27th Annual Scandinavian Atherosclerosis Conference

April 8th-9th, 2021 Virtual meeting

2021 Program

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Organized by

SCANDINAVIAN SOCIETY FOR ATHEROSCLEROSIS RESEARCH

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27th Annual Scandinavian Atherosclerosis Conference

April 8th-9th 2021 Virtual meeting

Thursday, April 8th, 2021

8.30 – 8.35	Welcome **Anne Langsted** *(Denmark)*
THE NIKKILÄ MEMORIAL LECTURE	
8.35 – 8.40	Introduction of the 2020/21 Nikkilä Lecturer **Katariina Öörni** *(Finland)*
8.40 – 9.10	*2020/21 Nikkilä Lecture* **Jan Borén** (*Sweden)*
9.10 – 9.25	Discussion
9.25 – 9.30	**BREAK**
SESSION I	**CARDIOVASCULAR DISEASE** Chaired by **Riikka Kivelä** *(Finland)* and **Kirsten Holven** *(Norway)*
09.30 – 09.45	Time to run: Late rather than early exercise decreases atherosclerosis **Milena Schönke** *(The Netherlands)**
09.45 – 10.00	Impaired high-density lipoprotein function in patient with heart failure **Congzhuo Jia** *(Sweden)*
10.00 – 10.15	Event-free FH patients >65 years of age are characterized by higher concentration of large HDL particles **Torunn Melnes** *(Norway)**
10.15 – 10.30	**BREAK**
10.30 – 10.55	*Invited speaker* Do omega-3 have a role in the prevention and treatment of cardiovascular disease? **Philip Calder** *(UK)*
10.55 – 11.00	Discussion
11.00 – 11.15	Elevated remnant cholesterol and 3-fold increased risk of peripheral artery disease: two population-based cohorts **Benjamin Nilsson Wadström** *(Denmark)**
11.15 – 11.30	PCSK9 as a novel player in vascular calcification under uremic conditions: in vitro, in vivo, and clinical evidences **Maria Giovanna Lupo** *(Italy)**
11.30 – 11.45	Genetic variation in SLC5A2 mimicking SGLT2-inhibition lowers risk of heart failure and death **Louise Ellegaard Bechmann** *(Denmark)**
11.45 – 12.45	**LUNCH BREAK**
SESSION II	**OTHER TOPICS** Chaired by **Frida Emanuelsson** *(Denmark)* and **Monique Mulder** *(The Netherlands)*

12.45 – 13.00	Association of the apolipoprotein M and sphingosine-1-phosphate complex with brown adipose tissue after cold exposure in humans **Christina Christoffersen** *(Denmark)*
13.00 – 13.15	Jet lag impairs metabolic BAT activity and increases fat mass in male but not female mice **Wietse In het Panhuis** *(The Netherlands)**
13.15 – 13.30	Of mice and men: Murine bile acids explain species differences in the regulation of bile acid and cholesterol metabolism **Sara Straniero** *(Sweden)*
13.30 – 13.55	*Invited speaker* A mouse model humanized for bile acids **Folkert Kuipers** *(The Netherlands)*
13.55 – 14.00	Discussion
14.00 – 14.15	**BREAK**
14.15 – 14.30	Adherence to established national dietary guidelines and risk of dementia: a prospective cohort study of 94,184 individuals **Emilie Westerlin Kjeldsen** *(Denmark)**
14.30 – 14.45	Quality of life and coping in homozygous familial hypercholesterolemia patients: a qualitative study **Janneke Mulder** *(The Netherlands)**
14.45 – 15.00	Physical activity at leisure time and work in risk of dementia - a prospective cohort study of 117,616 individuals **Ida Juul Rasmussen** *(Denmark)*
15.00 – 15.25	*Invited speaker* Lipoprotein transport in the artery wall **Philip Shaul** (*United States*)
15.25 – 15.30	Discussion
15.30 – 15.35	Closing remarks **Anne Langsted** (*Denmark*)
15.45 – 16.45	**General meeting of the *Scandinavian Society for Atherosclerosis Research*** Open for all participants, decision on next year's topics and chairpersons

Friday, April 9th, 2021

SESSION III	**LIPOPROTEINS AND LIPID TRANSPORT** Chaired by **Matteo Pedrelli** *(Sweden)* and **Minna Kaikkonen-Määttä** *(Finland)*
08.30 – 08.55	*Invited speaker* Role of PCSK9 beyond the liver **Giuseppe Danilo Norata** *(Italy)*
08.55 – 09.00	Discussion
09.00 – 09.15	Characterization of human apolipoprotein M protein variants with impaired S1P binding capacities **Stefan Hajny** *(Denmark)**
09.15 – 09.30	A novel gene affecting VLDL assembly/secretion **Willemien van Zwol** *(The Netherlands)**
09.30 – 09.45	Genetic variation in ABCA1 and risk of all-cause dementia, age-related macular degeneration, and ischemic heart disease **Liv Tybjærg Nordestgaard** *(Denmark)**
09.45 – 10.10	*Invited speaker* The polygenic nature of circulating lipid species levels **Samuli Ripatti** *(Finland)*
10.10 – 10.15	Discussion
10.15 – 10.35	**BREAK**
10.35 – 10.50	Concomitant glucose-dependent insulinotropic receptor (GIPR) and glucagon-like peptide-1 receptor (GLP1R) agonism stimulates TG-rich lipoprotein metabolism and attenuates atherosclerosis development **Robin van Eenige** *(The Netherlands)**
10.50 – 11.05	Per particle triglyceride-rich lipoproteins imply higher myocardial infarction risk than low-density lipoproteins: Copenhagen General Population Study **Mia Johansen** *(Denmark)**
SESSION IV	**INFLAMMATION AND VASCULAR BIOLOGY** Chaired by **Clare Hawkins** (Denmark) and **Patrick Rensen** (The Netherlands)
11.05 – 11.30	*Invited speaker* Immune checkpoints in atherosclerosis **Esther Lutgens** *(The Netherlands)*
11.30 – 11.35	Discussion
11.35 – 11.50	Severe α1-Antitrypsin Deficiency associated with reduced blood pressure and lower plasma triglycerides in the general population **Sine Voss Winther** *(Denmark)**

11.50 – 12.05	Macrophage ATP citrate lyase deficiency stabilizes atherosclerotic plaques **Sanne Verberk** *(The Netherlands)**
12.05 – 12.20	Intake of fermented dairy products induces a less pro-inflammatory postprandial peripheral blood mononuclear cell gene expression response than non-fermented dairy products **Amanda Rundblad** *(Norway)**
12.20 – 13.20	**LUNCH BREAK**
13.20 – 13.35	Immunological factors – the link between osteoporosis and enhanced vascular calcification? **Wera Pustlauk** *(Germany)**
13.35 – 13.50	Multinucleated variant endothelial cells are associated with local accumulation of LDL aggregates and CD45+ leukocytes in the human aortic subendothelial intima **Egor Chegodaev** *(Russia)**
13:50 – 14:05	Lysosomal lipoprotein processing in endothelial cells stimulates adipose tissue thermogenic adaptation **Alexander Fischer** *(Germany)**
14.05 – 14.30	*Invited speaker* MPO to inhibit vascular inflammation and atherothrombotic disease **Imran Rashid** *(USA)*
14.30 – 14.35	Discussion
14.35 – 14.50	Paper of the Year Award. Best Presentation Award. **Anne Langsted** (*Denmark*) and **Mette Christoffersen** *(Denmark)*
14.50 – 15.00	Closing remarks **Anne Langsted** (*Denmark*)

Oral Presentations – Abstracts –

Cardiovascular Disease

SESSION I

Time to run: Late rather than early exercise decreases atherosclerosis

Milena Schönke[1,2], Zhixiong Ying[1,2], Wietse In het Panhuis[1,2], Sander Kooijman[1,2], Patrick C.N. Rensen[1,2]

[1]Division of Endocrinology, Department of Medicine, Leiden University Medical Center, Leiden, The Netherlands. [2]Einthoven Laboratory for Experimental Vascular Medicine, Leiden University Medical Center, Leiden, The Netherlands.

The majority of metabolic processes are under circadian regulation and its disturbance increases the susceptibility to cardiometabolic diseases. While light exposure and food intake are known circadian regulators, it is unclear whether the beneficial health effects of exercise are restricted to unique time windows. We aimed to study whether the timing of exercise training differentially modulates the development of atherosclerosis and elucidate underlying mechanisms.
We endurance-trained atherosclerosis-prone female APOE*3-Leiden.CETP mice fed a Western-type diet, a well-established model for cardiometabolic disease, for one hour five times a week for four weeks either in their early or in their late active phase on a treadmill and assessed the development of atherosclerotic lesions in the aortic root.
Late, but not early, exercise reduced the size of atherosclerotic lesions by as much as 40% compared to sedentary animals. Concomitantly, the greatest loss of fat mass was observed with late training (+0.43 g with early vs. -0.49 g with late training). No correlation between cholesterol exposure and lesion size was evident, indicating a modulation of vascular inflammation in early atherosclerosis with late compared to early training. Strikingly, we observed a time-of-day-dependent effect of exercise training on the composition of the gut microbiota with an increased abundance of fecal bacteria producing butyrate, a short-chain fatty acid with proposed atheroprotective properties, after four weeks of late training.
Together, these findings clearly indicate that timing is a critical factor to amplify the beneficial anti-atherosclerotic effects of exercise with a great potential to further optimize training recommendations for patients.

Impaired high-density lipoprotein function in patient with heart failure

Congzhuo Jia, Johanna E. Emmens, Leong L. Ngd,e, Dirk J. van Veldhuisena, Kenneth Dicksteinf, Stefan D. Ankerh, Chim C. Langj, Gerasimos Filippatosk,l, John G.F. Cleland, Marco Metrao, Adriaan A. Voorsa, Rudolf A. de Boer, Uwe J.F. Tietge.

University of Groningen, University Medical Center Groningen, Department of Cardiology, Groningen, the Netherlands; University of Groningen, University Medical Center Groningen, Department of Pediatrics, Groningen, the Netherlands; Division of Clinical Chemistry, Department of Laboratory Medicine, Karolinska Institutet, Stockholm, Sweden; Department of Cardiovascular Sciences, Glenfield Hospital, University of Leicester; NIHR Leicester Biomedical Research Centre, Leicester, United Kingdom. University of Bergen, Bergen, Norway. Stavanger University Hospital, Stavanger, Norway; Department of Cardiology(CVK) and Berlin-Brandenburg Center for Regenerative Therapies(BCRT); German Centre for Cardiovascular Research (DZHK) partner site Berlin; Charite Universitatsmedizin Berlin, Germany; Department of Cardiology and Pneumology, University Medical Center Gottingen (UMG), Gottingen, Germany; School of Medicine Centre for Cardiovascular and Lung Biology, Division of Molecular and Clinical Medicine, University of Dundee, Dundee, UK; Nathional and Kapodistrian University of Athens, School of Medicine, Athens, Greece; University of Cyprus, school of Medicin, Nicosia, Cyprus; National Heart & Lung Institute, Royal Brompton&Harefield Hospitals, Imperial College, London, UK; Robertson Institute of Biostatistics and clinical trials unit, university of glasgow, glasgow,UK; Institute of cardiology, department of medical and surgical specialties, Radiological sciences and public health, university of brescia, Italy; Clincal Chemistry, Karolinska University Laboratory, Karolinska University Hospital, SE-14186 Stockholm, Sweden

Aims: We recently showed that, in patients with heart failure, lower high-density lipoprotein (HDL) cholesterol concentration was a strong predictor of death or hospitalization for heart failure. In a follow-up study, we suggested that this association could be partly explained by HDL proteome composition. However, whether the emerging concept of HDL function contributes to prognosis of heart failure patients, has not been addressed.

Methods and Results**:** We measured three key protective HDL function metrics, namely cholesterol efflux, antioxidative capacity, and anti-inflammatory capacity, at baseline and after 9 months in 446 randomly selected patients with heart failure from BIOSTAT-CHF. Additionally, the relationship between HDL functionality and HDL proteome composition was determined in 86 patients with heart failure. From baseline to 9 months, HDL cholesterol concentrations were unchanged, but HDL cholesterol efflux and anti-inflammatory capacity declined (both P<0.001). In contrast, antioxidative capacity increased (P<0.001). Higher HDL cholesterol efflux was associated with lower mortality after adjusting for BIOSTAT risk models and log HDL cholesterol (HR=0.81 [95% CI: 0.71–0.92], P=0.001). Other functionality measures were not associated with outcome. Several HDL proteins correlated with HDL functionality, mainly with cholesterol efflux. Apolipoprotein A1 emerged as the main protein associated with all three HDL functionality measures.

Conclusions**:** Better HDL cholesterol efflux at baseline was associated with lower mortality during follow up, independent of HDL cholesterol. HDL cholesterol efflux and anti-inflammatory capacity declined during follow-up in patients with heart failure. Measures of HDL function may provide clinical information in addition to HDL cholesterol concentration in patients with heart failure.

Event-free FH patients >65 years of age are characterized by higher concentration of large HDL particles

Torunn Melnes[1], Martin P. Bogsrud[2,3], Ida Thorsen[3], Julie Fossum[3], Jacob J. Christensen[1,3], Ingunn Narverud[1,3], Kjetil Retterstøl[1,4], Stine M. Ulven[1] and Kirsten B. Holven[1,3]

[1]Department of Nutrition, Institute of Basic Medical Sciences, University of Oslo, Oslo, Norway; [2]Unit for Cardiac and Cardiovascular Genetics, Department of Medical Genetics, Oslo University Hospital Ullevål, Oslo, Norway; [3] Norwegian National Advisory Unit on Familial Hypercholesterolemia, Department of Endocrinology, Morbid Obesity and Preventive Medicine, Oslo University Hospital Aker, Oslo, Norway; [4]The Lipid Clinic, Department of Endocrinology, Morbid Obesity and Preventive Medicine, Oslo University Hospital Aker, Oslo, Norway

Background and aim: Familial hypercholesterolemia (FH) is a genetic disorder characterized by lifelong elevated low-density lipoprotein cholesterol (LDL-C) and premature coronary heart disease (CHD). Cholesterol-lowering therapy (statins) reduces CHD risk, but have only been available for the last 25 years, thus, elderly (>65 years) FH patients have been untreated several decades of their life. Surprisingly, some of these have never experienced any CHD event, raising the question whether they present CHD-resistant characteristics. To our knowledge, there are no reports of comprehensive metabolite profiling in these individuals. Therefore, we aimed to characterize metabolic differences between elderly FH subjects with and without CHD.

Methods: We used a high-throughput nuclear magnetic resonance (NMR) spectroscopy platform to quantify a large number of metabolites in serum samples from 83 FH patients >65 years, and analyze differences between subjects with (n = 39) and without (n = 44) CHD.

Results: Mean age was 70 years in both groups (41 % and 55 % female in the CHD group and non-CHD group, respectively). The non-CHD group had significant higher levels of large and extra-large HDL particles, higher concentration of Apolipoprotein A-I (ApoA-I) and cholesterol in HDL and HDL2 particles, compared to the CHD group ($p<\leq 0.05$ for all). ≤

Conclusions: CHD resistant elderly FH patients have higher levels of large HDL particles and other HDL-related metabolites. The mechanisms behind the event-free survival among these patients remain unclear; hence, a deeper understanding of the metabolic profile in CHD-free elderly FH subjects may lead to development of novel preventive therapies.

Elevated remnant cholesterol and 3-fold increased risk of peripheral artery disease: two population-based cohorts

Benjamin Nilsson Wadström, MD, Anders Berg Wulff, MD, PhD, Kasper M. Pedersen MD, Børge G. Nordestgaard DMsc, Prof

Department of Clinical Biochemistry, Herlev and Gentofte Hospital, Copenhagen Denmark

Aim: Remnant cholesterol is observationally and causally associated with ischemic heart disease and ischemic stroke. Whether this is also true for
Peripheral Artery Disease (PAD) is not known. We tested the hypothesis that elevated remnant cholesterol is associated with increased risk of PAD.

Methods: A total of 107,169 individuals from the Copenhagen General Population Study examined in 2003–2015 were included in a prospective, observational association study. During 15 years of follow-up, 1,587 individuals were diagnosed with PAD. Hazard ratios were estimated using Cox regression models. Results were independently confirmed in 13,972 individuals from the Copenhagen City Heart Study examined in 1976-78, with 1,033 cases of PAD diagnosed during 43 years of follow-up.

Results: Higher levels of remnant cholesterol were associated with a stepwise increase in the risk of PAD up to a multivariable adjusted hazard ratio of 3.1 (95% confidence interval: 2.2-4.2) for individuals with remnant cholesterol concentrations 1.5 mmol/L compared to individuals with remnant cholesterol <0.5 mmol/L. Corresponding results for myocardial infarction and ischemic stroke were 2.6 (2.0-3.4) and 1.6 (1.3-2.0). Cumulative incidence of PAD at age 80 ranged from 2.9% in individuals with remnant cholesterol <0.5 mmol/L to 8.9% in individuals with remnant cholesterol 1.5 mmol/L. Results in the Copenhagen City Heart Study were similar.

Conclusions: Elevated remnant cholesterol is associated with a 3-fold increased risk of PAD, higher than for myocardial infarction or ischemic stroke. Clinical trials should evaluate the effect of remnant cholesterol lowering therapy in the context of PAD.

PCSK9 as a novel player in vascular calcification under uremic conditions: in vitro, in vivo, and clinical evidences

M.G. Lupo[1], A. Baragetti[2], M. Rattazzi[3], N. Ferri[1]

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AIM: CKD lead to a higher rate of cardiovascular death (CVD) due to severe alterations in lipidic profile and a massive vascular calcification (VC) of the tunica media in the vessels' wall. Indeed, due to the hyperphosphatemia triggered by the renal damage, vascular smooth muscle cells (VSMCs) in the tunica media trans-differentiate in osteoblastic-like cells. Proprotein convertase subtilisin/kexin type 9 (PCSK9) turned out as a cornerstone pharmacological target for familial hypercholesterolemia (FH), with two anti-PCSK9 monoclonal antibodies approved so far. Recently, PCSK9 plasma levels were associated with a higher calcification rate in the general, FH, CKD, and diabetic populations. Given these premises, the present study aims to shed light on the putative causal role of PCSK9 in VC under uremic conditions.ù

METHODS: Plasma PCSK9 levels were measured in 594-RI patients from PLIC cohort. VC rate and PCSK9 levels were evaluated in a uremic rat model. Control and PCSK9-overexpressing smooth muscle cells (SMCsPURO and SMCsPCSK9, respectively) were treated with inorganic phosphate (Pi) for 7 days and checked analyzed for calcium deposition and for expression of pro- and anti-calcific proteins.

RESULTS: In hypercholesterolemic patients, PCSK9 plasma levels negatively correlated with renal function. Uremic rats showed higher rate of VC and PCSK9 plasma levels, along with higher PCSK9 expression in livers and kidneys. Upon Pi treatment, SMCsPCSK9 showed an increase in calcium deposition with more Calcium/ALP/PCSK9-laden EVs-budding, in pro-calcific markers, and a decrease in anti-calcific mediators.

CONCLUSION: The present study indicates a direct role of PCSK9 on VC associated to a CKD condition. Further analysis on PCSK9 knockout models for CKD-mediated vascular calcification will attempt to prove the PCSK9 causality in VC process.

Genetic variation in SLC5A2 mimicking SGLT2-inhibition lowers risk of heart failure and death

Louise E. Bechmann, MD[1,2], Frida Emanuelsson, MD PhD[1], Børge G. Nordestgaard, MD DMSc[2,3,4,5], Marianne Benn, MD DMSc[1,2]

[1]Department of Clinical Biochemistry, Rigshospitalet, Copenhagen University Hospital, Blegdamsvej 9, 2100 Copenhagen, Denmark; [2]Faculty of Health and Medical Sciences, Department of Clinical Medicine, University of Copenhagen, Blegdamsvej 3B, 2200 Copenhagen, Denmark; [3]Department of Clinical Biochemistry and [4]The Copenhagen General Population Study, Herlev and Gentofte Hospital, Copenhagen University Hospital, Borgmester Ib Juuls Vej 1, 2730 Herlev, Denmark, and [5]The Copenhagen City Heart Study, Frederiksberg and Bispebjerg Hospital, Copenhagen University Hospital, Nordre Fasanvej 57, 2000 Frederiksberg, Denmark.

Background: Treatment with sodium-glucose co-transporter 2(SGLT2)-inhibitors reduces the risk of hospitalization for heart failure and all-cause mortality, but the mechanism is unclear.
Objectives: We hypothesized that genetic variation in SLC5A2, encoding SGLT2, mimics pharmacological SGLT2-inhibition on risk of heart failure and all-cause mortality, and also allows examination of potential mediators on risk of heart failure. Investigated mediators were related to glycemic control, body mass, blood pressure, circulating blood volume, and lipids.

Methods: 114,932 individuals from two similar studies of the Danish general population, the Copenhagen City Heart Study and the Copenhagen General Population Study, were included and genotyped for three variants in the SLC5A2 gene. Genetic variants were examined for association with risk of heart failure (N=6,407) and all-cause mortality (N=16,779) after up to 42 years of follow-up, and for potential mediators of the association with heart failure.

Results: SLC5A2 genotypes lowered risk of heart failure by up to 33% and all-cause mortality up to 21%. Lower plasma glucose mediated 3.5% (95%CI: 0.8%-8.0%; p=0.01) of the effect of SLC5A2 genotype on risk of heart failure.

Conclusion: Genetic variation in SLC5A2, encoding SGLT2, is causally associated with an up to 33% lower risk of heart failure and 21% lower risk of all-cause mortality. The effect on heart failure was partly mediated through a lifelong lower plasma glucose.

Oral Presentations – Abstracts –

Other Topics

SESSION II

Association of the apolipoprotein M and sphingosine-1-phosphate complex with brown adipose tissue after cold exposure in humans

Anna Borup[1,6], Ida Donkin[2], Mariëtte R. Boon[3], Martin Frydland[4], Borja Martinez-Tellez[3], Annika Loft[5], Sune H. Keller[5], Andreas Kjaer[5], Jesper Kjaergaard[4], Christian Hassager[4], Romain Barrès[2], Patrick C.N. Rensen[3], Christina Christoffersen[1,6,7]

[1]Department of Clinical Biochemistry, Rigshospitalet, Copenhagen, Denmark, [2]Novo Nordisk Foundation Center for Basic Metabolic Research, Faculty of Health and Medical Sciences, University of Copenhagen, Copenhagen, Denmark, [3]Department of Medicine, Division of Endocrinology, and Einthoven Laboratory for Experimental Vascular Medicine, Leiden University Medical Center, Leiden, The Netherlands, [4]Department of Cardiology, Rigshospitalet, Copenhagen, Denmark, [5]Department of Clinical Physiology, Nuclear Medicine & PET and Cluster for Molecular Imaging, Rigshospitalet and University of Copenhagen, Copenhagen, Denmark, [6]Department of Biomedical Sciences, University of Copenhagen, Denmark, [7]Department of Clinical Biochemistry, Bispebjerg Hospitalet, Denmark.

Background: The HDL-associated apolipoprotein M (apoM) and its ligand sphingosine-1-phosphate (S1P) may control energy metabolism, as supported by apoM-deficient mice showing a favorable metabolic phenotype with increased triglyceride turnover and protection against obesity-induced insulin resistance. In addition, apoM deficiency is associated with increased vascular permeability and brown adipose tissue (BAT) mass and activity, and these effects are partly mediated by the S1P receptor 1.

Method: In the current study, we explored the connection between plasma apoM/S1P levels and parameters of BAT as measured via 18F-FDG PET/CT after cold exposure using three different protocols in humans.

Results: Fixed (n=15) vs personalized (n=20) short-term cooling protocols decreased and increased apoM (-8.4%, p=0.032 vs 15.7%, p<0.0005) and S1P (-41.0%, p<0.0005 vs 19.1%, p<0.005) plasma levels, respectively. Long-term cooling (n=44) had no effect on plasma apoM or S1P levels. Plasma apoM and S1P did not correlate significantly to BAT volume and activity in the individual study using fixed or personalized cooling protocols. The short-term studies combined, showed that increased changes in plasma apoM correlated with BAT volume (β:0.39, 95% CI [-0.01-0.78], P=0.054) and metabolic activity (β:0.44, 95% CI [0.06-0.81], P=0.024) after adjusting for study design.

Conclusion: Plasma apoM and S1P levels are altered in response to cold exposure and may be linked to changes in BAT metabolic activity and volume. Our results highlight a possible role of the apoM/S1P complex on human BAT biology.

Jet lag impairs metabolic BAT activity and increases fat mass in male but not female mice

Wietse In het Panhuis, Ricky Siebeler, Milena Schönke, Patrick C.N. Rensen, Sander Kooijman

Department of Medicine, Division of Endocrinology, and Einthoven Laboratory for Experimental Vascular Medicine, Leiden University Medical Center, Leiden, the Netherlands

Aim:
Circadian disturbances, regularly occurring by shift work or social jet lag, are not only associated but also causally linked to cardiometabolic disease. However, it is unclear if sex plays a role in the adverse effects of circadian disturbances. Therefore, we aimed to elucidate in mice whether the effects of circadian disturbances in the form of jet lag on energy metabolism are sex-dependent.

Methods & results:
We exposed chow-fed male and female C57Bl/6J mice to 6h phase advances every 3 days to induce jet lag for 10 weeks. While jet lag induced an initial significant increase in fat mass in males, which became a trend towards the end of the study, females did not show increased fat mass. To investigate clearance and organ distribution of TG-derived FA, we injected mice with glycerol tri[3H]oleate-labeled TRL particles at the onset of the dark phase one day after jet lag. Jet lag delayed [3H]oleate clearance in both sexes, but more pronounced in males, and decreased [3H]oleate uptake by brown adipose tissue in males only. To investigate adaptation to jet lags, we individually housed mice in metabolic cages for a week and observed shifts in rhythms of locomotor activity, food intake and energy expenditure. While females adapted quickly to the new light-dark schedule after a jet lag with respect to these parameters, males did not adapt properly as rhythms of these parameters tended to flatten.

Conclusions:
Male mice adapt less easily to circadian disturbances in the form of jet lags compared to female mice, which may explain their decreased clearance of TRL-derived FA by brown adipose tissue contributing to an increase in fat mass. We anticipate that future studies on circadian disturbances should consider sex as a potentially important factor that may eventually contribute to personalized advice for shift workers.

Of mice and men: Murine bile acids explain species differences in the regulation of bile acid and cholesterol metabolism

Sara Straniero, Amit Laskar, Christina Savva, Jennifer Härdfeldt, Bo Angelin and Mats Rudling

Metabolism Unit; Endocrinology, Metabolism and Diabetes, and Integrated Cardio Metabolic Center (ICMC), Department of Medicine, Karolinska Institutet at Karolinska University Hospital, Huddinge, S-141 86, Stockholm, Sweden

Compared to humans, rodents have higher synthesis of cholesterol and bile acids, and faster clearance and lower levels of serum LDL cholesterol. They also paradoxically increase bile acid synthesis in response to bile duct ligation. Another species difference is their production of hydrophilic 6-hydroxylated muricholic acids (MCAs) capable of antagonizing the activation of farnesoid-X-receptors by human bile acids and to exert anti-diabetogenic effects. We hypothesized that the presence of MCAs is key for many of these metabolic differences between mice and humans.

We thus studied the effects of genetic deletion of the Cyp2c70 gene, previously proposed to control MCA formation. Compared to WT animals, Cyp2c70-KO mice completely lacked MCAs, and displayed >50% reductions in bile acid and cholesterol synthesis and hepatic LDL receptor number, leading to a marked increase in serum LDL cholesterol. The doubling of bile acid synthesis following bile duct ligation in WT animals was abolished in KO mice, despite extinguished intestinal Fgf15 expression in both groups. Accumulation of cholesterol-enriched particles ("Lp-X") in serum was almost eliminated in KO mice. Livers of KO mice were increased 18% in weight and serum markers of liver function indicated liver damage. In contrast to WT animals, Cyp2c70-KO mice on high-fat diet showed a significant increase in serum LDL cholesterol; this increase was markedly lower in Cyp2c70 KO on high-fat diet with administration of MCAs.

In conclusion, the presence of MCAs is key for many of the known metabolic differences in mice versus humans. The Cyp2c70-KO mouse may be useful in studies exploring potential therapeutic targets for human disease.

Adherence to established national dietary guidelines and risk of dementia: a prospective cohort study of 94,184 individuals

Emilie W. Kjeldsen[1], Jesper Q. Thomassen[1], Katrine L. Rasmussen[1], Børge G. Nordestgaard[2], Anne Tybjærg-Hansen[1], Ruth Frikke-Schmidt[1]

[1]Rigshospitalet, Copenhagen University Hospital, Department of Clinical Biochemistry, Copenhagen, Denmark [2]Herlev and Gentofte Hospital, Copenhagen University Hospital, Department of Clinical Biochemistry, Herlev, Denmark

Background: Recent estimates suggest that up to 40% of all dementia cases may be preventable, primarily by treating or acting on well-established cardiovascular risk factors such as diabetes, hypertension, smoking, and physical inactivity. Whether adherence to dietary guidelines contributes to improved cognitive health remains unknown.

Methods: We tested whether non-adherence to national dietary guidelines was associated with risk of non-Alzheimer's dementia – a dementia subtype related with vascular risk factors - and Alzheimer's disease in 94,184 individuals from the prospective Copenhagen General Population Study. As a positive control we tested whether non-adherence to dietary guidelines was associated with vascular diseases including ischemic cerebrovascular disease(ICVD) and ischemic heart disease(IHD).

Results: Low adherence to dietary guidelines was associated with an atherogenic lipid profile including significantly higher levels of total cholesterol, LDL cholesterol, non-HDL cholesterol, triglycerides, remnant cholesterol and apoB(P-values from 9.3x10-228 to 1.8x10-8). We found that the hazard ratio for low adherence versus high adherence to dietary guidelines was 1.54(95% confidence interval 1.18-2.00) for non-Alzheimer's dementia in an age and sex adjusted model. In a multifactorial adjusted model, the corresponding value was 1.43(1.00-1.80). We did not observe any association with Alzheimer's disease. As expected, our positive control showed that low adherence to dietary guidelines was associated with significantly increased risk of ICVD and IHD in multifactorial adjusted models.

Conclusions: The present study provides evidence for preventing the part of dementia that is mainly due to vascular factors, and that focusing on implementation of national dietary guidelines will be of major importance for improved individual and public health.

Quality of life and coping in homozygous familial hypercholesterolemia patients: a qualitative study

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Aim: Homozygous Familial Hypercholesterolemia (HoFH) evokes extremely premature cardiovascular disease (CVD) and death. Healthcare professionals estimate the burden of disease as disastrous. Remarkably, it is unknown whether patients indeed experience such catastrophic burden. Moreover, no systematic description exists how patients cope with HoFH.

Methods: Patients with genetically confirmed HoFH, >18 yrs, treated at 3 specialized HoFH-centres in the Netherlands, were invited to participate in semi-structured interviews. Interviews were transcribed verbatim and analysed according to the principles of grounded theory. In addition, the EQ-5D-5L and the Threatening Medical Situations Inventory (TMSI) were administered to address quality of life (QoL) and coping.

Results: In total, 20 HoFH-patients were interviewed (50% women, mean age 40 yrs, 60% with CVD, 10% on apheresis). Coding of the transcripts resulted in a conceptual model, centred around disease perception. Individual TMSI-results generally corresponded to the interviews, most showing both monitoring (information-seeking behaviour) and blunting (distractive strategies). The mean EQ-5D-5L health utility score was lower than the normal Dutch population average: 0.783 vs. 0.869. However, because of the skewed distribution, the median (0.839) was only 5% below the Dutch population (0.887).

Conclusions: In daily life, HoFH-patients use different effective coping mechanisms and are less preoccupied with their condition than would be expected. Our study shows that the objective elevated risk of CVD and premature death is only slightly affecting subjective quality of (daily) life in this patient group. Awareness of coping mechanisms can prevent iatrogenic effects in patient-physician interaction, and might help to improve QoL and treatment compliance.

Physical activity at leisure time and work in risk of dementia - a prospective cohort study of 117,616 individuals

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Background: Up to 40% of all dementia cases may be preventable, primarily by treating or acting on well-established cardiovascular risk factors such as diabetes, hypertension, smoking, and physical inactivity. Whether physical inactivity is associated with risk of non-Alzheimer's dementia – a disease influenced by cardiovascular risk factors – and whether a given association is independent of physical activity at work remains unknown.

Methods: In 117,616 individuals from the Copenhagen General Population Study and the Copenhagen City Heart Study with up to 43 years of follow-up, we tested whether physical inactivity is associated with risk of non-Alzheimer's dementia and Alzheimer's disease.

Findings: Multifactorially adjusted hazard ratios for low versus high physical activity at leisure time was 1.60 (95% confidence interval 1.40-1.83) for non-Alzheimer's dementia. Corresponding values after additional adjustment for physical activity at work or apolipoprotein E (APOE) genotype were 1.60 (1.40-1.83) and 1.82 (1.34-2.15). After exclusion of follow-up periods within two, five, or ten years from baseline, corresponding hazard ratios were 1.75 (1.47-2.08), 1.54 (1.27-1.86), and 1.40 (1.12-1.76), respectively, when analyses were multifactorially and APOE adjusted. Combining physical activity at leisure time and at work, physical activity at leisure time had the largest influence on risk of non-Alzheimer's dementia. No such association with Alzheimer's disease was observed.

Interpretation: Physical inactivity at leisure time is associated with increased risk of non-Alzheimer's dementia, independent of physical activity at work and APOE genotype and even after exclusion of follow-up period ten years from baseline. The present study thus supports public health advice on increased physical activity at leisure time aimed at preventing non-Alzheimer's dementia, the large part of dementia related to cardiovascular risk factors.

Oral Presentations – Abstracts –

Lipoproteins and Lipid Transport

SESSION III

Characterization of human apolipoprotein M protein variants with impaired S1P binding capacities

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Aim: The apolipoprotein M (apoM) / Sphingosine-1-Phosphate (S1P) complex plays a vital role in metabolic and inflammatory processes. Models which isolate the individual contribution of apoM and S1P are however not available. So far discovered effects can be thus only attributed to the entire apoM/S1P complex. We addressed the conundrum by validating human apoM protein variants with the aim to impair S1P binding, thereby establishing a novel model system.

Methods: Computational models were used to identify mutations in the human apoM binding pocket which likely effect S1P binding. These mutations were validated in in vitro assays and further introduced into animal models.

Results: Among the in silico validated human apoM mutants, two favourable recombinant variants, termed A and B, were characterized in vitro. Both mutants maintained the native apoM protein structure. Moreover, variant A revealed 14-fold decreased S1P binding affinities compared to wild type apoM, whereas variant B did not bind the ligand. Erythrocyte depended S1P release was furthermore ~ 40% decreased, comparing variant A and B with wild type apoM. Next, a mouse model of variant B was generated and is currently being evaluated. Changes in lipid metabolism are evident.

Conclusion: We identified two human apoM protein variants with decreased and diminished S1P binding capacities. In silico and in vitro testing led to the generation of a novel mouse model which allows to distinguish between apoM and S1P mediated effects, thus potentially improving the understanding of the apoM-S1P axis.

A novel gene affecting VLDL assembly/secretion

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Background: Compromised secretion of very low-density lipoprotein (VLDL) can result in hepatic lipid accumulation, a risk factor for non-alcoholic fatty liver disease (NAFLD). Basic knowledge of VLDL assembly and the secretion pathway may help to find solutions for NAFLD. Here, we present a novel gene, SMLR1, identified through contextual co-expression analysis with APOC3 as anchor. Information on SMLR1 in the public domain is restricted to data showing that expression is strictly confined to liver and small intestine. Here, we present a first study on the role of SMLR1 in hepatic and plasma lipid metabolism.

Methods: Using somatic CRISPR/Cas9 gene editing technology, we downregulated Smlr1 expression in livers of wild-type male and female mice (n=10/group) fed a chow diet. Liver lipids were extracted according to Bligh & Dyer method. VLDL secretion rate was assessed after intraperitoneally injected poloxamer. Lipoprotein profiling was conducted using FPLC. Immortalized human hepatoma cells where used for localization studies.

Results: Downregulation of Smlr1 at the mRNA level (80%) and protein level (67%), resulted in 50% reduction of plasma cholesterol and triglycerides levels ($p<0.001$ for both), and increased hepatic lipid levels (>2.9fold, $p<0.001$). In line, VLDL secretion rate was reduced by 45%. Lipoprotein profiling revealed reductions of cholesterol in both HDL and LDL. Immunofluorescence studies indicate that SMLR1 is localized in the endoplasmic reticulum (ER) and Golgi complex.

Conclusion: This study uncovers Smlr1 as a key gene in the regulation of plasma and hepatic lipid metabolism. Localized in the ER and Golgi complex, the protein is anticipated to play a role in the trafficking of lipoproteins in hepatocytes. Future studies will be focussed on proteins that interact with SMLR1 to elucidate its role in VLDL assembly and secretion pathways.

Genetic variation in ABCA1 and risk of all-cause dementia, age-related macular degeneration, and ischemic heart disease

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Aim: The adenosine triphosphate-binding cassette transporter A1(ABCA1) is a major cholesterol transporter expressed in liver, brain and the eye. ABCA1 mediates cholesterol and phospholipid efflux to lipid-poor apolipoproteins and is essential for the biogenesis of high-density lipoprotein(HDL) cholesterol in the circulation and HDL-like particles in the brain. Genome-wide association studies of age-related macular degeneration(AMD) and dementia have found the ABCA1 gene to be significantly associated with these diseases. Whether genetic variation in ABCA1 is associated with AMD and dementia in cohorts of the general population remains unknown. We tested the hypothesis that genetic variation in ABCA1 is associated with risk of all-cause dementia, non-Alzheimer's dementia, Alzheimer's disease, all-cause AMD, dry AMD, wet AMD, and ischemic heart disease(IHD).

Methods: In a prospective cohort study of the Danish general population(n=89,185), we tested the genetic association between an HDL cholesterol weighted ABCA1 allele score, stratified into 3 groups, and risk of all-cause dementia, non-Alzheimer's dementia, Alzheimer's disease, all-cause AMD, dry AMD, wet AMD, and ischemic heart disease.

Results: The ABCA1 allele score in 3 groups with highest HDL cholesterol versus lowest was associated with hazard ratios (95% confidence intervals) of 1.21(1.08-1.35) for all-cause dementia, 1.31(1.08-1.35) for non-Alzheimer's dementia, 1.13(0.98-1.31) for Alzheimer's disease, 1.19(1.02-1.39) for all-cause AMD, 1.10(0.90-1.36) for dry AMD, 1.20(1.00-1.45) for wet AMD, and 1.06 (0.98-1.14) for IHD.

Conclusions: Genetically high HDL cholesterol due to variation in ABCA1 was associated with higher risk of all-cause dementia, non-Alzheimer's dementia, and age-related macular degeneration, but not with Alzheimer's disease or ischemic heart disease.

Concomitant glucose-dependent insulinotropic receptor (GIPR) and glucagon-like peptide-1 receptor (GLP1R) agonism stimulates TG-rich lipoprotein metabolism and attenuates atherosclerosis development

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Aim: Tirzepatide, a dual GIP/GLP-1 receptor agonist, was recently shown to cause robust weight loss in patients with Type II Diabetes (Frias et al. 2018). Since GIPR agonism stimulates lipolysis in white adipose tissue and GLP1R agonism promotes brown adipose tissue (BAT) thermogenesis, we hypothesized that combining GIPR and GLP1R agonism enhances the fatty acid (FA) flux to BAT to facilitate thermogenesis, thereby alleviating dyslipidemia and atherosclerosis development.

Methods: Dyslipidemic Western-type diet fed female APOE*3-Leiden.CETP mice were subcutaneously injected with either vehicle, a GIPR agonist (GIPFA-085; 300 nmol/kg/day), a GLP1R agonist (GLP-140; 30 nmol/kg/day) or both agonists for up to 10 weeks. Plasma triglyceride (TG) levels were measured, and TG-rich lipoprotein (TRL) metabolism was assessed using injection of glycerol tri[3H]oleate and [14C]cholesteryl oleate-labeled TRL-like particles. In the aortic valve region, atherosclerotic lesions were scored.

Results: GLP1R agonism lowered body weight (-2.0 g) and increased the uptake of VLDL-TG-derived FA by BAT (+157%) compared to vehicle. On these parameters concomitant GIPR and GLP1R agonism outperformed GLP1R agonism alone (body weight -2.8 g; VLDL-TG derived FA uptake by BAT +191%). Concomitant GIPR and GLP1R agonism, but not GLP1R agonism or GIPR agonism alone, tended to lower plasma TG levels (-46%) and markedly increased hepatic TRL-remnant uptake (+67%). Importantly, concomitant GIPR and GLP1R agonism decreased atherosclerotic lesion progression (-35% severe lesions).

Conclusion: Concomitant GIPR and GLP1R agonism stimulates TRL lipolysis and clearance more than the individual agonists and correspondingly attenuates atherosclerosis development. Current studies evaluate the effects of co-treatment on atherosclerosis in an obese setting.

Per particle triglyceride-rich lipoproteins imply higher myocardial infarction risk than low-density lipoproteins: Copenhagen General Population Study

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Objective: Apolipoprotein B (apoB)-containing triglyceride-rich lipoproteins and low-density lipoproteins (LDL) are each causal for myocardial infarction and atherosclerotic cardiovascular disease; however, the relative importance is unknown. We tested the hypothesis that for the same number of apoB-containing particles from smaller LDL through to larger triglyceride-rich lipoproteins, the risk of myocardial infarction is similar.

Methods and Results: We included 29,039 individuals with no history of myocardial infarction nested within 109,751 individuals from the Copenhagen General Population Study. Particle number of apoB-containing lipoprotein subfractions were measured using nuclear magnetic resonance spectroscopy. During a mean follow-up of 10 years, 2,309 individuals developed myocardial infarction. Multivariable adjusted hazard ratios for myocardial infarction per 1·1015 particles were higher with larger size and more triglyceride content of apoB-containing lipoproteins using ten different subfractions, ranging from 11 (95% confidence interval, 5.6-22) for extra extra large very low-density lipoproteins (VLDL), to 1.06 (1.05-1.07) for extra small VLDL, to 1.02 (1.01-1.02) for intermediate-density lipoproteins (IDL), through to 1.01 (1.01-1.01) for small LDL. When combining the particle number of six VLDL subfractions and combining IDL and three LDL subfractions, hazard ratios for myocardial infarction per 1·1017 particles were 3.5 (2.7-4.5) for VLDL and 1.3 (1.2-1.4) for IDL and LDL combined.

Conclusions: For the same number of apoB-containing particles (1·1017 particles/L), the hazard ratio for myocardial infarction was 3.5-fold for VLDL and 1.3-fold for IDL and LDL combined. These findings imply biologically that VLDL particles are more atherogenic than LDL particles, and clinically that VLDL should be measured separately.

Oral Presentations – Abstracts –

Inflammation and Vascular Biology

SESSION IV

Severe α1-Antitrypsin Deficiency associated with reduced blood pressure and lower plasma triglycerides in the general population

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Introduction: Individuals with severe α1-antitrypsin deficiency have increased elastase activity causing continuous degradation of elastin resulting in an early onset of chronic obstructive lung disease. It has been suggested, that the increased elastase activity over time, also affects the elastic properties of the arterial walls, and thereby perhaps blood pressure and susceptibility to cardiovascular disease. We tested whether severe α1-antitrypsin deficiency affects blood pressure and susceptibility to cardiovascular disease in the general population.

Methods: We genotyped 91,429 individuals from the Copenhagen General Population Study and 190 patients with α1-antitrypsin deficiency from the Danish α1-antitrypsin deficiency registry and recorded blood pressure, plasma lipids and cardiovascular disease as outcomes.

Results: In the combined study, α1-antitrypsin genotype was associated with stepwise decreases in systolic blood pressure and diastolic blood pressure of up to 4.5 mmHg for systolic blood pressure and up to 1.8 mmHg for diastolic blood pressure, in ZZ vs MM individuals (Ps for trend<0.05). We found that plasma triglycerides were significantly lower in ZZ individuals compared with MM individuals (0.4 mmol/L, P< 0.05); no other plasma lipids differed consistently by α1-antitrypsin genotype. Finally, there was no association between the α1-antitrypsin genotype and risk of ischemic heart disease, acute myocardial infarction, hypertension or ischemic cerebrovascular disease (Ps for trend>0.06).

Conclusion: We found that individuals with severe α1-antitrypsin deficiency compared with MM individuals had lower systolic and diastolic blood pressure and reduced plasma triglycerides in the Danish general population.

Macrophage ATP citrate lyase deficiency stabilizes atherosclerotic plaques

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Atherosclerosis is a lipid-driven chronic inflammatory disorder of the arteries in which macrophages play a key role. While these innate immune cells can worsen disease progression by propagating inflammation, macrophages can also stabilize atherosclerotic plaques by promoting the formation of a fibrous cap and by clearing apoptotic cells to prevent necrotic core formation. Hence, reshaping deranged macrophage functions could provide new therapeutic options for atherosclerosis management. The last decade, intracellular metabolic pathways and enzymes emerged as crucial regulators of macrophage activation.

Here, we define a formerly unknown role of the metabolic enzyme ATP citrate lyase (Acly) in regulating both plaque and macrophage phenotype. Since we found Acly to be activated in inflammatory macrophages and in human atherosclerotic plaques, we hypothesized that targeting Acly in macrophages can improve atherosclerosis outcome.

Using a conditional genetic knockout mouse model, we found that myeloid Acly deficiency induces a stabilized plaque phenotype characterized by increased collagen deposition and fibrous cap thickness, along with a smaller necrotic core. After in-depth functional, lipidomic, metabolic, and transcriptional characterization, we linked this plaque phenotype to deregulated fatty acid and cholesterol biosynthesis and defective LXR activation. This led to macrophages being more prone to undergo apoptosis, whilst presenting an increased capacity to phagocytose apoptotic cells.

Together, our results indicate that targeting macrophage metabolism can improve atherosclerosis outcome and reveal Acly as a promising therapeutic target to stabilize atherosclerotic plaques.

Intake of fermented dairy products induces a less pro-inflammatory postprandial peripheral blood mononuclear cell gene expression response than non-fermented dairy products

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Possible health effects of intake of whole-dairy foods are inconclusive, however, high-fat and non-fermented dairy may be associated with increased all-cause mortality and coronary heart disease risk. Although intake of saturated fat is known to increase inflammation and LDL-C, results are conflicting regarding intake of dairy fat that consists of about 65% saturated fat. We aimed to investigate how intake of four high-fat meals with different dairy products, but similar fat content, affects postprandial peripheral blood mononuclear cell (PBMC) expression levels of inflammation and lipid metabolism related genes, and plasma metabolites.

Healthy subjects (n = 47) consumed four different high-fat meals composed of either butter, cheese, whipped cream, or sour cream in a randomized controlled cross-over study. We assessed fasting and postprandial PBMC gene expression with a NanoString Immunology Panel, plasma metabolites with NMR spectroscopy, and circulating inflammatory markers with ELISA.

Using a linear mixed model, we found that expression of genes related to lymphocyte activation, cytokine signaling, chemokine signaling, and cell adhesion were differentially altered between the four meals. In general, intake of the fermented products cheese and sour cream reduced, while intake of the non-fermented products butter and whipped cream increased, expression of these genes. Plasma amino acid concentrations increase after intake of cheese compared to the other meals, and the amino acid changes correlated with several of the differentially altered genes. Lipid metabolism related genes were altered in the same direction after intake of all four high-fat dairy meals.

In conclusion, intake of fermented dairy products, especially cheese, induces a less inflammatory postprandial PBMC gene expression response than non-fermented dairy products. Increased amino acid concentrations after intake of cheese may partially mediate this effect.

Immunological factors – the link between osteoporosis and enhanced vascular calcification?

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Osteoporosis and low bone mineral density were identified as independent risk factors for enhanced vascular calcification and cardiovascular diseases, increasing mortality in those patients. Common risk factors for both disorders, like age, lack of physical activity, and menopause are insufficient to explain a mutual pathogenic mechanism. However, broad evidence emphasises the important role of systemic inflammation in both diseases, indicating a potential immunological regulation.

To address this question, peripheral immune cell subsets in blood from osteoporotic patients as well as non-osteoporotic, age-matched controls were quantified by flow cytometry and sera were screened for soluble factors using different multiplex immunoassays. In addition, the capacity of female and male sera pools to impact osteogenic differentiation of smooth muscle cells (SMC) was assessed.

Analysis of immune cell subsets indicated a distinct increase of neutrophils and platelets in osteoporotic patients, while no differences in lymphocyte, monocyte and natural killer cell subsets were detected. In sera MCP-1, BAFF, and PDGF-BB were found to be significantly increased in osteoporotic patients, while IL-18, SDF-1, OPG and OPN were significantly reduced compared to non-osteoporotic controls. Since increased BAFF levels could be associated with higher neutrophil counts and increased platelet numbers could be associated with PDGF-BB levels, neutrophils and platelets might be potential main sources of BAFF- and PDGF-BB, respectively. Interestingly, stimulation of SMC with osteoporotic sera resulted in an earlier onset as well as enhanced calcification irrespective of the sex.

Our findings of dysregulated soluble and cellular immunological factors strongly support an immunological link between osteoporosis and vascular calcification. Reduced level of OPG and OPN, two inhibitors of vascular calcification, found in osteoporotic patients, might additionally accelerate the development of atherosclerotic lesions in these patients.

Multinucleated variant endothelial cells are associated with local accumulation of LDL aggregates and CD45+ leukocytes in the human aortic subendothelial intima

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Background: At the early stages of atherogenesis, low-density lipoprotein (LDL) particles and immune cells penetrate into the intimal layer of the arterial wall through the endothelium. In adult humans, the luminal surface of the arterial wall is a heterogeneous monolayer of cells with varying morphology, including typical endothelial cells (ECs) and multinucleated variant endothelial cells (MVECs). We hypothesized that distribution of MVECs in the endothelial monolayer can explain the distribution pattern of early atherosclerotic lesions.

Methods: To test our hypothesis we obtained en face preparations of intact adult (22-59 years old) aortic wall sections. We compared the distribution of MVECs in the endothelial monolayer with the localization of LDL aggregates and CD45+ lymphocytes in subendothelial intima.

Results: In primary culture, MVECs demonstrated increased phagocytic activity as compared to mononuclear ECs. We have shown that unaffected aortic intima contains associates of LDL particles that are non-randomly distributed. That indicated that MVECs may be involved in the accumulation of LDL in the subendothelial layer through increased transcytosis. Study of unaffected aortic intima revealed non-random distribution of leukocytes in the subendothelial layer and increased localization of CD45+ leukocytes in the subendothelial layer adjacent to MVECs.

Conclusions: In this study, we revealed a relationship between the localization of MVECs in the endothelial layer and clusters of leukocytes in the adjacent subendothelial layer of human aortic intima. Therefore, MVEC formation can serve as a trigger of early atherogenesis events.

Lysosomal lipoprotein processing in endothelial cells stimulates adipose tissue thermogenic adaptation

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In response to cold exposure, thermogenic adipocytes internalize large amounts of fatty acids after lipoprotein lipase-mediated hydrolysis of triglyceride-rich lipoproteins (TRL) in the capillary lumen of brown adipose tissue (BAT) and white adipose tissue (WAT). Thermogenic adipose tissue activity has been shown to beneficially affect cardiovascular outcomes in mice and men.

Using intravital microscopy, MRI imaging, electron microscopy and magnetic cell isolation techniques, we show that in cold-exposed mice, vascular endothelial cells in adipose tissues endocytose substantial amounts of entire TRL particles. We show that this process is dependent on the fatty acid translocase CD36, which is expressed in high levels on endothelial cells isolated from murine and human BAT. The lipoproteins subsequently follow the endosomal-lysosomal pathway, where they undergo lysosomal acid lipase (LAL)-mediated processing. Endothelial cell-specific LAL deficiency results in impaired thermogenic capacity as a consequence of reduced recruitment of brown and brite/beige adipocytes and impaired angiogenic proliferation. Mechanistically, TRL processing by LAL induces proliferation of endothelial cells, and adipocyte precursor proliferation and differentiation via beta-oxidation-dependent production of reactive oxygen species, which in turn stimulates hypoxia-inducible factor-1α-dependent proliferative responses.

In conclusion, this study for the first time demonstrates a physiological role for TRL particle uptake into BAT and WAT and establishes endothelial lipoprotein processing as an important determinant of adipose tissue remodeling during thermogenic adaptation.