0.0651</td>
<td>0.0456</td>
<td>NS</td>
</tr>
</tbody>
</table>

Fatty acids concentrations

Subdivision 1. Basic Science

Presentation Preference Electronic poster presentation

Additional information
Blockade of Tim-4 aggravates atherosclerosis

Abstract nr. 216
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Introduction: Proteins of the transmembrane T cell immunoglobulin and mucin domain (Tim) family are expressed by numerous immune cells, recognize phosphatidylserine (PS) exposing cells and exert either a costimulatory or coinhibitory role. Tim-4, present on macrophages and antigen-presenting cells, has been shown to play a critical role in the clearance of apoptotic cells, regulates the number of PS-expressing activated T cells, and is genetically associated with triglyceride levels. Since both apoptosis and the presence of activated T cells contribute to atherosclerotic lesion formation, we investigated whether interference in Tim-4 function would affect atherosclerosis.

Methods and Results: LDLr−/− mice were fed a Western-type diet for 4 weeks while being treated twice a week i.p. with an anti-Tim-4 (21H12) mAb that blocks PS recognition and phagocytosis or an isotype control (rat IgG1). Treatment with anti-Tim-4 increased the area of atherosclerotic lesion in the aortic root by 45% (7.76±1.07%) compared with control mice (5.37±0.51%, P<0.01), independent of plasma cholesterol and triglyceride levels. Anti-Tim-4-treated mice showed increased activated T cell numbers and 'late' apoptotic cells in the circulation. Additionally, anti-Tim-4 treatment induced splenomegaly, enhanced splenocyte proliferation and increased IFNγ+ (Th1) and IL-4+ (Th2) cells.

Conclusion: Blockade of Tim-4 aggravates atherosclerosis likely by prevention of phagocytosis of PS-expressing apoptotic cells and activated T cells by Tim-4-expressing cells.

Subdivision 1. Basic Science

Presentation Preference Oral presentation
Additional information
Features psychovegetative disorders in patients with chronic cerebral ischemia and ways of their correction

Abstract nr. 217
Author Sultanhodjaeva, Nadira, Postgraduate Medical Institute, Tashkent, Uzbekistan
Topic Primary & Secondary prevention of CVD; Lifestyle Measures and Pharmacological Intervention
Keywords Intervention, Lifestyle, Pathogenesis, Pharmacology

Modern metabolic preparations, interfering with metabolic processes in the organism, normalize first of all a biological basis of the adapted reaction of the person. The purpose of our research was studying dynamics of cognitive and emotional sphere at patients - invalids with ChIB on a background of an atherosclerosis of vessels of the brain at stages of rehabilitation. By way of complex rehabilitation we applied a preparation mildronat.

Materials and methods of research. 45 patients in the age of from 30 till 55 years (middle age 42+3,76) were surveyed. The estimation of efficiency of treatment was based on results of following researches: clinic-neurological research, psychological – emotional research, in the present work were used test of Spielberg in modification (132.) Screening scale of diagnostics of dementia were researched clinically on the basis of criteria of the American psychiatric association - DSM-IY by means of "the Brief scale of estimation of the mental status" (Mini-Mental State Examination, agant. Folstein et al., 1975) which defines quantitative and quality standard of cognitive defect, and cardiointervalography.

As a result of researches at patients was observed the high degree both situational, and to personal uneasiness and also an easy and average degree dementia before the treatment, and also result CIG have shown moderated sympaticotony. On a background of treatment at patients positive dynamics from psychological – emotional spheres was observed: the tendency to decrease as the situational and personal uneasiness, the moderate expressiveness cognitive frustrations. Dynamics of research of 2 groups has shown the to decrease both personal, and situational uneasiness under Spielberg’s test, and also obvious reduction of expressiveness of cognitive frustrations. Vegetative sphere of the given patients has sharply decreased to normotony. Therefore, the application of mildronat which possesses not only vasoactive and antioxidant, it is also neuroprotective and which’s metabolic properties which influencing to subsystem of emotional-affective reaction is pathogeneticly proved.

Subdivision 4. Not applicable. Abstract matches with track c

Presentation Preference Electronic poster presentation
Additional information
High-sensitivity C-reactive protein levels across countries and ethnicities

Abstract nr. 218
Author Izar, Maria Cristina, Federal University of Sao Paulo, Santana De Parnaiba, Brazil
Co-author(s) - Fonseca, Francisco Antonio
Topic Epidemiology of CVD; The Risk Factor Concept
Keywords Cardiovascular Disease, Epidemiology, Inflammation, Prevention

Background: Despite substantial differences in ethnicities, habits, culture, prevalence of traditional cardiovascular risk factors and affordable therapies, atherosclerosis remains the major cause of death in developing and developed countries. However, regardless of these inequalities, inflammation is currently recognized as the common pathway for the major complications of atherosclerosis, stroke, and ischemic heart disease.

Methods: A PubMed search was conducted for ‘high-sensitivity C-reactive protein’ (hs-CRP) in combination with race, ethnicity, gender, prevalence, geographic, epidemiology, cardiovascular, obesity, diabetes, hypertension, cholesterol, smoking, ischemic heart disease, stroke, and mortality. There is no systematic approach implemented for the selection of articles in this review. Instead, it was based on relevance to the topic. Additional articles identified from reference lists of relevant publications were also included.

Results and Conclusions: This review described marked differences in the cardiovascular mortality across countries and ethnicities, which can be attributed to inequalities in the prevalence of classic risk factors and stage of cardiovascular epidemiological transition. However, hs-CRP seems to add prognostic information for cardiovascular risk and mortality even after multiple adjustments. Taking into account the perception of cardiovascular disease as an inflammatory disease, the more widespread use of hs-CRP appears to be a valid tool to identify people at risk, independently of the ancestry or geographic region. Further, the large Canakinumab ANtiinflammatory Thrombosis Outcome Study (CANTOS) trial involving subjects from Europe, Asia, Africa, and Americas is ongoing and important questions will be answered, including the need for different cutoffs of hs-CRP, the relevance of this biomarker for different ethnicities and the validity of an antiinflammatory treatment for people at risk.

Subdivision 4. Not applicable. Abstract matches with track c

Presentation Preference Oral presentation
Additional information
The prevalence of heterozygous familial hypercholesterolemia in Tyumen region of Russian Federation

Abstract nr. 219
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Co-author(s) - Boytsov, Sergey

Keywords Cardiovascular Disease, Familial Hypercholesterolemia

Background: Heterozygous familial hypercholesterolemia (FH) is an autosomal dominant disorder known to be associated with elevated cholesterol levels and increased risk of premature coronary artery disease. Historically, the community prevalence of FH is estimated to be one in 500; however, recent data suggest that this is an underestimate. The Copenhagen General Population Study determined that the prevalence in individuals classified as definite or probable FH approached one in 137. The prevalence of FH in Russia has not previously been evaluated. The aim of our study is to investigate the prevalence of FH in the Russian population.

Materials and methods: The study was of a randomly selected, community-based population comprising 1,630 people of Tyumen region of Russian Federation (from the ESSE-RF epidemiological study). The level of low-density lipoprotein cholesterol was measured in all participants. All subjects were interviewed to assess statin treatment. All participants who had low-density lipoprotein cholesterol (LDL-cholesterol) higher 4.9 mmol/l and who had LDL-cholesterol lower 4.9 mmol/l but had statin therapy were examined by experts in FH. The diagnosis of FH was determined using the Dutch Lipid Clinical Network Criteria (DLCN).

Results: We examined 126 participants from 142 who had the level of low-density lipoprotein cholesterol higher 4.9 mmol/l and 5 participants from 11 who had statin treatment (aged 59 (53-62) years). The prevalence of individuals classified with definite FH (DLCN criteria >8 points) was 0.31% (one in 323), probable FH (6–8 points) was 0.67% (one in 149), definite or probable FH combined (>5 points) 0.98% (one in 102), possible FH 6.87% (one in 15) (3–5 points).

Conclusion: The prevalence of FH in the Russian population is higher than estimated value.

Subdivision 4. Not applicable. Abstract matches with track c

Presentation Preference Oral presentation

Additional information
Plant sterol supplementation on top of lipid-lowering therapies in familial hypercholesterolemia

Abstract nr. 220
Author Izar, Maria Cristina, Federal University of Sao Paulo, Santana De Parnaiba, Brazil
Co-author(s) - Fonseca, Francisco Antonio
Co-author(s) - Machado, Valeria
Co-author(s) - Fonseca, Henrique Andrade
Co-author(s) - Fonzar, Waleria Toledo
Topic Dyslipidemia; Lipids, Lipoproteins and Apolipoproteins
Keywords Familial Hypercholesterolemia, Hypolipidemic Drugs, Lipids, Nutraceuticals

Background: Familial hypercholesterolemia (FH) is the most common inherited disorder of lipid metabolism, resulting in very high levels of LDL-cholesterol (LDL-C) from birth and increased premature coronary disease. Underdiagnosed and undertreated, this condition often requires combined lipid-lowering therapy (LLT), with room for further interventions. Plant sterols (PS) supplementation, by reducing intestinal cholesterol absorption, can further lower LDL-cholesterol in 10%, but the combination of high-dose statin, ezetimibe and PS has not been addressed yet in FH individuals. We tested the effects of plant sterols on top of two intensive LLT on LDL-C, sterols synthesis and absorption markers.

Methods and results: Forty-two individuals of both genders with confirmed diagnosis of FH, aged 49-60 years were prospectively included. Study design was PROBE (randomized, open label, with parallel arms and blinded endpoints). After a 4-week washout period of previous LLT, eligible subjects were randomized to receive simvastatin 80mg or simvastatin 80mg plus ezetimibe 10mg in a blinded fashion for 12 weeks. After this period, 2g of phytosterols, as free sterols were given in 500mg capsules with meals for additional 12 weeks. Both LLTs reduced total- and LDL-C, triglycerides and ApoB, while addition of phytosterols further reduced LDL-cholesterol only in the group receiving simvastatin/ezetimibe (P=0.031). Simvastatin increased campesterol, decreased desmosterol, while combined therapy reduced absorption markers and reduced desmosterol plasma levels (P<0.05 vs baseline, for all).

Conclusions: This study has shown that PS supplementation in FH benefited those individuals treated with simvastatin plus ezetimibe, but not those receiving simvastatin alone. In addition to ezetimibe, PS can counterbalance the increased sterols absorption besides improving lipid profile. Our study confirms the relevance of a more intensive blockade of cholesterol absorption and the validity of phytosterols supplementation for patients with FH.
Individual profiles showing variables of lipid profile by treatment

Subdivision 3. Clinical Studies

Presentation Preference Electronic poster presentation

Additional information
Cardiovascular risk factors in patients with rheumatoid arthritis in combination with hypertension.

Abstract nr. 221
Author Sirenko, Oksana, Dnipropetrovsk medical academy, Dnipropetrovsk, Ukraine
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Co-author(s) - Lysunets', Tetyana
Topic Epidemiology of CVD; The Risk Factor Concept
Keywords Hypertension, Inflammation, Obesity, Risk Factor

The objective was to evaluate the frequency of cardiovascular risk factors and hypertension in patients with rheumatoid arthritis depending on body weight. The study involved 100 patients with rheumatoid arthritis and stably selected therapy for more than 6 months at the age from 45 to 65 years (mean age 53,19 ± 5,40 years). Traditional cardiovascular risk was assessed, taking into account risk factors by SCORE scale and amended for patients with RA. The levels of total cholesterol, triglycerides, C-reactive protein, serum creatinine, body mass index, body area index were determined. Arterial hypertension was diagnosed in 41 (41%) patients with rheumatoid arthritis and was associated with traditional risk factors (age, obesity), rheumatoid factor, hyperuricemia and the duration of glucocorticoid therapy. 10-year risk of fatal cardiovascular events matched by SCORE in patients with rheumatoid arthritis was 1,48 ± 1,94%, with consideration of 1,5 coefficient- 1,98 ± 2,53%, which is considered medium risk. Overweight and obesity have been established in 67 (67%) patients with rheumatoid arthritis. Body mass index was associated with duration of rheumatoid arthritis inflammation activity, duration of therapy with glucocorticoids. Patients overweight had the highest level of performance inflammation, the risk of cardiovascular complications. Identification of hypertension and obesity increases the information content of the risk assessment of cardiovascular events in rheumatoid arthritis.

Subdivision 3. Clinical Studies

Presentation Preference Electronic poster presentation
Additional information
Anti Inflammatory Effect of High Complex Carbohydrate Diet and Physical Activity in Severely Obese Volunteers

Abstract nr. 223
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Topic Primary & Secondary prevention of CVD; Lifestyle Measures and Pharmacological Intervention
Keywords Inflammation,Nutrition,Obesity

**Aim:** The presence of low grade, internal inflammation is one of the main causes for development of insulin resistance, type 2 diabetes mellitus and atherosclerosis. The aim of the study is to evaluate the effect of Life style modifications on the inflammatory profile of obese volunteers.

**Methods:** Blood samples were taken before and after 8 months of intensive life modification program, including consumption of high-complex carbohydrate diet and intensive physical activity in a group of apparently healthy severely obese volunteers.

**Results:** Substantial improvement was noted in the biometric, metabolic and inflammatory biomarkers. A reduction was found in BMI and in the concentrations of CRP, triglycerides, LDL, total cholesterol, insulin concentration, HOMA-R, the adhesion molecule ICAM1 and the pro-inflammatory cytokines TNF-alpha and IL6. Erythrocyte Sedimentation Rate and the degree of red cell aggregation were reduced. However, a significant increment in fibrinogen concentrations was noted.

**Conclusion:** The study shows the beneficial anti inflammatory properties of this intervention program. The pro-aggregating properties of fibrinogen following intense physical activity are probable counterbalanced by the anti-aggregatory properties of an improved lipid profile and an attenuated acute phase response. The study suggests that strenuous physical activity is not advised for untrained obese individuals.

Subdivision 3. Clinical Studies

Presentation Preference Electronic poster presentation
Additional information
Objectives
We developed a highly sensitive and specific LPL-ELISA and reported that most lipoprotein lipase (LPL) in the circulating plasma is bound to remnant lipoproteins (RLP) specifically. We have further investigated the relationship between circulating LPL and remnant lipoproteins in plasma with and without heparin injection.

Methods
LPL mass and activity of pre-heparin and post-heparin plasma were determined in 40 healthy volunteers with TC, TG, LDL-C, HDL, RLP-C, RLP-TG and other plasma parameters. Superose 6B was used to fractionate RLP under the presence of tetrahydrolipstatin, the inhibitor of LPL. LPL activity was determined by enzymatic method (Imamura et al. J Lipid Res. 2008; 49:1431)

Results
LPL concentration was determined in post-heparin and pre-heparin and plasma in 40 volunteers (65±20ng/mL, 382±42 ng/ml, respectively). More than 70 % of LPL was found in RLP in pre-heparin plasma, while less than 30% of LPL was found but significantly increased in RLP in post-heparin plasma. Addition of tetrahydrolipstatin (1μg/mL) significantly inhibited the LPL activity and movement of LPL to HDL fraction from RLP. RLP was apoC3 and apoC1 rich as well as apoE rich. In vitro study showed that addition of apoC1 and apoC3 significantly reduced LPL activity (50% and 70 %, respectively). These results indicated that LPL binds to RLP with apoC1 and apoC3 and inhibits LPL activity in pre-heparin plasma.

Conclusion
Highly sensitive and specific LPL-ELISA assay made it possible to investigate the plasma circulating LPL in RLP with and without heparin injection. Tetrahydrolipstatin significantly inhibit LPL activity and prevented the hydrolysis of RLP in both pre-heparin and post-heparin plasma.
Low concentration of LPL in RLP kept large particle size and delayed the metabolism of remnant lipoproteins in plasma.

Subdivision 3. Clinical Studies

Presentation Preference Oral presentation
Additional information
Dissecting molecular mechanisms of fatty liver disease that promote atherogenesis

Abstract nr. 225
Author Sivasubramaniyam, Tharini, University of Toronto, Toronto, Canada
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Co-author(s) - Schroer, Stephanie A
Co-author(s) - Robbins, Clinton
Co-author(s) - Woo, Minna
Topic The Pathogenesis of Atherosclerosis; Immunity, Inflammation, and the Endothelium
Keywords Atherosclerosis, Pathogenesis

Fatty liver is an emerging independent risk factor for atherosclerosis. However, the common association between fatty liver and other risk factors precludes definitive conclusions about the causal role of fatty liver per se in atherogenesis. Thus, the exact mechanisms by which fatty liver increases atherosclerosis risk are largely unknown. The Janus kinase-signal transducers and activators of transcription (JAK-STAT) pathway is a major signalling pathway downstream of cytokines and growth factors. In the liver, we and others previously showed that deletion of JAK2 led to spontaneous development of profound fatty liver on chow diet. Interestingly, those defects commonly associated with fatty liver including systemic insulin resistance, inflammation and glucose intolerance were absent in these mice. Thus we asked whether fatty liver in the absence of the other commonly associated risk factors affected atherogenesis. L-JAK2−/− in both atherosclerosis-prone APOE−/− and LDLR−/− models, after 12wks of atherogenic diet showed similarly profound fatty liver without glucose intolerance or insulin resistance. These mice in both athero-prone models developed over a 2-fold increase in plaque burden compared to controls as assessed by Oil-Red-O staining of the descending aorta and the plaques in the aortic arch appeared more advanced with increased macrophage content and significantly less luminal smooth muscle actin. We had previously shown that JAK2 was required for GH signaling in liver resulting in low circulating insulin-like growth factor-1 (IGF-1) and hypothesized this to play a role in the increased atherosclerosis. To establish the causal role of reduced systemic IGF1 in the increased atherosclerosis observed in hepatic JAK2-deficient mice, L-JAK2−/− APOE−/− mice were infused with IGF-1 analog or vehicle while on an atherogenic diet for 12wks. Preliminary data show that restoring circulating IGF-1 attenuates fatty liver and atherosclerotic plaque burden in hepatic JAK2 deficient mice. Thus, our studies show an essential role of hepatic JAK2 in the protection against atherosclerosis through circulating IGF-1 and define a liver-centric mechanism in the maintenance of healthy vasculature.

Funding: This work was supported by operating grants from Canadian Institute of Health Research MOP-191501 and MOP-201188 to Minna Woo. Tharini Sivasubramaniyam and Sally Shi are supported by the CIHR Doctoral Research Award.
Subdivision 1. Basic Science

Presentation Preference Oral presentation
Additional information
Diagnosis of the apoB Dyslipoproteinemias: The apoB algorithm AP

Abstract nr. 227
Author Graaf, Jacqueline de, Radboud UMC, Nijmegen, Netherlands
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Topic Dyslipidemia; Lipids, Lipoproteins and Apolipoproteins
Keywords Apolipoproteins, Cardiovascular Disease, Lipoproteins, Triglyceride-Rich Proteins

The problem: Excellence in clinical care begins with accurate diagnosis. Accurate diagnosis allows risk to be assessed most precisely and the most appropriate therapy to be chosen. Using only lipids, it is not possible to diagnose all apoB dyslipoproteinemias.

Objective: To diagnose all the major apoB dyslipoproteinemias based on total cholesterol, triglycerides and apoB.

Results: The major apoB dyslipoproteinemias are due to the elevation of one or more of the apoB containing lipoprotein particles: chylomicron particles, VLDL particles, chylomicron and VLDL particles, chylomicron and VLDL remnant particles, LDL particles and Lp(a) particles. With the exception of elevated Lp(a), all can be differentiated based on total cholesterol, triglycerides and apoB and therefore each can be specifically identified and treated.

The specific advantages are:
1. The hypertriglyceridemias- chylomicronemia, chylomicrons and VLDL, VLDL and remnant disorder can all be easily distinguished, which is essential as they differ in cardiovascular risk and treatment.
2. Remnant disorder (familial dysbetalipoproteinemia), which is highly atherogenic, can now be diagnosed in routine clinical care and is more common than appreciated.
3. In patients with the atherogenic lipoprotein phenotype with high TG and low HDL-c but normal LDL-C, elevated LDL particle number can be recognized by high apoB levels.
4. Non-HDL-C will not substitute for apoB in this approach and a series of discordance analyses have shown apoB is a more accurate marker of cardiovascular risk than non-HDL-C.

Conclusion: We present a diagnostic algorithm of the apoB dyslipoproteinemias based on apoB, total cholesterol and triglyceride. The apoB APP, which can be downloaded for free from the internet in may 2015, will produce the correct answer once total cholesterol, triglycerides and apoB are entered. The differential diagnosis, pathophysiology and treatment for all the apoB dyslipoproteinemias are also provided on the APP. Accurate diagnosis has always been a pillar of medical care. It is time for lipidology to rediscover the value of accurate diagnosis.

Subdivision 3. Clinical Studies

Presentation Preference Oral presentation
Additional information
Statin use and low density lipoprotein cholesterol goal attainment in a high cardiovascular risk population in the Netherlands

Abstract nr. 228
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Co-author(s) - van-Riemsdijk, Melanie
Co-author(s) - Herings, Ron
Topic Epidemiology of CVD; The Risk Factor Concept
Keywords Cardiovascular Disease, LDL, Prevention, Risk Factor

Background/objective: Low density lipoprotein cholesterol (LDL-C) is a key therapeutic target for cardiovascular (CV) risk reduction. Meta-analysis of statin trials as well as a trial involving a non-statin LDL-C lowering treatment, ezetimibe, suggest a linear relationship between LDL-C and risk of major CV events. The objective of the current study was to study statin treatment and LDL-C goal attainment in a real-world high-risk population in the Netherlands.

Methods: From the PHARMO Database Network, patients aged ≥18 years with an LDL-C measurement in 2012 (index date) were selected and hierarchically categorized in following mutually exclusive categories: 1) familial hypercholesterolemia (FH), 2) recent acute coronary syndrome (ACS; within 1-year pre index date); 3) coronary heart disease (CHD); 4) ischemic stroke; 5) peripheral artery disease (PAD) or 6) diabetes mellitus (DM). Statin use at index date was assessed and patients covered by a prescription within 45 days were considered to be taking the medication.

Results: Of 61,839 patients meeting the inclusion criteria, 1,132 (2%) were included in FH; 2,431 (4%) in recent ACS; 6,292 (10%) in CHD; 2,868 (5%) in ischemic stroke; 3,017 (5%) in PAD; and 46,099 (75%) in DM. Overall, 65% were taking statins. Recent ACS had the highest proportion of patients taking a statin (77%); although, only 23% were taking a high intensity statin (atorvastatin ≥40mg, rosuvastatin ≥20mg, or simvastatin 80mg). The percentage of patients achieving an LDL-C level <100 mg/dl was 54% overall and ranged from 23% for FH to 58% for ACS. When an LDL-C <70 mg/dl was considered, overall achievement was 19% and ranged from 4% for FH to 20% for DM. The likelihood of achieving an LDL-C <70 mg/dl was significantly higher among patients covered with a statin (p <0.0001).

Conclusion: Overall statin use in the cohort was modest with only 13% taking high intensity statins. The majority of high CV risk patients did not achieve an LDL-C <70 mg/dl, the goal for this population according to European Society of Cardiology guidelines. The treatment goal for this
population in the Netherlands is LDL-C <100 mg/dl, which was achieved by 54% of patients.

Subdivision 4. Not applicable. Abstract matches with track c

Presentation Preference Oral presentation
Additional information
Novel aortic dissection model by pharmacologically-induced endothelial dysfunction

Abstract nr. 230
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Co-author(s) - Tamaki, Toshiaki
Topic The Pathogenesis of Atherosclerosis; Immunity, Inflammation, and the Endothelium
Keywords Animal model, Blood pressure, Cardiovascular Disease, Endothelium

Aortic dissection (AD) is life-threatening aortic disease which has only surgical operation or antihypertensive drug as therapeutic strategies. AD is considered to be based on hypertension and degradation of media as well as aortic aneurysm progression. Recently, it has been reported that endothelial dysfunction also might be necessary for AD onset. However, since appropriate AD model animals have not been developed yet, the detailed pathological mechanism of AD is still unknown. Therefore, we tried to develop a novel mice model showing a high rate of AD and examine the involvement of endothelial dysfunction in AD onset.

To induce endothelial dysfunction, $N^\omega$-nitro-l-arginine methyl ester (l-NAME), a nitric oxide synthase (NOS) inhibitor, was used. Ten mg/kg/day of l-NAME were orally administered in drinking water to C57BL/6 mice from the age of 7 weeks. Three weeks later, the administration of angiotensin II (Ang II) (1000 ng/kg/min, 6 weeks) and β-aminopropionitrile (BAPN) (150 mg/kg/day, 2 weeks) were performed with the osmotic mini pumps. This protocol, Ang II plus BAPN administration has been established as a pharmacologically-induced aortic aneurysm model (Kanematsu et. al. Hypertension. 2010). Incidence of AD was determined by the formation of false lumen under Elastica van Gieson’s staining. Incidence of AD and lethal rupture was significantly increased in Ang II, BAPN and l-NAME (ABL) group compared with Ang II and BAPN (AB) group. Vascular cell adhesion molecule-1 (VCAM-1) expression, matrix metalloproteinase (MMP)-2/9 activities and the expressions of inflammatory cytokines were also significantly increased in ABL group.

Since pitavastatin is known to have endothelial protective effect, the effect of pitavastatin on our novel AD model was examined to clarify the involvement of endothelial dysfunction on AD onset. Administration of pitavastatin significantly suppressed the incidence of AD and rupture compared to ABL group. With Griess method, it was observed that NO production in aorta was increased in pitavastatin administered mice compared to control or l-NAME treated mice.

Our present study proposed the novel pharmacologically-induced AD model mice, which might be involved in endothelial dysfunction. In the future, our AD model should be useful for understanding of AD mechanisms and developing new therapeutic strategies.
Subdivision 1. Basic Science

Presentation Preference Mini-oral presentation

Additional information
Adherence to national guideline in primary and secondary prevention of cardiovascular diseases in The Netherlands: the LifeLines cohort study

Abstract nr. 231
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Topic Primary & Secondary prevention of CVD; Lifestyle Measures and Pharmacological Intervention
Keywords Cardiovascular Disease, Dyslipidemia, Epidemiology, Prevention

Objective: Cardiovascular disease (CVD) is the leading cause of death worldwide. While there is indisputable evidence that statin treatment reduces the burden of CVD, undertreatment remains an issue of concern in primary and secondary prevention. The aim of this study was to assess the use of lipid-lowering drugs (LLD) among 70,292 participants in The Netherlands as a proxy of adherence to the national guideline for prevention and treatment of CVD.

Methods: LifeLines is a population-based prospective cohort study in the three Northern provinces of The Netherlands. At baseline, all participants completed questionnaires, underwent a medical examination and lab testing. In those participants who did not report CVD, the 10-year risk of cardiovascular morbidity or mortality was estimated. Subsequently, we assessed how many participants were eligible to use LLD and then analyzed how many indeed reported LLD use.

Results: In primary prevention, 23% (753 of 3268) of those eligible for LLD, reported treatment with LLD, while in secondary prevention this was 69% (899 of 1302). In primary prevention, patients with diabetes mellitus were best treated (67%). Notably, of the patients with stroke, only 47% (182 of 386) reported LLD.

Conclusions: Despite clear guidelines and multiple national initiatives to improve CVD risk management, adherence to guidelines for the treatment of CVD in The Netherlands remains a major challenge. This study calls out for improving public awareness and improving primary and secondary care to prevent unnecessary CVD related morbidity and death.

Subdivision 5. Not applicable. Abstract matches with track d
Presentation Preference Oral presentation
Additional information
Effect of a low-fat spread with added plant sterols on biomarkers of endothelial dysfunction and low-grade inflammation in hypercholesterolemic subjects

Abstract nr. 232
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Topic Primary & Secondary prevention of CVD; Lifestyle Measures and Pharmacological Intervention
Keywords Inflammation, Intervention, Lifestyle

Aim: Plant sterols (PS) lower LDL-cholesterol, an established risk factor for coronary heart disease. Endothelial dysfunction and low-grade inflammation are two important features in the development of atherosclerosis. Data on the effect of PS on biomarkers of endothelial function and/or low-grade inflammation are scarce. The aim of the current study was to investigate the effect of regular intake of PS on biomarkers of endothelial dysfunction and low-grade inflammation.

Methods: This study was designed as a double-blind, randomized, placebo-controlled, parallel-group study. After a 4-week run-in period, 240 hypercholesterolemic but otherwise healthy men and women consumed a low-fat spread with added PS (3 g/d) or a placebo spread for 12 weeks. Endothelial dysfunction biomarkers (von Willebrand factor, soluble intracellular adhesion molecule 1 (sICAM-1), soluble endothelial-selectin and soluble vascular cell adhesion molecule 1 (sVCAM-1)) and low-grade inflammation biomarkers (C-reactive protein, serum amyloid A, interleukin-6, interleukin-8, tumour necrosis factor-α and sICAM-1) were measured using a multiarray detection system based on electro-chemiluminescence technology. Biomarkers were available for a subset (n=100) of the population and were combined into z-scores. This study was registered at clinicaltrials.gov (NCT01803178).

Preliminary results: The intake of PS did not significantly affect most of the biomarkers of endothelial dysfunction and low-grade inflammation. Only sVCAM-1 was significantly reduced (log(sVCAM-1) = -0.08 ng/mL (95%CI: -0.14; -0.02)) after PS intake compared to placebo. The z-scores for endothelial dysfunction (-0.12; 95%CI: -0.28; 0.04) and low-grade inflammation (-0.12; 95%CI: -0.32; 0.07) were not significantly changed after PS intake compared to placebo.

Conclusions: Biomarkers of endothelial dysfunction and low-grade inflammation were not significantly affected upon regular PS intake in hypercholesterolemic men and women.
Subdivision 3. Clinical Studies

Presentation Preference Mini-oral presentation
Additional information
EVIDENCE OF THE “FLAVOCITRIN” – INDUCED BENEFIT IN STATIN INTOLERANT HIGH CV RISK PATIENTS WITH INSULIN RESISTANT CONDITIONS

Abstract nr. 233
Author Kvantaliani , Tamar, Medical Center "Healing Home", Tbilisi, Georgia
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Co-author(s) - Akhvlediani , Manana
Topic Dyslipidemia; Lipids, Lipoproteins and Apolipoproteins
Keywords Cardiovascular Disease,Dyslipidemia,HDL, Metabolism

The purpose of study was to assess the feasibility and clinical benefit of application "Flavocitrin"- citrus extract, that contains polyphenol hesperidin and polymethoxylised flavonoids (nobiletin and tangeritin) to lipidlowering therapy of patients who fail to achive LDL cholesterol target on maximal statin dosing regimen and to statin intolerant patients.

A two-month combined therapy with flavocitrin and statins was performed in 25 CHD patients with metabolic syndrome, in whom long-term statin therapy did not provide sustained inhibition of lipid disorder (I group); 19 patients that appiered intolerant to statin therapy were given flavocitrin as monotherapy (II group). 32 similar patients who received only statins during two-month, formed the control group (III).

All participants underwent measurement of plasma lipoprotein profile, high sensitive CRP, fibrinogen (Fi), parameters of hemostasis, C-peptide, lipid hydroperoxide (LPO) as the direct indicator of lipid peroxidation degree.

In groups of patients receiving flavocitrin (I,II) statistically significant reduction of plasma LPO meanings (P <0.001) and inflammatory markers were revealed on the background of relatively unaltered cholesterol particles, and increase (P>0.05) of HDL-cholesterol. This tendency was mostly expressed in insulin-resistent patients. In this regard, four-week flavocitrin therapy proved to be protective in prevention of oxidative stress and further progression of dyslipidemia. The opposite response was brought out in control group where average values of LPO activity, HDL, LDL, CRP and Fi remained almost unchanged.

Data presented in current study display the significant efficacy of pharmacotherapy with F when given as monotherapy as well as in combination with statines in management of dislipidemia and metabolic disorders. Action of citrus flavonoids appear to realize mainly by trigering special mechanisms of antioxidant protection through inhibition of LDL oxidation, platelet aggregation and anti-inflammatory effect on vascular endothelium.

Our results emphasize the need for further investigation of the associated therapy with citrus flavonoids and statins in patient populations with high susceptibility to LDL oxidation, notably individuals at high CV risk.

Subdivision 3. Clinical Studies
Presentation Preference Electronic poster presentation
Additional information
Analysing endothelial dysfunction in type 2 Diabetes Mellitus patients using Flow Mediated Dilatation score.

Abstract nr. 235
Author Saboo, Banshi, Ahmedabad, India
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Co-author(s) - Patel, Feny
Co-author(s) - Kadri, Mahira
Co-author(s) - Patel, Swati
Co-author(s) - Chandarana, Hardik

Topic The Pathogenesis of Atherosclerosis; Immunity, Inflammation, and the Endothelium
Keywords Atherosclerosis, Cardiovascular Disease, Endothelium, Inflammation

Background:
The risk of CVD in type 2 diabetes mellitus is 4% higher than in healthy counterparts. The first stage to CVD is endothelial dysfunction along with vascular injury leading to atherosclerotic changes in the tunica intima of the arteries. Endothelial dysfunction can be analysed to diagnose early atherosclerotic changes and arterial stiffness. Roles of hyperglycemia, diabetic dyslipidemia and inflammation in the acceleration of vascular injury can be detected earlier and treated so as to avoid severe cardiac events.

Objective:
To determine early stage CVD risk in type 2 DM patient using FMD (flow mediated dilatation) score – correlating it with acceleration of inflammatory process of vascular injury.

Method:
A total of 50 (36 F and 14 M) patients with type 2 DM of more than 10 years with age above 50 years were screened for FMD score along with 30 (17 F 13 M) healthy controls, using Angiodefender (Everist Genomics Ann Arbor, MI, USA). Pro inflammatory cytokines- TNF alpha, IL-6, IL-1 were measured using standard ELISA kits. As surrogates for disease activity C-reactive protein and ESR levels were determined. A Framingham risk score was also assessed in order to evaluate coronary heart disease risk at 10 years in per cent.

Result:
The FMD score in 50 type 2 DM patients showed that 70% (n=35) patients suffered from impaired endothelial function and increased arterial thickness; 16% (n=8) patients suffered from endothelial dysfunction, arterial stiffness and atherosclerosis whereas the remaining 14% had normal endothelial function. On the other hand in the healthy counterparts, the FMD score was normal in 80% (n=24) patients. The pro inflammatory cytokines were either normal or high in the patients with impaired endothelial function. C-reactive proteins and ESR levels also varied from high to normal in patients with endothelial dysfunction. The Framingham risk score also matched with 20% high risk in patients with lower flow mediated dilatation.

Conclusion:
The flow mediated dilatation score can be effectively used as a marker to determine the vascular injury and endothelial dysfunction in patients with type 2 DM.

Subdivision 3. Clinical Studies

Presentation Preference Oral presentation
Additional information
Predicted reduction in the risk of cardiovascular events in patients treated with high-intensity statins

Abstract nr. 236
Author Karlson, Björn, AstraZeneca, Mölndal, Sweden
Co-author(s) - Palmer, Michael
Co-author(s) - Nicholls, Stephen
Co-author(s) - Lundman, Pia
Co-author(s) - Barter, Philip
Topic Dyslipidemia; Lipids, Lipoproteins and Apolipoproteins
Keywords Cardiovascular Disease, LDL, Pharmacology

The 2010 Cholesterol Treatment Trialists' Collaboration (CTTC) meta-analysis of 26 clinical trials determined the reduction in the risk of major vascular event (MVE), coronary heart disease (CHD) death, death by other cardiac causes and all-cause mortality for every 1.0 mmol/L (38.7 mg/dL) statin-mediated reduction in low-density lipoprotein-cholesterol (LDL-C). We aimed to determine the potential impact of high-intensity statin therapy on cardiovascular events by applying average statin-induced LDL-C reductions to the results from the CTTC meta-analysis. The least-squares mean (LSM) change in LDL-C was determined using 6735 patient exposures to atorvastatin 40 and 80 mg and rosuvastatin 20 and 40 mg from 12 randomised clinical trials included in the VOYAGER database. The resulting predicted risk reduction with high-intensity statin therapy was then estimated using the results from the CTTC meta-analysis. LSM reductions in LDL-C for atorvastatin 40 and 80 mg were 2.0 mmol/L and 2.2 mmol/L, respectively. LSM reductions in LDL-C for rosuvastatin 20 and 40 mg were 2.2 mmol/L and 2.4 mmol/L, respectively. The estimated rate ratios achieved with these high-intensity statins were substantial and consistently below 1.0. The table shows the individual rate ratios for atorvastatin 40 and 80 mg and rosuvastatin 20 and 40 mg. In conclusion, taking into account the considerable number of people who are candidates for statin therapy, this analysis indicates that high-intensity statins have the potential to prevent a substantial number of cardiovascular events. Additionally, these results show that the magnitude of risk reduction is dependent on the choice and dose of statin therapy.

Analysis and medical writing support was funded by AstraZeneca.
### Subdivision 3. Clinical Studies

<table>
<thead>
<tr>
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<th>Estimated rate ratios (95% CI)(^a) achieved using LSM change in LDL-C</th>
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<tbody>
<tr>
<td></td>
<td>MVE(^b)</td>
</tr>
<tr>
<td><strong>ATV 40 mg</strong></td>
<td>0.60</td>
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<tr>
<td></td>
<td>(0.56–0.66)</td>
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<tr>
<td><strong>ATV 80 mg</strong></td>
<td>0.58</td>
</tr>
<tr>
<td></td>
<td>(0.53–0.63)</td>
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<tr>
<td><strong>RSV 20 mg</strong></td>
<td>0.58</td>
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<tr>
<td></td>
<td>(0.53–0.63)</td>
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<tr>
<td><strong>RSV 40 mg</strong></td>
<td>0.55</td>
</tr>
<tr>
<td></td>
<td>(0.50–0.60)</td>
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</tbody>
</table>

Published rate ratios per 1.0 mmol/L (38.7 mg/dL) LDL-C reduction: MVE=0.78 (95% CI 0.76–0.80); all-cause mortality=0.90 (95% CI 0.87–0.93); CHD death=0.80 (95% CI 0.74–0.87); and death by other cardiac causes=0.89 (95% CI 0.81–0.98).

\(^a\)Calculated using the delta method; \(^b\)Includes major coronary events, coronary revascularisation, or stroke

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**Presentation Preference:** Oral presentation

**Additional Information:**

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Predicted impact of statins on 10-year atherosclerotic cardiovascular disease risk: Results from VOYAGER

Abstract nr. 237
Author Palmer , Michael, Keele, United Kingdom
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Co-author(s) - Lundman , Pia
Co-author(s) - Barter , Philip
Co-author(s) - Karlson , Björn
Topic Primary & Secondary prevention of CVD; Lifestyle Measures and Pharmacological Intervention
Keywords Cardiovascular Disease,Dyslipidemia,LDL

**Background:** Reductions in low-density lipoprotein cholesterol (LDL-C) resulting from statin therapy have been shown to lead to reductions in atherosclerotic cardiovascular disease (ASCVD) risk. We used data from the VOYAGER meta-analysis database, comprising 32,258 patients from 37 randomised trials, to estimate the reduction in 10-year ASCVD risk as a result of lipid parameter modification with three different statins and doses.

**Methods:** 29,486 patients who would be considered candidates for high-intensity statin therapy, as defined by the 2013 American College of Cardiology/American Heart Association (ACC/AHA) blood cholesterol guideline, were selected from the VOYAGER database. Using the 2013 ACC/AHA assessment of cardiovascular risk guideline and based on a patient’s total cholesterol and high-density lipoprotein cholesterol levels, the change in ASCVD risk was calculated as a ratio of on-treatment to baseline risk for each patient. Least-squares mean (LSM) ratios of 10-year ASCVD risk were calculated for atorvastatin 10–80 mg, rosuvastatin 5–40 mg and simvastatin 10–80 mg. Hypothetical cohorts of 100,000 subjects each were created, with different baseline risks ranging from 7.5% to 80%. Within each cohort, the potential numbers of ASCVD events prevented were estimated for each statin and dose.

**Results:** The LSM ratios of 10-year ASCVD risk for atorvastatin 10–80 mg, rosuvastatin 5–40 mg and simvastatin 10–80 mg are shown in the table. With increasing baseline ASCVD risk and increasing statin dose, an associated increase in the predicted number of ASCVD events prevented over a 10-year period was observed (Figure).

**Conclusion:** Reductions in the number of predicted ASCVD events is dependent on baseline ASCVD risk and the choice and dose of statin. Effective statin therapy can potentially prevent a clinically significant number of ASCVD events, particularly in patients at high ASCVD risk. These results highlight the importance of using the appropriate intensity statin, and the benefits of the use of high-intensity statins, defined by the 2013 ACC/AHA blood cholesterol guideline as rosuvastatin 20 and 40 mg and atorvastatin 40 and 80 mg, in moderate-to-high risk patients.

Analysis and medical writing support was funded by AstraZeneca.
Subdivision 5. Not applicable. Abstract matches with track d

Presentation Preference Oral presentation

Additional information
Lipid Abnormalities Remain High among Treated Hypertensive Patients with Stable CHD: Results of the Dyslipidemia International Study (DYSIS) II Belgium

Abstract nr. 238
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Co-author(s) - Radermecker, Regis P.
Co-author(s) - Gitt, Anselm
Co-author(s) - Ashton, Veronica
Co-author(s) - Horack, Martin
Co-author(s) - Lautsch, Dominik
Co-author(s) - Ambegaonkar, Baishali
Topic Dyslipidemia; Lipids, Lipoproteins and Apolipoproteins
Keywords Dyslipidemia, Hypertension, LDL, Lipids

Background: Despite treatment with lipid lowering therapy (LLT), elevated lipid abnormalities persist among hypertensive patients with coronary heart disease (CHD), putting them at risk for future cardiovascular events. Both hypertension and hyperlipidemia are very frequent comorbidities among CHD patients and therefore tight control of both should be targeted.

Objective: To identify the prevalence of lipid abnormalities and unmet needs among hypertensive patients with stable CHD in Belgium currently receiving LLT.

Methods: DYSIS II is a multicenter, observational cross-sectional study conducted from May-September 2013 in 10 outpatient care centers in Belgium. Eligible adult patients had a documented history of CHD (past acute coronary syndrome (ACS) events >3 months before enrollment), full lipid profile available 0-12 months prior to enrollment, on LLT for ≥3 months, and were not participating in randomized clinical trials involving medication. Patient characteristics, risk factors, treatment patterns, and laboratory values were collected. LDL-C lipid target achievement was assessed based on ESC/EAS guidelines. Patients were identified as having hypertension based on data collected through the study case report form.

Results: Among 265 hypertensive stable CHD patients currently on LLT (80.4% male, mean age 70.3 ± 9.5 years), 98.5% had hypercholesterolemia, 87.9% previous percutaneous coronary intervention or coronary artery bypass graft, 59.2% history of ACS, 56.7% led a sedentary lifestyle, 51.2% family history of CHD, 50.2% were former smokers, 47.5% type 2 diabetes mellitus, and 9.8% were current smokers. Half the patients had a blood pressure measurement <140/<90 mmHG (systolic/diastolic), with 97.4% (n=258) receiving antihypertensive therapy. 113 (42.6%) patients achieved LDL-C <70 mg/dl while being treated with the following LLT: 82.3% statin monotherapy, 10.9% statin plus ezetimibe, 5.3% combination statin plus other non-statin, and
1.5% non-statin monotherapy. Mean atorvastatin equivalent dose was 28 ± 22 mg/day. Patients mean lipid values are provided in Table 1.

**Conclusion:** Overall, mean LDL-C values were approximately 5.2 mg/dl from recommended LDL-C target, with about 57% of LLT treated hypertensive stable CHD patients in Belgium not achieving the recommended target. Additional effective lipid lowering strategies are needed among these very high risk patients to prevent future cardiovascular events.

**Table 1: Mean lipid profiles**

<table>
<thead>
<tr>
<th>Subdivision</th>
<th>LLT Treated Patients n=265</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low density lipoprotein (LDL) cholesterol</td>
<td>75.2 ± 24.6 mg/dl</td>
</tr>
<tr>
<td>Total cholesterol</td>
<td>150.2 ± 33.1 mg/dl</td>
</tr>
<tr>
<td>Triglycerides</td>
<td>135.2 ± 98.1 mg/dl</td>
</tr>
<tr>
<td>Non-HDL cholesterol</td>
<td>101.4 ± 32.6 mg/dl</td>
</tr>
</tbody>
</table>

**Table 1: Mean lipid profiles**

Subdivision 1. Basic Science

Presentation Preference Electronic poster presentation

Additional information
LDL-C Target Attainment among Treated ACS Patients in Hong Kong and Taiwan: The Dyslipidemia International Study (DYSIS) II ACS Results

Abstract nr. 239
Author Yan , Bryan P., Chinese University of Hong Kong, Hong Kong, Hong Kong
Co-author(s) - Chiang , Fu-Tien
Co-author(s) - Gitt , Anselm
Co-author(s) - Horack , Martin
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Co-author(s) - Balaji , Hiremagalur Parthasarathy
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Topic Dyslipidemia; Lipids, Lipoproteins and Apolipoproteins
Keywords ACS,Dyslipidemia,LDL,Lipids

Background: Patients presenting with acute coronary syndrome (ACS) remain at very high risk of future cardiovascular events. Providing optimal therapy for effective control of risk factors including dyslipidemia, hypertension and diabetes is critical to reduce future complications.

Objective: To identify the prevalence of lipid abnormalities and therapeutic gaps among ACS patients receiving lipid lowering therapy (LLT) in Hong Kong and Taiwan.

Methods: DYSIS II is a multinational, observational cross-sectional study conducted in 18 hospitals in Hong Kong (6 centers) and Taiwan (12 centers). Consecutive adult patients hospitalized for an ACS event with full lipid profiles available within 24 hours of admission, on LLT ≥3 months or not treated at all, not participating in randomized clinical trials involving any medication, and alive at discharge were eligible. Patient characteristics, risk factors, treatment patterns, and laboratory values were collected. Low density lipoprotein cholesterol (LDL-C) target attainment was assessed based on 2011 ESC/EAS guidelines.

Results: Among 270 ACS patients (76.3% male, mean age 64.4 ± 11.9 years), 65.2% had hypertension, 50.6% hyperlipidemia, 44.7% metabolic syndrome, 40.4% led a sedentary lifestyle, 39.2% type 2 diabetes, 32.2% history of coronary heart disease (CHD), 26.7% current smokers, and 26.7% had a family history of CHD. 125 (46.3%) patients were on LLT: 92.8% statin monotherapy, 4.0% statin plus ezetimibe, 2.4% statin plus other non-statin, and 0.8% non-statin monotherapy. Mean atorvastatin equivalent dose was 14 ± 12 mg/day. Among LLT patients, only 28.8% were able to reach the <70 mg/dl LDL-C target (mean LDL-C 89.6 ± 35.0 mg/dl).

Conclusion: Overall, mean LDL-C values were approximately 20 mg/dl from recommended LDL-C target with over 70% of LLT treated ACS patients in Hong Kong and Taiwan not reaching the recommended target. Additional effective lipid lowering strategies for LDL-C target attainment are needed among these very high risk patients.
Subdivision 1. Basic Science

Presentation Preference Electronic poster presentation
Additional information
Serum matrix metalloproteinase 8 and complement system activation in acute coronary syndromes

Abstract nr. 240
Author Salminen, Aino, University of Helsinki, Helsinki, Finland
Co-author(s) - Sorsa, Timo
Co-author(s) - Meri, Seppo
Co-author(s) - Pussinen, Pirkko J
Co-author(s) - Pesonen, Erkki
Topic Epidemiology of CVD; The Risk Factor Concept
Keywords Cardiovascular Disease, Epidemiology, Immunity, Inflammation

The complement system has a central role in innate immunity and contributes to various diseases, including cardiovascular diseases. Complement is extensively activated in atherosclerotic lesions, in thrombosis, and in the myocardium of ischemic hearts. Complement component C3 is the central component in complement activation. Serum matrix metalloproteinase (MMP)-8 and tissue inhibitor of metalloproteinase (TIMP)-1 are promising novel biomarkers of cardiovascular diseases. MMP-8 is a collagen-degrading enzyme that is present in atherosclerotic lesions. The expression and activation of MMP-8 is increased during inflammation. However, the origin of serum MMP-8 is not completely clear.

We studied the association of serum concentrations of C3 and C4, and CRP, MMP-8 and TIMP-1 in 343 patients with acute coronary syndrome (ACS) and 326 healthy controls matched by age and sex.

The median concentrations of MMP-8 were 47 ng/ml in healthy subjects, 82 ng/ml in patients with unstable angina pectoris (UAP), and 124 ng/ml in patients with myocardial infarction (MI) (p < 0.001). The concentrations of TIMP-1 and MMP-8/TIMP-1 molar ratios were also higher in patients with UAP and AMI compared to controls. Mean C3 concentrations were 1.87 mg/ml in healthy subjects, 1.66 mg/ml in patients with UAP, and 1.69 mg/ml in patients with AMI (p < 0.001). Serum C3 levels were inversely correlated with serum MMP-8 levels (r = -0.18, p < 0.001). C4 concentrations did not differ between the groups and they did not correlate with MMP-8. Serum MMP-8 was correlated with CRP (r = 0.39, p < 0.001), but serum C3 did not show correlation with CRP. In a multivariate model adjusted for age, gender, and smoking, the concentrations of MMP-8 (directly), CRP (directly), and C3 (inversely) remained significantly associated with ACS.

Decreased concentrations of C3 in serum reflect the activation of the complement system in patients with ACS. Serum MMP-8 may be associated with complement activation, but it also has an independent association with ACS.

Subdivision 4. Not applicable. Abstract matches with track c

Presentation Preference Oral presentation
Additional information
The cut-off values of anthropometric indices for identifying subjects at risk for metabolic syndrome in Iranian elderly men.

Abstract nr. 241
Author Gharipour, Mogan, Isfahan, Iran
Co-author(s) - Sadeghi, masoumeh
Topic Epidemiology of CVD; The Risk Factor Concept
Keywords Cardiovascular Disease, Epidemiology, Metabolism, Obesity

AIM: This study aimed to investigate which anthropometric indices could be a better predictor of metabolic syndrome (MetS) and the cut-off points for these surrogates to appropriately differentiate MetS in the Iranian elderly. METHOD: The present cross-sectional study was conducted on a sample of Isfahan Healthy Heart Program (IHHP). MetS was defined according to Third Adult Treatment Panel (ATPIII). In total, 206 elderly subjects with MetS criteria were selected. Anthropometric indices were measured and plotted using receiver operating characteristic (ROC) curves. RESULTS: WC followed by WHtR yielded the highest area under the curve (AUC) (0.683; 95% CI 0.606-0.761 and 0.680; 95% CI 0.602-0.758, resp.) for MetS. WC at a cut of 94.5 cm resulted in the highest Youden index with sensitivity 64% and 68% specificity to predict the presence of ≥2 metabolic risk factors. BMI had the lowest sensitivity and specificity for MetS and MetS components. WC has the best ability to detect MetS which followed by WHtR and BMI had a lower discriminating value comparatively. CONCLUSION: WC is the best predictor for predicting the presence of ≥2 metabolic risk factors among Iranian elderly population and the best value of WC is 94.5 cm. This cut-off values of WC should be advocated and used in Iranian men until larger cross-sectional studies show different results. Subdivision 4. Not applicable. Abstract matches with track c

Presentation Preference Oral presentation
Additional information
Oxidised low-density lipoproteins and hyperlipidaemia cause platelet activation through a pathway that requires CD36 and phospholipase C\(\gamma\)2

Abstract nr. 242
Author Woodward, Casey, University of Hull, Hull, United Kingdom
Co-author(s) - Wraith, Katie
Co-author(s) - Naseem, Khalid
Topic Dyslipidemia; Lipids, Lipoproteins and Apolipoproteins
Keywords Atherosclerosis, LDL, Thrombosis

Introduction: Dyslipidemia and particularly increased circulating low-density lipoproteins (LDL) are contributing factors to atherosclerosis. LDL can become trapped vessel walls where it becomes oxidatively modified (oxLDL) and contributes to the formation of atherosclerotic plaques. However, recent evidence suggests that patients with established cardiovascular disease have oxLDL circulating in the bloodstream. OxLDL is ligand for the scavenger receptor CD36 which is present on the surface of platelets and macrophages. Previously we have shown that oxLDL binding to CD36 induces multiple activatory responses including secretion, shape change and aggregation through a tyrosine kinase dependent mechanism.

Aim: To assess the molecular pathways responsible for oxLDL-mediated platelet hyperreactivity with an emphasis on the role of phospholipase C \(\gamma\)2 (PLC\(\gamma\)2).

Results: Immobilised oxLDL, but not nLDL, supported adhesion, activation and spreading of human platelets. The incubation of platelets with the pan src family kinase and pan phospholipase C inhibitors blocked platelet spreading but not adhesion. To determine whether PLC\(\gamma\)2 was responsible, we immunoprecipitated PLC\(\gamma\)2 from human platelets stimulated with oxLDL and probed for phosphorylation status. PLC\(\gamma\)2 was phosphorylated on tyrosine (tyr)\(^{753}\) and tyr\(^{759}\) by oxLDL in a time and dose dependent manner. Using an assay for IP\(_3\) as a marker of PLC activity, we show that oxLDL triggers activation of PLC \(\gamma\)2. Pharmacological blocking of CD36 with the antibody FA6.152 or lipid SSO prevented phosphorylation of PLC\(\gamma\)2. Similarly the phosphorylation and activation of PLC\(\gamma\)2 was prevented by inhibitors of Src family and Syk kinases. In order to confirm these findings, we used PLC\(\gamma\)2\(^{-/-}\) mice. PLC\(\gamma\)2\(^{-/-}\) mice showed diminished phosphotyrosine profiles upon stimulation with oxLDL and did not spread under static conditions compared with wild type controls.

Conclusion: This study has begun to show that oxLDL stimulates the activation of PLC\(\gamma\)2 through a CD36-Src-Syk pathway and this may offer further insight as to how hyperlipidaemia may promote platelet hyperreactivity.

Subdivision 1. Basic Science

Presentation Preference Electronic poster presentation

Additional information
Metabolic syndrome (MetS) is a major public health concern and increase in the incidence of MetS caused a rise in the rates of global morbidity, and mortality due to cardiovascular disease and diabetes. Lifestyle modification, a healthy diet, and pharmacological treatment and bariatric surgery are recommended in order to control this syndrome. Molecular mechanisms of metabolic disorders are essential in order to develop novel, valid therapeutic strategies. MicroRNA-33 plays imperative regulatory roles in a variety of biological processes including collaboration with sterol regulatory element-binding protein (SREBP) to maintain cholesterol homeostasis, high-density lipoprotein formation, fatty acid oxidation, and insulin signaling. Investigation of these molecules and their genetic targets may potentially identify new pathways involved in complex metabolic disease processes, improve our understanding of metabolic disorders, and influence future approaches to the treatment of obesity. This article reviews the role of miRNA-33 in metabolic syndrome, and highlights the potential of using miRNA-33 as a novel biomarker and therapeutic target for this syndrome.
Abstract nr. 246
Author Alejandro, Gugliucci, Touro University-California, Vallejo, U.S.A.
Topic Dyslipidemia; Lipids, Lipoproteins and Apolipoproteins
Keywords Atherosclerosis, Cardiovascular Disease, Functionality, HDL

**Background:** Solving the HDL paradox will necessitate the development of techniques to explore HDL function that are practical and well adapted to clinical studies and eventually become useful in patient monitoring. PON1 is a key player in HDL function and its activity is modified by inflammation/acute phase. To make some inroads into studying active PON1 distribution across HDL subclasses we had previously developed a zymogram method that we validated and employed in several studies.

**Objective:** To modify and optimize our method and employ it in a pilot study to explore HDL PON1 function changes in acute inflammation, as a model we employed post cerebrovascular accident (CVA) patients. We hypothesize that with this methodology we can detect changes in PON1 distribution in these patients after the episode and follow their temporal course.

**Material and Methods:** Native lipoproteins from serum are separated in a 4-12% gradient gel and activity is detected in situ using para-nitro-phenylacetate, scanning and densitometry. A total of 10 patients (men/women = 6/4, mean age 66.0 ± 12.0 years), diagnosed with ischemic CVA were studied. The study was approved by the Ethics Committee of Showa University. Blood examinations were performed at 3 sequential points (i.e., admission, 1 day, 7 days).

**Results:** The new method allows for a 1 step, shorter zymogram process as compared to our previous procedure that needed a coupled reaction. When we applied it to acute post-CVA patients the method shows that the significant drops in PON1 1 day after the event (25 +/- 7 %, p 0.03) correspond to changes in PON1 distribution in HDL subclasses or to specific loss of activity in very large and very small HDL. The changes are more apparent for HDL3, with recovery after one week paralleled by changes in CRP.

**Conclusions:** We have developed a practical, 1 step zymogram method to measure PON1 activity in HDL subclasses. With this tool the effects of inflammation on HDL antioxidant function can be followed up. Our pilot, proof of principle data show quick deleterious effects of acute phase and inflammation on PON1 distribution in HDL particles.
Figure 3. PON1 activity in HDL subclasses separated by native gradient electrophoresis gels

PON1 zymogram of 2 representative subjects at admission (0) 1 and 7 days. HDL were separated by their hydrodynamic diameter in an 8 × 10 × 0.15 cm non-denaturing 4-12% gradient polyacrylamide gel electrophoresis (Novex® 4-12% Tris-Glycine gel, Invitrogen, Carlsbad, CA, USA). PON1 activity in lipoprotein subclasses was determined by the enzymatic detection of PON1 hydrolysis of paranitrophenylacetate in situ. Note (arrows) that the drop in PON1 total activity as shown in Figure 1 is accompanied by reduced PON1 activity in both very large HDL2 and small HDL3, suggesting changes in HDL maturation that produce dysfunction. Note that the changes are transient and tend to recover in 7 days.

Subdivision 1. Basic Science

Presentation Preference Electronic poster presentation
Additional information
Macrophage Notch1 promotes neointima formation in mechanically-injured femoral arteries

Abstract nr. 247
Author Koga, Jun-ichiro, Kyushu University, Fukuoka, Japan
Topic The Pathogenesis of Atherosclerosis; Immunity, Inflammation, and the Endothelium
Keywords Animal model, Atherosclerosis, Inflammation, Intervention

**Background:** Restenosis remains a major complication of vascular intervention. Activated macrophages accumulating in injured vessels promote neointima formation. We previously demonstrated that the Notch ligand Delta-like 4 (Dll4) activates macrophages and accelerates atherogenesis, but the role of each Notch receptor expressed by macrophages in the pathogenesis of restenosis is unknown. The present study tested the hypothesis that macrophage Notch1 promotes neointima formation after vascular injury.

**Method and results:** Using the Cre/LoxP system, we established conditional mouse strains that lack or overexpress Notch1 in a myeloid cell lineage, mostly macrophages in vascular lesions (MΦ-Notch1-KO and MΦ-Notch1-Tg). To clarify the role of macrophage Notch1 in vascular disease, we used a wire injury model in these mice. Notch1 deletion suppressed neointima formation in femoral arteries, while Notch1 overexpression tended to accelerate lesion development (the intima/media ratio: Control, 1.9±0.1; MΦ-Notch1-KO, 1.0±0.2*; MΦ-Notch1-Tg, 2.5±0.2; N=8-9, *p<0.01). Macrophage accumulation to the injured arteries was lower in MΦ-Notch1-KO mice compared to Control, especially in the adventitia. The expression of monocyte chemotactic protein-1 (MCP-1) mRNA was lower in injured arteries of MΦ-Notch1-KO mice. Peritoneal macrophages from MΦ-Notch1-KO mice showed decreased chemotactic activity to MCP-1 in vitro. In the macrophage cell line RAW264.7, enforced expression of constitutively active Notch1 induced pro-inflammatory molecules IL-1β, IL-6, MCP-1 and iNOS, typical markers of M1 macrophages. Conditioned media (CM) from control macrophages induced growth and migration of cultured smooth muscle cells (SMC), but these effects were suppressed in CM from Notch1-KO macrophages. Furthermore, we crossed MΦ-Notch1-KO and MΦ-Notch1-Tg mice with LDL receptor-deficient mice and fed a high cholesterol diet. In this hyperlipidemic condition, deletion of macrophage Notch1 also decreased neointima formation and macrophage accumulation (the intima/media ratio: Control, 3.1±0.3; MΦ-Notch1-KO, 1.4±0.3*; MΦ-Notch1-Tg, 2.4±0.3; N=9-11 each; *p<0.001 vs. Control).

**Conclusion:** Macrophage Notch1 promotes the development of vascular lesions, offering a new therapeutic target.
Subdivision 1. Basic Science

Presentation Preference Oral presentation

Additional information
Combination EZ/Prava is superior to Pravastatin for suppressing Carotid atherosclerosis of patients with Hypercholesterolemia

Abstract nr. 248
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Topic The Pathogenesis of Atherosclerosis; Immunity, Inflammation, and the Endothelium
Keywords Atherosclerosis,Dyslipidemia,Lipids,Therapy

Objective: We compared the effectiveness of pravastatin plus ezetimibe with that of pravastatin for preventing an increase of carotid artery intima-media thickness (IMT) in patients with hypercholesterolemia.

Methods: This study was a single center, open-label, parallel-group trial. Sixty subjects with hypercholesterolemia and LDL cholesterol levels ≥120 mg/dL on pravastatin therapy were randomized to either continue pravastatin at 5-10 mg/day combined with ezetimibe at 10 mg/day (EZ/Prava, n=33) or to receive a dose of pravastatin at 10-20 mg/day (Prava, n=27). The primary endpoint was the change of the carotid IMT after 24 months.

Results: LDL cholesterol showed a significant decrease from baseline in both groups after 24 months, with decreases of 25.1% (p<0.001) and 6.3% (p=0.026) in the EZ/Prava and Prava, respectively. The IMTs at 24 months were 1.10±0.21 mm (-5.2% vs. baseline, p=0.0012) and 1.09±0.30 mm (-2.1% vs. baseline, p=0.07) in the EZ/Prava and Prava, respectively. There was a significantly greater decrease in the compared with the Prava (p=0.019).

Conclusions: Compared with Prava, EZ/Prava had a superior effect on LDL cholesterol and more effectively controlled the progression of IMT during two years of treatment.

Subdivision 3. Clinical Studies

Presentation Preference Electronic poster presentation
Additional information
Relationship of oxidative-antioxidants changes of LDL with coronary heart disease and some atherosclerosis risk factors in men population of Novosibirsk

Abstract nr. 249
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Topic Epidemiology of CVD; The Risk Factor Concept
Keywords Atherosclerosis, Epidemiology, LDL, Risk Factor

Associations of coronary heart disease (CHD) and certain atherosclerosis risk factors with parameters of atherogenic oxidation-antioxidant changes in low density lipoprotein (LDL) in men population were studied.

A population-based survey of 1024 Novosibirsk men 47-73 years old was performed. Program of the survey included the questionnaires, standardized cardiological survey, anthropometry, blood pressure measurement, ECG recording. In 223 people (21.8%) had «definitely CHD» (stable angina pectoris, FC II-IV) by a validated epidemiological, clinical and functional criteria.

Biochemical studies included the determinations of blood total cholesterol (CH), triglyceride (TG), high density lipoprotein cholesterol (HDL-CH), high sensitive C-reactive protein (hsCRP), baseline lipid peroxidation (LPO) and fat-soluble antioxidants in LDL, LDL resistance to oxidation, concentration of autoantibodies to oxidized LDL (oxLDL).

For the Novosibirsk male population as regional values are 10-90% cut-off point percentile distribution of studied atherogenic oxidation-antioxidant changes of LDL. Correlations were found between baseline LPO level in LDL and hsCRP level, between LDL resistance to oxidation and blood lipid profile, body mass index (BMI) and the presence of CAD, between autoantibodies to oxLDL and hsCRP level, BMI, between antioxidants content in LDL, especially alpha-tocopherol, and blood lipid profile, hsCRP level, BMI. Elevated level of LPO products in LDL, decreased antioxidants content in LDL and, especially, decreased resistance of LDL to oxidation in men independently associated with elevated levels of CH, TG, hsCRP, reduced HDL-CH, increased BMI. Positive correlations and independent associations between parameters of LDL oxidative changes, especially of decreased LDL resistance to oxidation, and CHD were revealed. Negative correlations between parameters of LDL antioxidative changes, especially of decreased LDL alpha-tocopherol content, and CHD were revealed also. The incidence of CHD is higher at index of initial LPO level in LDL >0,8 (nM MDA/mg LDL protein) and decreased LDL resistance to oxidation (at rates in initial stage of LDL oxidation >5,4 and in progressive stage of LDL oxidation >13,2). On the other hand, the incidence of CHD is lower in index of alpha-tocopherol in LDL >1,06 mg/mg protein LDL.
The results confirm the data about key atherogenic role of oxidized LDL. The study was supported by RSCF, project N 14-45-00030.

Subdivision 1. Basic Science

Presentation Preference Oral presentation
Additional information
Key inflammatory biomarkers of atherosclerotic plaques instability: results of arterial wall and blood studies

Abstract nr. 250
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Topic The Pathogenesis of Atherosclerosis; Immunity, Inflammation, and the Endothelium
Keywords Endothelium, Inflammation, Pathogenesis, Vulnerable Plaque

The aim of the study was to revealed the key significant inflammatory, destructive, oxidative and endothelial dysfunction biomarkers of coronary atherosclerotic plaques instability and investigate their blood levels in men with coronary atherosclerosis (CA).

Concentrations of inflammatory (tumor necrotic factor, TNF-alpha, interleukins, IL-1-beta, IL-6, IL-8, IL-18, soluble ligand of CD40 receptor, sCD40L, high sensitive C-reactive protein, hsCRP, monocyte chemotactic protein-1, MCP-1, endothelial monocyte activating protein II, adhesives molecules, sICAM-1 and sVCAM-1), destructive (matrix metalloproteinase, MMP-3, MMP-7, MMP-9, tissue inhibitor of metalloproteinase, TIMP-1 and endothelin-1), oxidative (concentrations of lipid peroxidation products, LPO, including in low density lipoproteins, LDL, proteins oxidative modification, paraoxonase activity, antioxidants concentrations, lipid parameters) and endothelial dysfunction biomarkers were studied in blood and in atherosclerotic plaques of coronary artery in 84 men with CA.

Blood levels of hsCRP, IL-8, IL-6, sCD40L, oxidized LDL apolipoproteins and lipoprotein (a) were higher, but blood levels of sVCAM, TIMP-1, NO metabolites and resistance of LDL to oxidation were lower in men with prevalence of unstable atherosclerotic plaques in coronary arteries compared to men with prevalence of stable atherosclerotic plaques in coronary arteries. Blood levels of hsCRP, IL-6, IL-8, oxidized proteins, NO metabolites and sVCAM were correlated with coronary artery atherosclerotic plaques instability. Moreover, strong positive correlations of blood levels of hsCRP, IL-6, IL-8 and MCP-1 with their concentrations in coronary artery atherosclerotic plaques were revealed only.

Thus, according to study results the inflammatory biomarkers such as hsCRP, IL-6, IL-8 and MCP-1 can be a key inflammatory biomarkers of atherosclerotic plaques instability in blood.

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Subdivision 1. Basic Science

Presentation Preference Oral presentation
Additional information