

Literature update week 02 (2019)

[1] Vallee Marcotte B, Guenard F, Lemieux S et al. **Fine mapping of genome-wide association study signals to identify genetic markers of the plasma triglyceride response to an omega-3 fatty acid supplementation.** The American journal of clinical nutrition 2019.

PM: <http://www.ncbi.nlm.nih.gov/pubmed/?term=30624603>

ABSTRACT

Background: Using a genome-wide association study (GWAS) approach, our group previously computed a genetic risk score (GRS) from single nucleotide polymorphisms (SNPs) of 10 loci that affect the plasma triglyceride (TG) response to an omega-3 (n-3) fatty acid (FA) supplementation. Objectives: The objective was to compute a novel and more refined GRS using fine mapping to include a large number of genetic variants. Methods: A total of 208 participants of the Fatty Acid Sensor (FAS) Study received 5 g fish oil/d, containing 1.9-2.2 g eicosapentaenoic acid and 1.1 g docosahexanoic acid, for 6 wk. Plasma TG concentrations were measured before and after supplementation. Dense genotyping and genotype imputation were used to refine mapping around GWAS hits. A GRS was computed by summing the number of at-risk alleles of tagging SNPs. Analyses were replicated in samples of the FINGEN study. Results: A total of 31 tagging SNPs associated with the TG response were used for GRS calculation in the FAS study. In a general linear model adjusted for age, sex, and body mass index, the GRS explained 49.73% of TG response variance ($P < 0.0001$). Nonresponders to the n-3 FA supplementation had a higher GRS than did responders. In the FINGEN replication study, the GRS explained 3.67% of TG response variance ($P = 0.0006$). Conclusions: Fine mapping proved to be effective to refine the previous GRS. Carrying increasing numbers of at-risk alleles of 31 SNPs confers a higher risk of being nonresponsive to n-3 FAs. The genetic profile therefore appears to be an important determinant of the plasma TG response to an n-3 FA supplementation and could be used to target those most likely to gain clinical benefit. This trial was registered at <http://www.clinicaltrials.gov> as NCT01343342.

[2] Nieman DC, Lila MA, Gillitt ND. **Immunometabolism: A Multi-Omics Approach to Interpreting the Influence of Exercise and Diet on the Immune System.** Annual review of food science and technology 2019.

PM: <http://www.ncbi.nlm.nih.gov/pubmed/?term=30633566>

ABSTRACT

Immunometabolism is an evolving field of scientific endeavor that merges immunology and metabolism and has provided valuable context when evaluating the influence of dietary interventions on exercise-induced immune dysfunction. Metabolomics, lipidomics, and proteomics provide a system-wide view of the metabolic response to exercise by simultaneously measuring and identifying a large number of small molecule metabolites, lipids, and proteins. Many of these are involved with immune function and regulation and are sensitive to dietary influences, especially acute carbohydrate ingestion from either sugar beverages or fruits such as bananas. Emerging evidence using large multi-omics data sets supports the combined intake of fruit sugars and phytochemicals by athletes during heavy exertion as an effective strategy to improve metabolic recovery, augment viral defense, and counter postexercise inflammation and immune dysfunction at the cell level. Multi-omics methodologies have given investigators new outcome targets to assess the efficacy of various dietary interventions for physiologically stressed athletes.

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[3] Farrokhi E, Ghatreh-Samani K, Salehi-Vanani N, Mahmoodi A. **The effect of resveratrol on expression of matrix metalloproteinase 9 and its tissue inhibitors in vascular smooth muscle cells.** ARYA atherosclerosis 2018; 14:157-162.

PM: <http://www.ncbi.nlm.nih.gov/pubmed/?term=30627191>

ABSTRACT

BACKGROUND: Matrix metalloproteinase 9 (MMP-9) is involved in extracellular matrix degradation and remodeling. An increase in MMP-9 expression by vascular component cells plays an important role in atherosclerotic plaque formation and rupture. Resveratrol, a polyphenolic substance, was suggested to play a role in preventing the progress of atherosclerotic disease. The aim of this study was to investigate the effect of resveratrol on MMP-9 and tissue inhibitors of metalloproteinases (TIMPs) in vascular smooth muscle cells (VSMCs) after treatment with H₂O₂. **METHODS:** Cultured VSMCs were pre-treated with 0.2 mM of H₂O₂ before stimulation with different concentration of resveratrol. Expression of MMP-9, TIMP-1, and TIMP-3 genes were measured using real-time polymerase chain reaction (PCR) method, and MMP-9 protein level was detected using western blot analysis. **RESULTS:** Resveratrol at 120 μmol/l concentration reduced the elevated level of MMP-9 induced by H₂O₂ in VSMCs as 1.85 +/- 0.35 folds (P < 0.050) and 8.70 +/- 1.20 folds (P < 0.050) after 24 and 48 hours, respectively. Resveratrol increased the diminished level of TIMP-1 induced by H₂O₂ as 2.5 +/- 0.48 folds following the treatment with 120 μmol/l after 48 hours (P < 0.050). **CONCLUSION:** Resveratrol as an antioxidant can decrease MMP-9 production, not only by suppressing MMP-9 expression, but also by augmenting TIMP-1 production. Altogether, resveratrol as an antioxidant can regulate the MMP-9/TIMP-1 balance, and may be considered as a preservative agent in the treatment and prevention of atherosclerosis.

[4] Fasehee H, Fakhraee M, Davoudi S et al. **Cancer biomarkers in atherosclerotic plaque: Evidenced from structural and proteomic analyses.** Biochem Biophys Res Commun 2019.

PM: <http://www.ncbi.nlm.nih.gov/pubmed/?term=30616890>

ABSTRACT

Atherosclerosis and cancer are the leading causes of mortality around the world that share common pathogenic pathways. The aim of this study is the investigation of the protein profile of atherosclerotic plaque in order to find similar biomarker between cancer and atherosclerosis. The small pieces of human coronary artery containing advanced atherosclerotic plaque is obtained from patients during bypass surgery. Structural characterization of type V plaque, including fibrous connective tissue, necrotic lipid core, cholesterol clefts and calcium deposits are performed using high resolution transmission electron microscopy (HR-TEM). The protein profile of atherosclerosis plaque is also analyzed using 2-dimensional electrophoresis and matrix-assisted laser desorption-ionization time-of-flight (MALDI-TOF). TEM analysis shows that vascular smooth muscle cells (VSMCs) exhibit different and uncommon morphologies in atherosclerotic plaque which is correlated to the proliferative state of the cells. The proteomics analysis reveals proteins related to atherosclerosis formation including Mimecan, Ras Suppressor Protein-1 (RSUP-1) and Cathepsin D which identified as biomarker of cancerous tumors. The expression of Mimecan and RSUP-1 is down-regulated in atherosclerotic plaque while the expression of Cathepsin D is up-regulated. These data support that atherosclerotic plaque presents some degree of tumorigenesis with the significant activity of VSMCs as the key player in atherogenesis.

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[5] Desmarais F, Bergeron KF, Rassart E, Mounier C. **Apolipoprotein D overexpression alters hepatic prostaglandin and omega fatty acid metabolism during the development of a non-inflammatory hepatic steatosis.** *Biochimica et biophysica acta. Molecular and cell biology of lipids* 2019.

PM: <http://www.ncbi.nlm.nih.gov/pubmed/?term=30630053>

ABSTRACT

Apolipoprotein D (ApoD) is a secreted lipocalin associated with neuroprotection and lipid metabolism. Overexpression of ApoD in mouse neural tissue induces the development of a non-inflammatory hepatic steatosis in 12-month-old transgenic animals. Previous data indicates that accumulation of arachidonic acid, ApoD's preferential ligand, and overactivation of PPARgamma are likely the driving forces in the development of the pathology. However, the lack of inflammation under those conditions is surprising. Hence, we further investigated the apparent repression of inflammation during hepatic steatosis development in aging transgenic animals. The earliest modulation of lipid metabolism and inflammation occurred at 6months with a transient overexpression of L-PGDS and concomitant overproduction of 15d-PGJ2, a PPARgamma agonist. Hepatic lipid accumulation was detectable as soon as 9months. Inflammatory polarization balance varied in time, with a robust anti-inflammatory profile at 6months coinciding with 15d-PGJ2 overproduction. Omega-3 and omega-6 fatty acids were preferentially stored in the liver of 12-month-old transgenic mice and resulted in a higher omega-3/omega-6 ratio compared to wild type mice of the same age. Thus, inflammation seems to be controlled by several mechanisms in the liver of transgenic mice: first by an increase in 15d-PGJ2 production and later by a beneficial omega-3/omega-6 ratio. PPARgamma seems to play important roles in these processes. The accumulation of several omega fatty acids species in the transgenic mouse liver suggests that ApoD might bind to a broader range of fatty acids than previously thought.

[6] Pai SA, Munshi RP, Panchal FH et al. **Plumbagin reduces obesity and nonalcoholic fatty liver disease induced by fructose in rats through regulation of lipid metabolism, inflammation and oxidative stress.** *Biomedicine & pharmacotherapy = Biomedecine & pharmacotherapie* 2019; 111:686-694.

PM: <http://www.ncbi.nlm.nih.gov/pubmed/?term=30611993>

ABSTRACT

BACKGROUND: Chronic consumption of fructose causes obesity and nonalcoholic fatty liver disease (NAFLD). Currently available therapies have limitations; hence there is a need to screen new molecules. Plumbagin is a naphthoquinone present in the roots of *Plumbago* species which has hypolipidemic and hepatoprotective activities. METHODS: Rats were divided into five groups: normal control, disease control, orlistat, plumbagin (0.5 mg/kg and 1 mg/kg body weight). The normal control group received standard diet and drinking water while the remaining groups received fructose in drinking water alongwith the standard diet for 16 weeks. Orlistat and plumbagin were administered orally from the 9(th) week-16(th) week. The body weight, calorie intake and weights of visceral adipose tissue and liver were determined. Blood glucose, insulin, lipid profile and liver function tests were determined. Antioxidant and inflammatory parameters, lipids and collagen were determined in the liver. Gene expression of SREBP-1c and PPAR-alpha were determined in the liver. The histopathology of the adipose tissue and liver were also studied. RESULTS: Fructose feeding resulted in a significant increase in the body weight gain, calorie intake, visceral fat, liver weight, blood glucose and insulin and caused dyslipidemia which was mitigated by plumbagin. Plumbagin exerted antioxidant, anti-inflammatory and anti-fibrotic effects in the liver and reduced the hepatic lipids. Plumbagin reduced the gene expression of SREBP-1c and increased that of PPAR-alpha. Plumbagin reduced the hypertrophy of adipocytes and

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ameliorated the degenerative changes in the liver. CONCLUSION: Plumbagin thus seems to be a promising molecule for the management of obesity and NAFLD.

[7] Raafat SN. **Response to letter to the editor: The sole and combined effect of simvastatin and platelet rich fibrin as a filling material in induced bone defect in tibia of albino rats.** Bone 2018.

PM: <http://www.ncbi.nlm.nih.gov/pubmed/?term=30612981>

ABSTRACT

[8] Seidah NG, Prat A, Pirillo A et al. **Novel strategies to target PCSK9: beyond monoclonal antibodies.** Cardiovascular research 2019.

PM: <http://www.ncbi.nlm.nih.gov/pubmed/?term=30629143>

ABSTRACT

Since the discovery of the role of PCSK9 in the regulation of low density lipoprotein-cholesterol (LDL-C) in 2003 a paradigm shift in the treatment of hypercholesterolemia has occurred. The PCSK9 secreted into the circulation is a major downregulator of the LDL-receptor (LDLR) protein, as it chaperones it to endosomes/lysosomes for degradation. Humans with loss-of-function of PCSK9 exhibit exceedingly low levels of LDL-C and are protected from atherosclerosis. As a consequence, innovative strategies to modulate the levels of PCSK9 have been developed. Since 2015 inhibitory monoclonal antibodies (evolocumab and alirocumab) are commercially available. When subcutaneously injected every 2-4 weeks, they trigger a approximately 60% LDL-C lowering and a 15% reduction in the risk of cardiovascular events. Another promising approach consists of a liver-targetable specific PCSK9 siRNA which results in approximately 50-60% LDL-C lowering that lasts up to 6 months (phase II-III clinical trials). Other strategies under consideration include: (i) antibodies targeting the C-terminal domain of PCSK9, thereby inhibiting the trafficking of PCSK9-LDLR to lysosomes; (ii) small molecules that either prevent PCSK9 binding to the LDLR, its trafficking to lysosomes or its secretion from cells; (iii) complete silencing of PCSK9 by CRISPR-Cas9 strategies; (iv) PCSK9 vaccines that inhibit the activity of circulating PCSK9. Time will tell whether other strategies can be as potent and safe as monoclonal antibodies to lower LDL-C levels.

[9] Navar AM, Roe MT, White JA et al. **Medication Discontinuation in the IMPROVE-IT Trial.** Circulation. Cardiovascular quality and outcomes 2019; 12:e005041.

PM: <http://www.ncbi.nlm.nih.gov/pubmed/?term=30630361>

ABSTRACT

BACKGROUND: Although cholesterol-lowering medications can reduce the risk of recurrent cardiovascular events, premature discontinuation limits effectiveness. Discontinuation rates have not been systematically reported for lipid-lowering trials. METHODS AND RESULTS: We evaluated medication discontinuation in IMPROVE-IT (Improved Reduction of Outcomes: Vytorin Efficacy International Trial), which evaluated placebo+simvastatin versus ezetimibe+simvastatin in patients hospitalized with the acute coronary syndrome and followed longitudinally postdischarge. Reasons for discontinuation were evaluated from randomization through study end (median 71.9 [interquartile range 51.8-85.8] months). Kaplan-Meier (KM) discontinuation rates were evaluated at 30 days, 1 year,

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and through year 7, and compared by treatment arm and region, with Cox proportional hazards modeling used to evaluate predictors of discontinuation. Overall, 46.7% of subjects discontinued study medication (KM rate by study end 50.9% [95% CI, 50.1%-51.7%]). The risk of discontinuation was highest early in the trial but decreased with increasing time, with a terminal KM rate per 100 person-years of 8.4 (8.2-8.6) from years 1 to 7. Discontinuation was higher in the placebo+simvastatin versus ezetimibe+simvastatin arm (KM rate 52.0% versus 49.8%, $P=0.049$) and was highest in the United States (7-year KM rate 57.4%). In multivariable modeling, smoking, prior revascularization, hypertension, unstable angina, female sex, nonwhite race, and US location were associated with higher discontinuation rates. **CONCLUSIONS:** Although discontinuation was highest early and stabilized to 8% per year, because of prolonged follow-up, most discontinuation occurred after year 1. Adding ezetimibe to statin therapy did not increase discontinuation risk. Geographic differences and patient-level factors should be considered in trial design and analysis. **CLINICAL TRIAL REGISTRATION:** URL: <https://www.clinicaltrials.gov> . Unique identifier: NCT00202878.

[10] *Ronnqvist J, Hallberg P, Yue QY, Wadelius M. Fusidic Acid: A Neglected Risk Factor for Statin-Associated Myopathy. Clinical Medicine Insights. Cardiology* 2018; 12:1179546818815162.

PM: <http://www.ncbi.nlm.nih.gov/pubmed/?term=30618488>

ABSTRACT

Background: Statins are widely used lipid-lowering drugs used for the prevention of cardiovascular disease. Statins are known to cause myopathy, an adverse drug reaction with various clinical features rhabdomyolysis. **Objective:** To describe clinical characteristics of statin-treated individuals who experienced myopathy and identify risk factors of statin-associated myopathy. **Methods:** A retrospective study was conducted on cases of statin-associated myopathy reported to the Swedish Medical Products Agency. Clinical factors were compared between cases and statin-treated controls not diagnosed with myopathy. Statistical methods were univariate and multivariate logistic regression and results were presented as odds ratio (OR) with 95% confidence interval (CI). To correct for multiple comparisons, the cutoff for statistical significance was set to $P < .0017$. **Results:** In total, 47 cases of statin-associated myopathy were compared with 3871 treated controls. Rhabdomyolysis was diagnosed in 51% of the cases. Markers for cardiovascular disease were more common in cases than controls. Statistical analysis revealed the following independent risk factors for myopathy: high statin dose (OR = 1.54, calculated using the standard deviation 19.82, 95% CI = 1.32-1.80, $P < .0001$), and concomitant treatment with fusidic acid (OR = 1002, 95% CI = 54.55-18 410, $P < .0001$), cyclosporine (OR = 34.10, 95% CI = 4.43-262.45, $P = .0007$), and gemfibrozil (OR = 12.35, 95% CI = 2.38-64.10, $P = .0028$). **Conclusions:** The risk of myopathy increases with statin dose and cotreatment with cyclosporine and gemfibrozil. Concomitant fusidic acid has previously only been noted in a few case reports. Considering that use of fusidic acid may become more frequent, it is important to remind of this risk factor for statin-associated myopathy.

[11] *Orekhov AN, Grechko AV, Romanenko EB et al. Novel approaches to anti-atherosclerotic therapy: Cell-based models and herbal preparations (Review of our own data). Curr Drug Discov Technol* 2018.

PM: <http://www.ncbi.nlm.nih.gov/pubmed/?term=30621565>

ABSTRACT

Atherosclerosis is a chronic arterial disease characterized by vascular inflammation, accumulation of lipids in the arterial wall, and formation and growth of atherosclerotic plaques followed by ischemia. In

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subclinical atherosclerosis, cholesterol retention in subendothelial cells leads to induction of local inflammation, generation of foam cells and lesion formation, followed by a chain of other pathogenic events. Atherosclerotic progression can frequently be fatal, since plaque rupture may lead to thrombosis and acute events, such as myocardial infarction, stroke and sudden death. Traditional anti-atherosclerotic therapy is mainly focused on improving blood lipid profile and does not target various stages of plaque progression. Obviously, treating the disease at initial stages is better than beginning treatment at advanced stages and, in that regard, current atherosclerosis management can be improved. Cholesterol retention is an important component of atherogenesis that precedes plaque formation. Therapeutic targeting of cholesterol retention may be beneficial for preventing further atherogenic progression. For this purpose, we suggest using herbal preparations due to good tolerability and suitability for long-lasting treatment. We developed test systems based on cultured human intimal aortic cells for rapid screening of potential anti-atherogenic drugs. With the help of these test systems, we selected several natural substances with significant anti-atherogenic activity and further use these compounds to prepare herbal preparations for anti-atherosclerotic therapy. These preparations were clinically tested and showed good safety and a potent anti-atherogenic potential.

[12] *Jamil A, Mirza MA, Anwer K et al. Co-delivery of Gemcitabine and Simvastatin through PLGA polymeric nanoparticles for the treatment of pancreatic cancer: In-vitro characterization, cellular uptake and pharmacokinetic studies. Drug development and industrial pharmacy* 2019;1-34.

PM: <http://www.ncbi.nlm.nih.gov/pubmed/?term=30632800>

ABSTRACT

Despite the ongoing extensive research, cancer therapeutics still remains an area with unmet needs which is hampered by shortfall in the development of newer medicines. The present study discusses a nano-based combinational approach for treating solid tumor. Dual loaded nanoparticles encapsulating gemcitabine HCl (GM) and simvastatin (SV) was fabricated by double emulsion solvent evaporation method and optimized. Optimized nanoparticles showed a particle size of 258 +/- 2.4 nm, PDI of 0.32 +/- 0.052 and zeta potential of -12.5 mV. The size and the morphology of the particles were further confirmed by transmission electron microscopy (TEM) and scanning electron microscopy (SEM) respectively of the particles. The entrapment efficiency of GM and SV in the NPs was 38.5 +/- 4.5% and 72.2 +/- 5.6%, respectively. The in vitro release profile was studied for 60 hours and showed Higuchi release pattern. The cell toxicity was done using MTT assay and lower IC50 was obtained with the nanoparticles as compared to the pure drug. The bioavailability of GM and SV in PLGA nanoparticles were enhanced by 1.4 fold and 1.3 fold respectively, compared to drug solution. The results revealed that co-delivery of GM and SV could be used for its oral delivery for the effective treatment of pancreatic cancer.

[13] *Itkonen MK, Tornio A, Neuvonen M et al. Clopidogrel and Gemfibrozil Strongly Inhibit the CYP2C8-dependent Formation of 3-Hydroxydesloratadine and Increase Desloratadine Exposure In Humans. Drug metabolism and disposition: the biological fate of chemicals* 2019.

PM: <http://www.ncbi.nlm.nih.gov/pubmed/?term=30630815>

ABSTRACT

A recent in vitro study suggested that CYP2C8 is essential in the metabolism of desloratadine, a H1 receptor antagonist. If the proposed biotransformation mechanism takes place in vivo in humans,

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desloratadine could serve as a selective CYP2C8 probe substrate in drug-drug interaction studies. Glucuronide metabolites of clopidogrel and gemfibrozil act as time-dependent inhibitors of CYP2C8, but they have not been compared clinically. We conducted a randomized cross-over study in eleven healthy subjects to characterize the involvement of CYP2C8 in desloratadine metabolism and to compare the CYP2C8 inhibitory strength of clopidogrel (300 mg, and 75 mg on 2 following days) with that of gemfibrozil (600 mg b.i.d. for five days). Compared with placebo (control), clopidogrel increased the area under the plasma concentration-time curve (AUC_{0-infinity}) and peak concentration (C_{max}) of desloratadine to 280% (P = 310(-7)) and 165% (P = 0.0006), respectively. The corresponding increases by gemfibrozil were to 462% (P = 410(-7)) and 174% (P = 0.0006). Compared with placebo, clopidogrel and gemfibrozil decreased 3-hydroxylopratadine AUC_{0-71h} to 52% (P = 510(-5)) and 6% (P = 210(-8)). Moreover, the 3-hydroxydesloratadine:desloratadine AUC_{0-71h} ratios were 21% (P = 710(-10)) and 1.7% (P = 810(-11)) of control during the clopidogrel and gemfibrozil phases. Our results confirm that CYP2C8 plays a critical role in the formation of 3-hydroxydesloratadine in humans, making desloratadine a potential CYP2C8 probe substrate. Furthermore, the findings corroborate the previous estimates that clinically relevant doses of clopidogrel cause strong CYP2C8 inhibition, while those of gemfibrozil almost completely inactivate the enzyme in humans.

[14] *Yandrapalli S, Gupta S, Andries G et al. Drug Therapy of Dyslipidemia in the Elderly. Drugs Aging 2019.*

PM: <http://www.ncbi.nlm.nih.gov/pubmed/?term=30613912>

ABSTRACT

Abnormal lipoprotein metabolism is an important and modifiable risk factor for atherosclerotic cardiovascular disease (ASCVD), which has been shown in numerous studies to lead to adverse cardiovascular outcomes. As cardiovascular disease (CVD) remains the major cause of morbidity and mortality globally, management of dyslipidemia is a key component of primary and secondary risk-reduction strategies. Because ASCVD risk increases with age, as the population ages, many more people—particularly the elderly—will meet guideline criteria for drug treatment. Statins (HMG-CoA reductase inhibitors) have an unequivocal benefit in reducing ASCVD risk across age groups for secondary prevention. However, the benefit of these drugs for primary prevention in those > 75 years of age remains controversial. We strongly believe that statins should be offered for primary prevention to all older individuals after a shared decision-making process that takes polypharmacy, frailty, and potential adverse effects into consideration. When considering statin therapy in the very old, competing risks of death, and therefore the likelihood that patients will live long enough to benefit from drug therapy, should inform this process. Combination therapies with ezetimibe or proprotein convertase subtilisin-kexin type 9 (PCSK9) inhibitors should be considered to facilitate the use of tolerable doses of statins. Future investigations of dyslipidemia therapies must appropriately include this at-risk population to identify optimal drugs and drug combinations that have a high benefit:risk ratio for the prevention of ASCVD in the elderly.

[15] *Schwartz SM, Virmani R, Majesky MW. An update on clonality: what smooth muscle cell type makes up the atherosclerotic plaque? F1000Research 2018; 7.*

PM: <http://www.ncbi.nlm.nih.gov/pubmed/?term=30613386>

ABSTRACT

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Almost 50 years ago, Earl Benditt and his son John described the clonality of the atherosclerotic plaque. This led Benditt to propose that the atherosclerotic lesion was a smooth muscle neoplasm, similar to the leiomyomata seen in the uterus of most women. Although the observation of clonality has been confirmed many times, interest in the idea that atherosclerosis might be a form of neoplasia waned because of the clinical success of treatments for hyperlipemia and because animal models have made great progress in understanding how lipid accumulates in the plaque and may lead to plaque rupture. Four advances have made it important to reconsider Benditt's observations. First, we now know that clonality is a property of normal tissue development. Second, this is even true in the vessel wall, where we now know that formation of clonal patches in that wall is part of the development of smooth muscle cells that make up the tunica media of arteries. Third, we know that the intima, the "soil" for development of the human atherosclerotic lesion, develops before the fatty lesions appear. Fourth, while the cells comprising this intima have been called "smooth muscle cells", we do not have a clear definition of cell type nor do we know if the initial accumulation is clonal. As a result, Benditt's hypothesis needs to be revisited in terms of changes in how we define smooth muscle cells and the quite distinct developmental origins of the cells that comprise the muscular coats of all arterial walls. Finally, since clonality of the lesions is real, the obvious questions are do these human tumors precede the development of atherosclerosis, how do the clones develop, what cell type gives rise to the clones, and in what ways do the clones provide the soil for development and natural history of atherosclerosis?

[16] *McGlory C, Gorissen SHM, Kamal M et al. Omega-3 fatty acid supplementation attenuates skeletal muscle disuse atrophy during two weeks of unilateral leg immobilization in healthy young women. FASEB journal : official publication of the Federation of American Societies for Experimental Biology 2019:fj201801857RRR.*

PM: <http://www.ncbi.nlm.nih.gov/pubmed/?term=30629458>

ABSTRACT

Omega-3 (n-3) fatty acid supplementation enhances muscle protein synthesis and muscle size. Whether n-3 fatty acid supplementation attenuates human muscle disuse atrophy is unknown. We determined the influence of n-3 fatty acid supplementation on muscle size, mass, and integrated rates of myofibrillar protein synthesis (MyoPS) following 2 wk of muscle disuse and recovery in women. Twenty women (BMI = 23.0 +/- 2.3 kg/m², age = 22 +/- 3 yr) underwent 2 wk of unilateral limb immobilization followed by 2 wk of return to normal activity. Starting 4 wk prior to immobilization, participants consumed either 5 g/d of n-3 fatty acid or an isoenergetic quantity of sunflower oil (control). Muscle size and mass were measured pre- and postimmobilization, and after recovery. Serial muscle biopsies were obtained to measure integrated (daily) MyoPS. Following immobilization, the decline in muscle volume was greater in the control group compared to the n-3 fatty acid group (14 vs. 8%, P < 0.05) and was not different from preimmobilization at recovery in the n-3 fatty acid group; however, it was still lower in the control group (P < 0.05). Muscle mass was reduced in the control group only (P < 0.05). MyoPS was higher in the n-3 group compared with the control group at all times (P < 0.05). We conclude that n-3 fatty acid supplementation attenuates skeletal muscle disuse atrophy in young women, which may be mediated by higher rates of MyoPS.-McGlory, C., Gorissen, S. H. M., Kamal, M., Bahniwal, R., Hector, A. J., Baker, S. K., Chabowski, A., Phillips, S. M. Omega-3 fatty acid supplementation attenuates skeletal muscle disuse atrophy during two weeks of unilateral leg immobilization in healthy young women.

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[17] *van der Veen JN, Lingrell S, McCloskey N et al. A role for phosphatidylcholine and phosphatidylethanolamine in hepatic insulin signaling. FASEB journal : official publication of the Federation of American Societies for Experimental Biology 2019:fj201802117R.*

PM: <http://www.ncbi.nlm.nih.gov/pubmed/?term=30615497>

ABSTRACT

Phosphatidylethanolamine N-methyltransferase (PEMT) is an important enzyme in hepatic phosphatidylcholine (PC) biosynthesis. *Pemt*(-/-) mice fed a high-fat diet are protected from obesity and whole-body insulin resistance. However, *Pemt*(-/-) mice develop severe nonalcoholic steatohepatitis (NASH). Because NASH is often associated with hepatic insulin resistance, we investigated whether the increased insulin sensitivity in *Pemt*(-/-) mice was restricted to nonhepatic tissues or whether the liver was also insulin sensitive. Strikingly, the livers of *Pemt*(-/-) mice compared with those of *Pemt*(+/+) mice were not insulin resistant, despite elevated levels of hepatic triacylglycerols and diacylglycerols, as well as increased hepatic inflammation and fibrosis. Endogenous glucose production was lower in *Pemt*(-/-) mice under both basal and hyperinsulinemic conditions. Experiments in primary hepatocytes and hepatoma cells revealed improved insulin signaling in the absence of PEMT, which was not due to changes in diacylglycerols, ceramides, or gangliosides. On the other hand, the phospholipid composition in hepatocytes seems critically important for insulin signaling such that lowering the PC:phosphatidylethanolamine (PE) ratio improves insulin signaling. Thus, treatments to reduce the PC:PE ratio in liver may protect against the development of hepatic insulin resistance.-Van der Veen, J. N., Lingrell, S., McCloskey, N., LeBlond, N. D., Galleguillos, D., Zhao, Y. Y., Curtis, J. M., Sipione, S., Fullerton, M. D., Vance, D. E., Jacobs, R. L. A role for phosphatidylcholine and phosphatidylethanolamine in hepatic insulin signaling.

[18] *Summerhill V, Karagodin V, Grechko A et al. Vasculoprotective Role of Olive Oil Compounds via Modulation of Oxidative Stress in Atherosclerosis. Frontiers in cardiovascular medicine 2018; 5:188.*

PM: <http://www.ncbi.nlm.nih.gov/pubmed/?term=30622950>

ABSTRACT

Existing evidence supports the significant role of oxidative stress in the endothelial injury, and there is a direct link between increased oxidative stress, and the development of endothelial dysfunction. Endothelial dysfunction precedes the development of atherosclerosis and subsequent cardiovascular disease (CVD). The overproduction of reactive oxygen species facilitates the processes, such as oxidative modification of low-density lipoproteins and phospholipids, reduction in the NOS-derived nitric oxide, and the functional disruption of high-density lipids that are profoundly involved in atherogenesis, inflammation, and thrombus formation in vascular cells. Thus, under oxidative stress conditions, endothelial dysfunction was found to be associated with the following endothelial alterations: reduced nitric oxide bioavailability, increased anticoagulant properties, increased platelet aggregation, increased expression of adhesion molecules, chemokines, and cytokines. In this review, we summarized the evidence indicating that endothelial damage triggered by oxidation can be diminished or reversed by the compounds of olive oil, a readily available antioxidant food source. Olive oil bioactive compounds exhibited a potent capability to attenuate oxidative stress and improve endothelial function through their anti-inflammatory, anti-oxidant, and anti-thrombotic properties, therefore reducing the risk and progression of atherosclerosis. Also, their molecular mechanisms of action were explored to establish the potential preventive and/or therapeutic alternatives to the pharmacological remedies available.

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[19] Zhang J, Shi X, Hao N et al. **Simvastatin Reduces Neutrophils Infiltration Into Brain Parenchyma After Intracerebral Hemorrhage via Regulating Peripheral Neutrophils Apoptosis.** Frontiers in neuroscience 2018; 12:977.

PM: <http://www.ncbi.nlm.nih.gov/pubmed/?term=30631264>

ABSTRACT

Statins, known for their lipid-lowering effects, also have immunomodulatory properties. This study aims to examine whether systematic simvastatin administration could decrease polymorphonuclear neutrophils (PMNs) infiltration into brain tissue, as well as alleviate neuroinflammation in a rat model of intracerebral hemorrhage (ICH). The ICH model was induced in adult male Sprague-Dawley rats by an injection of autologous blood. Animals randomly received simvastatin (i.p. 2 mg/kg) or vehicle daily from 5 days before ICH until sacrificed. Routine blood counts, brain water content, neurological scoring, immunofluorescence and RT-PCR were conducted to evaluate the anti-inflammatory effect of simvastatin following ICH. Furthermore, flow cytometric and western blotting analysis were implemented for elucidating the mechanisms involved in simvastatin-induced reduction of neutrophil brain-invading. Elevated PMNs count and neutrophil-to-lymphocyte ratio in circulation were detected in rat model of ICH, which was reversed by using simvastatin. Simvastatin effectively alleviated PMNs infiltration and proinflammatory factors release in perihematomal area, as well as attenuated ICH-induced brain edema and neurological deficits. Simvastatin significantly downregulated the expression of antiapoptotic protein-Mcl-1 while increased the level of proapoptotic protein-Bax and cleaved caspase 3 in PMNs. Simvastatin treatment significantly alleviated PMNs brain-infiltrating and subsequent neuroinflammatory reaction after ICH, in part by accelerating peripheral PMNs apoptosis through disorganized the expression of apoptotic related proteins. Our data provided new evidence for simvastatin application on patients with ICH.

[20] Suguro R, Chen S, Yang D et al. **Anti-hypercholesterolemic Effects and a Good Safety Profile of SCM-198 in Animals: From ApoE Knockout Mice to Rhesus Monkeys.** Frontiers in pharmacology 2018; 9:1468.

PM: <http://www.ncbi.nlm.nih.gov/pubmed/?term=30618759>

ABSTRACT

Although several lipid-lowering agents have been introduced for the treatment of atherosclerosis (AS), currently marketed medications have not solved the problem completely. This study aims to investigate the effects of leonurine (SCM-198) on dyslipidemia in mammals with ApoE knockout (ApoE(-/-)) mice, New Zealand white rabbits and senile Rhesus monkeys fed with high fat diet were dosed daily with leonurine or atorvastatin. The serum total cholesterol (TC), triglyceride (TG), low density lipoprotein (LDL), and high-density lipoprotein (HDL) were determined. Moreover, in Rhesus monkeys, bodyweight, arterial ultrasound of right common carotid artery, Apolipoprotein A1 (ApoA1) and ApoB levels, hematologic and toxicological examinations were detected. Serum TC and TG in both mice and rabbits were significantly reduced by SCM-198 and atorvastatin. In the 10 mg/kg SCM-198 group of monkeys, maximum TC reduction of 24.05% was achieved at day 150, while 13.16% LDL reduction achieved at day 60, without arterial morphologic changes or adverse events. Atorvastatin (1.2 mg/kg) showed similar effects as SCM-198 in improving lipid profiles in monkeys, yet its long-term use could induce tolerance. Furthermore, leonurine suppressed genes expression of fatty acid synthesis, such as fatty acid synthase (FASN), stearoyl-CoA desaturase (SCD-1), sterol regulatory element-binding protein (SREBF) in liver in

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high fat diet feeding ApoE(-/-) mice. SCM-198, with a reliable safety profile, is of high value in improving lipid profiles in mammals, providing an alternative to a substantial population who are statin-intolerant.

[21] Matsuo K, Hom MS, Yabuno A et al. **Association of statins, aspirin, and venous thromboembolism in women with endometrial cancer.** *Gynecologic oncology* 2019.

PM: <http://www.ncbi.nlm.nih.gov/pubmed/?term=30616901>

ABSTRACT

OBJECTIVE: The anti-thrombogenic effects of statins and aspirin have been reported in various malignancies but have not been well examined in endometrial cancer. This study examined the association between statin and/or aspirin use and venous thromboembolism (VTE) risk in endometrial cancer. METHODS: This is a multi-center retrospective study examining 2527 women with endometrial cancer between 2000 and 2015. Statin and aspirin use at diagnosis was correlated to VTE risk during follow-up on multivariable analysis. RESULTS: There were 132 VTE events with a 5-year cumulative incidence rate of 6.1%. There were 392 (15.5%) statin users and 219 (8.7%) aspirin users, respectively. On multivariable analysis, statin use was associated with an approximately 60% decreased risk of VTE when compared to non-users (5-year cumulative rates 2.5% versus 6.7%, adjusted-hazard ratio [HR] 0.42, 95% confidence interval [CI] 0.19-0.92, P=0.030) whereas aspirin did not demonstrate statistical significance (2.0% versus 6.5%, adjusted-HR 0.54, 95%CI 0.19-1.51, P=0.24). There was a trend of joint effect between statin and aspirin although it did not demonstrate statistical significance: VTE risks for dual statin/aspirin user (adjusted-HR 0.27, 95%CI 0.04-2.07), statin alone (adjusted-HR 0.40, 95%CI 0.18-0.93), and aspirin alone (adjusted-HR 0.51, 95%CI 0.16-1.64) compared to non-use after adjusting for patient characteristics, tumor factors, treatment types, and survival events (P-interaction=0.090). When stratified by statin type, simvastatin demonstrated the largest reduction of VTE risk (5-year cumulative rates 1.1% versus 6.7%, adjusted-HR 0.17, 95%CI 0.02-1.30, P=0.088). Obesity, absence of diabetes mellitus, type II histology, and recurrent disease were the factors associated with decreased VTE risk with statin use (all, P-interaction<0.05). CONCLUSION: Our study suggests that statin use may be associated with decreased risk of VTE in women with endometrial cancer.

[22] Bass A, Plotka A, Mridha K et al. **Pharmacokinetics, pharmacodynamics, and safety of bococizumab, a monoclonal antibody against proprotein convertase subtilisin/kexin type 9, in healthy subjects when administered in co-mixture with recombinant human hyaluronidase: A phase 1 randomized trial.** *Health science reports* 2018; 1:e61.

PM: <http://www.ncbi.nlm.nih.gov/pubmed/?term=30623096>

ABSTRACT

Aim: Prior to the discontinuation of bococizumab's clinical development, it was considered advantageous to develop an infrequent dosing regimen (eg, monthly). Therefore, we conducted a phase 1 study to evaluate the pharmacokinetics, pharmacodynamics, and safety of bococizumab when administered in co-mixture with recombinant human hyaluronidase (rHuPH20). Method: Healthy subjects (N = 60) were randomized equally among 4 groups that received a single subcutaneous dose of either bococizumab 150, 300, or 450 mg co-mixed with rHuPH20 or bococizumab 300 mg alone. Bioavailability and lipid-lowering effect of bococizumab were evaluated by using ANCOVA models. Results: In the groups administered bococizumab co-mixed with rHuPH20, dose-normalized C max and AUCinf were 26.6 to 39.1% and 18.3 to 36.6% greater, respectively, compared with bococizumab 300 mg

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alone. Despite these increases, mean percent reductions from baseline in low-density lipoprotein cholesterol were smaller in the bococizumab 300 mg + rHuPH20 group than in the bococizumab 300-mg group at Day 21 (52.2% and 59.5%, respectively) and were similar at Day 29 (51.7% and 49.6%, respectively). Compared with the group administered bococizumab 300 mg alone, the bococizumab 300 mg + rHuPH20 group did not show a significantly altered AUEC85 (ratio of adjusted means: 102.5%, 90% confidence interval: 96.1-109.3%) but did show a higher MaxELDL-C (ratio of adjusted means: 125.4%, 90% confidence interval: 103.3-152.2%), indicating diminution of efficacy. The most frequent adverse events were injection-site erythema, injection-site bruising, and nasopharyngitis; all injection-site adverse events were mild. Conclusion: Co-mixture with rHuPH20 increased the bioavailability of bococizumab without proportional increase in pharmacodynamic effect. Trial Registration: ClinicalTrials.gov, NCT02667223.

[23] Li Z, Huang Q, Sun L et al. **Atherogenic Index in Type 2 Diabetes and Its Relationship with Chronic Microvascular Complications.** *Int J Endocrinol* 2018; 2018:1765835.

PM: <http://www.ncbi.nlm.nih.gov/pubmed/?term=30627157>

ABSTRACT

Objective: This study was designed to investigate risk factors related to atherogenic index of plasma (AIP), as well as the relationship between AIP and chronic microvascular complications in patients with type 2 diabetes (T2DM). Methods: This study included 2523 patients with T2DM who had not been treated with lipid-lowering drugs and were admitted to the Department of Endocrinology at Zhongnan Hospital, Wuhan University, during the period from January 2015 to February 2018. Anthropometric indicators were measured after overnight fasting. Low-density lipoprotein cholesterol (LDL-C), high-density lipoprotein cholesterol (HDL-C), total cholesterol (TC), and triglyceride (TG) were detected by enzymatic analysis. Standard 75 g oral glucose tolerance testing was performed to measure 0 and 2 hr plasma levels of glucose and insulin. Insulin sensitivity was assessed with HOMA-IR. Results: Increase in AIP was associated with an increased risk for hypertension ($P < 0.05$), HbA1c ($P < 0.05$), HOMA-IR ($P < 0.05$), UA ($P < 0.05$), and decreased eGFR levels ($P < 0.05$). Furthermore, AIP values directly correlated with BMI ($r = 0.182$, $P < 0.001$), waist circumference ($r = 0.129$, $P < 0.001$), blood glucose index (FBG ($r = 0.153$, $P < 0.001$), PPBG ($r = 0.117$, $P < 0.001$), and HbA1c ($r = 0.074$, $P < 0.001$)), insulin resistance (HOMA-IR; $r = 0.112$, $P < 0.001$), and uric acid (UA, $r = 0.177$, $P < 0.001$). Multiple logistic regression analysis showed that waist circumference, HOMA-IR, FBG, systolic blood pressure, and UA were independent risk factors for AIP (all $P < 0.05$). The prevalence of diabetic neuropathy and metabolic syndrome was significantly higher among patients with higher AIP. Conclusion: AIP represents a clinically convenient indicator for the detection of T2DM with high risk of complications and associated diseases and thus is a good predictor and indicator for follow-up monitoring in the treatment of patients with high-risk type 2 diabetes.

[24] Heller M, Gemming L, Tung C, Grant R. **Oxidation of fish oil supplements in Australia.** *International journal of food sciences and nutrition* 2019:1-11.

PM: <http://www.ncbi.nlm.nih.gov/pubmed/?term=30626234>

ABSTRACT

Fish oils oxidise readily, forming primary and secondary oxidation products, which may be harmful for humans. Some recent studies reported that fish oil supplements in Australasia are oxidised above

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acceptable international limits, however other studies reported low levels of oxidation. This study employed peroxide and p-anisidine values determination to measure primary and secondary oxidation of fish oils in the Australian market. Of 26 supplements tested, 38% exceeded the limit for primary oxidation, 25% exceeded the limit for secondary oxidation and 33% exceeded the limit for total oxidation, according to international recommendations. Four specially marketed supplements were found to deliver significantly lower amounts of fish oil per capsule (165 vs. 577 mg, $p = .007$), yet cost significantly more on a per gram basis (\$2.97 vs \$0.39, $p < .001$). However, there were no differences in any oxidative markers between regular supplements and the specially marketed products.

[25] *Bordicchia M, Spannella F, Ferretti G et al. PCSK9 is Expressed in Human Visceral Adipose Tissue and Regulated by Insulin and Cardiac Natriuretic Peptides. International journal of molecular sciences 2019; 20.*

PM: <http://www.ncbi.nlm.nih.gov/pubmed/?term=30634533>

ABSTRACT

Proprotein convertase subtilisin/kexin type 9 (PCSK9) binds to and degrades the low-density lipoprotein receptor (LDLR), contributing to hypercholesterolemia. Adipose tissue plays a role in lipoprotein metabolism, but there are almost no data about PCSK9 and LDLR regulation in human adipocytes. We studied PCSK9 and LDLR regulation by insulin, atrial natriuretic peptide (ANP, a potent lipolytic agonist that antagonizes insulin), and LDL in visceral adipose tissue (VAT) and in human cultured adipocytes. PCSK9 was expressed in VAT and its expression was positively correlated with body mass index (BMI). Both intracellular mature and secreted PCSK9 were abundant in cultured human adipocytes. Insulin induced PCSK9, LDLR, and sterol-regulatory element-binding protein-1c (SREBP-1c) and -2 expression (SREBP-2). ANP reduced insulin-induced PCSK9, especially in the context of a medium simulating hyperglycemia. Human LDL induced both mature and secreted PCSK9 and reduced LDLR. ANP indirectly blocked the LDLR degradation, reducing the positive effect of LDL on PCSK9. In conclusion, PCSK9 is expressed in human adipocytes. When the expression of PCSK9 is induced, LDLR is reduced through the PCSK9-mediated degradation. On the contrary, when the induction of PCSK9 by insulin and LDL is partially blocked by ANP, the LDLR degradation is reduced. This suggests that NPs could be able to control LDLR levels, preventing PCSK9 overexpression.

[26] *Chaves LO, Carraro JCC, Vidigal FC, Bressan J. Higher Waist Circumference Is Related to Lower Plasma Polyunsaturated Fatty Acids in Healthy Participants: Metabolic Implications. Journal of the American College of Nutrition 2019:1-9.*

PM: <http://www.ncbi.nlm.nih.gov/pubmed/?term=30620245>

ABSTRACT

OBJECTIVE: We evaluated whether the relationship between waist circumference (WC) and cardiometabolic risk is related to usual diet and plasma fatty acid composition. METHODS: This cross-sectional study included 226 health professionals from 20 to 59 years old. Anthropometric features, oxidative stress, inflammatory markers, and plasma fatty acid profile were assessed. Dietary intake was evaluated with a semi-quantitative food frequency questionnaire, the quality of dietary habits by Healthy Eating Index, and insulin resistance by homeostasis model assessment-insulin resistance and triglyceride-glucose index. RESULTS: Higher WC was associated with lower concentrations of high-density lipoprotein cholesterol ($p = 0.000$) and adiponectin ($p = 0.000$) and higher uric acid levels ($p =$

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0.011). Plasma polyunsaturated fatty acid (PUFA) levels were negatively associated with weight ($p = 0.046$), systolic blood pressure ($p = 0.035$), fasting glucose ($p = 0.000$), triglyceride-glucose index ($p = 0.023$), and IL-1beta ($p = 0.037$). Individuals with elevated WC consumed more calories ($p = 0.002$), niacin ($p = 0.002$), and pyridoxine ($p = 0.017$), but less calcium ($p = 0.001$), phosphorus ($p = 0.016$), and vitamin B2 ($p = 0.011$). In addition, individuals with higher WC denoted lower PUFA concentrations ($p = 0.036$). CONCLUSION: The results suggest that participants with higher WC have lower plasma PUFA concentrations and higher levels of saturated fatty acids. This could be related to metabolic and inflammatory changes that could trigger increased risk of metabolic syndrome and cardiovascular disease.

[27] Lu M, Cui Y, Peng P et al. **Shape and Location of Carotid Atherosclerotic Plaque and Intraplaque Hemorrhage: A High-resolution Magnetic Resonance Imaging Study.** Journal of atherosclerosis and thrombosis 2019.

PM: <http://www.ncbi.nlm.nih.gov/pubmed/?term=30626781>

ABSTRACT

AIM: The present study aimed to investigate the association between shape and location of atherosclerotic plaques and intraplaque hemorrhage (IPH) in carotid arteries using magnetic resonance (MR) imaging. METHODS: Overall, 114 symptomatic patients (mean age: 64.9+/-10.9 years; 81 males) who underwent MR imaging and had advanced carotid plaques were included in analysis. IPH presence and carotid plaque shape and location (below and above bifurcation) were evaluated. The plaque shape was defined as follows: type-I: the arc-length of plaque is greater in the upstream; type-II: the arc-length of plaque in downstream and upstream is equal; and type-III: the arc-length of plaque is greater in downstream. The plaque shape and location were compared between plaques with and without IPH and their associations with IPH were determined. RESULTS: Of 181 detected plaques, 57 (31.5%) had IPH. Compared with plaques without IPH, those with IPH had higher incidence of the plaque shape of type-I (66.7% vs. 32.2%, $P=0.001$), lower incidence of plaque shape of type-III (24.6% vs. 50.0%, $P=0.001$), and were more likely located above carotid bifurcation (71.9% vs. 48.4%, $P=0.003$). The plaque shape of type-I (OR, 4.01; 95%CI, 1.36-11.83; $P=0.012$) and location above bifurcation (OR, 3.21; 95%CI, 1.07-9.61; $P=0.037$) of carotid plaques were significantly associated with IPH after adjusting for confounder factors. CONCLUSIONS: Carotid plaque shape and location are significantly associated with the occurrence of IPH. Our findings could provide new insights for the pathogenesis of IPH and vulnerably plaques.

[28] Naz S, Saleem MW, Haider AW. **Angioedema; An Unreported Adverse Effect Of Pitavastatin.** Journal of Ayub Medical College, Abbottabad : JAMC 2018; 30:603-604.

PM: <http://www.ncbi.nlm.nih.gov/pubmed/?term=30632346>

ABSTRACT

Angioedema is a life-threatening reaction characterized by swelling of the face, lips, tongue or larynx. Known adverse effects of Pitavastatin do not include angioedema. We report first case of a 55-year-old Asian male developing post exposure angioedema to 2 mg Pitavastatin. Note that the patient showed no history of hypersensitivity. Relationship between Pitavastatin and angioedema was assessed by Naranjo scale.

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[29] *Witkowski A, Carta S, Lu R et al. Oxidation of methionine residues in human apolipoprotein A-I generates a potent pro-inflammatory molecule. The Journal of biological chemistry* 2019.

PM: <http://www.ncbi.nlm.nih.gov/pubmed/?term=30635405>

ABSTRACT

Amyloid deposits of apolipoprotein A-I (apoA-I) and inflammation are common in atherosclerotic arteries. In this study, we investigated the interplay between oxidation of apoA-I methionine residues (Met(O)-ApoA-I), a known amyloidogenic modification of apoA-I, and the inflammatory response of immune cells. Soluble pre-fibrillar Met(O)-ApoA-I, but not apoA-I, induced intracellular accumulation of pro-interleukin (IL)-1beta and secretion of the pro-inflammatory cytokines tumor necrosis factor alpha (TNFalpha) and IL-6 in mouse bone marrow-derived macrophages (BMDMs) and human primary monocytes. Additionally, secretion of mature IL-1beta was also activated in human monocytes. The pro-inflammatory activity of Met(O)-ApoA-I was toll-like receptor 4 (TLR4)-dependent and CD36-independent and was solely determined by oxidation of apoA-I methionine residues, in particular Met-86 and Met-148. In contrast, amyloid fibrils or reconstituted high-density lipoproteins (HDL) generated from Met(O)-ApoA-I did not induce cytokine production in BMDMs. Although lipid-free Met(O)-ApoA-I remained functional in extracting lipids from cells and generating HDL, it gained strong pro-inflammatory properties that may aggravate local inflammation in the arteries and atherosclerosis. Our study indicates that oxidation of apoA-I methionine residues produces a potent danger-associated molecular pattern capable of stimulating pro-inflammatory cytokines secretion at levels similar to those induced by known pathogen-associated molecular patterns, such as lipopolysaccharide.

[30] *Paseban M, Butler AE, Sahebkar A. Mechanisms of statin-induced new-onset diabetes. Journal of cellular physiology* 2019.

PM: <http://www.ncbi.nlm.nih.gov/pubmed/?term=30618154>

ABSTRACT

Statins, with their lipid-lowering properties, are a first-line therapy for the prevention of cardiovascular diseases. Recent evidence, however, suggests that statins can increase the risk of new-onset diabetes (NOD). The molecular mechanisms of statin-induced NOD are not precisely known, although some pathophysiologic mechanisms have been suggested. Specific to the beta cell, these mechanisms include alterations in insulin secretion, changes in ion channels, modulation of signaling pathways, and inflammation/oxidative stress. Outwith the beta cell, other suggested mechanisms involve adipocytes, including alterations in adipocyte differentiation and modulation of leptin and adiponectin, and genetic and epigenetic mechanisms, including alterations in microRNA. The evidence supporting these and other mechanisms will be discussed. Greater understanding of the underlying mechanisms linking the onset of diabetes to statin therapy is essential and clinically relevant, as it may enable novel preventative or therapeutic approaches to be instituted and guide the production of a new generation of statins lacking this side effect.

[31] *Zhang Y, Guo Y, Shen X et al. Lower BMI is of not more benefit to diabetic complications. Journal of diabetes investigation* 2019.

PM: <http://www.ncbi.nlm.nih.gov/pubmed/?term=30628186>

ABSTRACT

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AIM: To investigate the relationship between different body mass index (BMI) levels and vascular complications in type 2 diabetic mellitus (T2DM) patients. METHODS: Data were collected from 3,224 individuals with T2DM (M/F: 1635/1589; age: 61.31+/-11.45 years), using a retrospective case study design. The association of BMI quintiles and DM vascular complications were assessed using multiple logistic regression models adjusting for age, sex, diabetes duration, smoking status, drinking and other confounders, using those with the lowest quintile of BMI as the reference group. RESULTS: With increasing BMI, the detection rate of diabetic peripheral neuropathy (DPN) and peripheral arterial disease (PAD) initially decreased and then it increased, while the detection rate of diabetic kidney disease (DKD) and carotid atherosclerotic plaques showed an upward trend, however the diabetic retinopathy (DR) was irregular. The odds ratios (OR) of DPN decreased as BMI increased from 21th percentile -80th percentile initially, and increased when BMI>80th percentile. The same result was shown in PAD. BMI>80th percentile exhibited a 1.426-fold risk of DKD and a 1.336 -fold risk of carotid atherosclerotic plaque. CONCLUSION: In patients with T2DM, the relationship between different BMIs and vascular complications varies. A U-shaped relationship is observed between BMI and DPN as well as BMI and PAD. BMI is positively correlated with DKD and carotid atherosclerotic plaque; however, it is not correlated with DR. This article is protected by copyright. All rights reserved.

[32] Khan R, Williams A, Dass DM et al. **Investigating the risk of incident diabetes mellitus among primary care patients treated with simvastatin in North-Central Trinidad.** Journal of family medicine and primary care 2018; 7:1555-1560.

PM: <http://www.ncbi.nlm.nih.gov/pubmed/?term=30613558>

ABSTRACT

Aim: To determine the risk of new-onset diabetes mellitus in patients treated with simvastatin at primary healthcare clinics in North Central Trinidad. Materials and Methods: A retrospective descriptive case-series study design was applied to 384 conveniently sampled patient medical records from the cluster of primary healthcare centers during the period of February 2016-May 2016. Information from the patient files were then recorded using a systematic data extraction form. The major inclusion criteria were non-diabetic patients who were compliant with daily simvastatin for a minimum period of 1 year. The risk of incident diabetes mellitus was calculated, using SPSS version 20.0. Chi-squared (χ^2) testing was performed to determine any association between new-onset diabetes mellitus and simvastatin use. Results: In all, 207 patients became diabetic during their treatment period translating into a 53.9% risk of incident diabetes mellitus ($\chi^2 = 2.3438$, $P = 0.1258$). A subgroup analysis of 133 subjects was performed to eliminate the confounders of family history of diabetes and age greater than 60 years. In this subgroup, 50 incident diabetics (37%) were identified and a statistically significant association was observed ($\chi^2 = 8.118$, $P = 0.0042$). Linear regression revealed that this association was dose-dependent with a corresponding 32% higher risk in patients taking 40 mg ($P = 0.001$) of simvastatin daily compared with 20 mg of simvastatin ($P = 0.094$). Linear regression also revealed that there was significant statistical association between onset of diabetes mellitus and duration of statin therapy ($P = 0.006$). Conclusion: In this population, simvastatin use is associated with a 53.9% increased risk of development of new-onset diabetes mellitus ($\chi^2 = 2.3438$, $P = 0.1258$). A statistically significant association was attained after subgroup analysis involving patients less than 60 years old and without a family history of diabetes with an incident risk of 37%. The increased risk of incident diabetes mellitus conferred by higher doses of simvastatin warrants consideration by physicians considering therapies for dyslipidemia in patients with multiple risk factors for diabetes mellitus.

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[33] Deng SJ, Alabi A, Gu HM et al. **Identification of amino acid residues in the ligand binding repeats of LDLR important for PCSK9 binding.** *Journal of lipid research* 2019.

PM: <http://www.ncbi.nlm.nih.gov/pubmed/?term=30617148>

ABSTRACT

Proprotein convertase subtilisin/kexin type 9 (PCSK9) promotes LDL receptor (LDLR) degradation, increasing plasma levels of LDL cholesterol and the risk of cardiovascular disease. We have previously shown that, in addition to the epidermal growth factor precursor homology repeat-A of LDLR, at least three ligand-binding repeats (LRs) of LDLR are required for PCSK9-promoted LDLR degradation. However, how exactly the LRs contribute to PCSK9's action on the receptor is not completely understood. Here, we found that substitution of Asp at position 172 in the linker between the LR4 and LR5 of full-length LDLR with Asn (D172N) reduced PCSK9 binding at pH 7.4 (mimic cell surface) but not at pH 6.0 (mimic endosomal environment). On the other hand, mutation of Asp at position 203 in the LR5 of full-length LDLR to Asn (D203N) significantly reduced PCSK9 binding at both pH 7.4 and pH 6.0. D203N also significantly reduced the ability of LDLR to mediate cellular LDL uptake while D172N had no detectable effect. These findings indicate that amino acid residues in the LRs of LDLR play an important role in PCSK9 binding to the receptor.

[34] Meeuwssen JAL, de Vries JJ, van Duijvenvoorde A et al. **Circulating CD14(+)CD16(-) classical monocytes do not associate with a vulnerable plaque phenotype, and do not predict secondary events in severe atherosclerotic patients.** *Journal of molecular and cellular cardiology* 2019.

PM: <http://www.ncbi.nlm.nih.gov/pubmed/?term=30629987>

ABSTRACT

AIMS: Mouse studies have established distinct monocyte subtypes that participate in the process of atherosclerotic lesion formation. The pro-inflammatory Ly6C(high) monocyte subtype actively contributes to murine plaque progression and destabilization. Also in humans, different peripheral monocyte subtypes have been identified, of which the CD14(+)CD16(-) classical monocyte is suggested to display similar pro-atherosclerotic properties as the murine Ly6C(high) subtype. We aimed to investigate if circulating CD14(+)CD16(-) classical monocytes associate with characteristics of a vulnerable carotid atherosclerotic plaque and if they associate with the risk of secondary adverse manifestations of atherosclerotic disease. METHODS AND RESULTS: We enrolled 175 carotid endarterectomy patients of the Athero-Express biobank in our study. Just prior to surgical procedure, blood was collected and peripheral blood mononuclear cells were isolated. Characterization of monocyte subsets was performed by flow cytometry. Plaque characteristics were semi-quantitatively scored for the presence of fat, collagen, intraplaque hemorrhage and calcification. Vessel density, smooth muscle cells and macrophages were assessed quantitatively on a continuous scale. All features of a vulnerable plaque phenotype, including low amounts of collagen and smooth muscle cells, and increased fat content, vessel density, intraplaque hemorrhage and plaque macrophages were not significantly associated with differential levels of peripheral classical CD14(+)CD16(-) monocytes or other monocyte subsets. Using Cox regression models to evaluate the prognostic value of circulating monocyte subtypes, we found that total counts of peripheral monocytes, as well as CD14(+)CD16(-) classical and other monocyte subtypes were not associated with the risk of secondary cardiovascular events during 3years follow-up. CONCLUSION: Circulating classical CD14(+)CD16(-) monocytes do not associate with specific vulnerable plaque characteristics. In addition, they do not predict secondary adverse manifestations. This suggests that in patients with established carotid artery disease, the

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circulating monocytes do not reflect plaque characteristics and have no value in identifying patients at risk for future cardiovascular events.

[35] *Rakipovski G, Rolin B, Nohr J et al. The GLP-1 Analogs Liraglutide and Semaglutide Reduce Atherosclerosis in ApoE(-/-) and LDLr(-/-) Mice by a Mechanism That Includes Inflammatory Pathways. JACC. Basic to translational science 2018; 3:844-857.*

PM: <http://www.ncbi.nlm.nih.gov/pubmed/?term=30623143>

ABSTRACT

The glucagon-like peptide-1 receptor agonists (GLP-1RAs) liraglutide and semaglutide reduce cardiovascular risk in type 2 diabetes patients. The mode of action is suggested to occur through modified atherosclerotic progression. In this study, both of the compounds significantly attenuated plaque lesion development in apolipoprotein E-deficient (ApoE(-/-)) mice and low-density lipoprotein receptor-deficient (LDLr(-/-)) mice. This attenuation was partly independent of weight and cholesterol lowering. In aortic tissue, exposure to a Western diet alters expression of genes in pathways relevant to the pathogenesis of atherosclerosis, including leukocyte recruitment, leukocyte rolling, adhesion/extravasation, cholesterol metabolism, lipid-mediated signaling, extracellular matrix protein turnover, and plaque hemorrhage. Treatment with semaglutide significantly reversed these changes. These data suggest GLP-1RAs affect atherosclerosis through an anti-inflammatory mechanism.

[36] *Kang EY, Chen TH, Garg SJ et al. Association of Statin Therapy With Prevention of Vision-Threatening Diabetic Retinopathy. JAMA ophthalmology 2019.*

PM: <http://www.ncbi.nlm.nih.gov/pubmed/?term=30629109>

ABSTRACT

Importance: Diabetic retinopathy is the leading cause of blindness in working-age adults. Studies have suggested that statins may reduce the risk of developing diabetic retinopathy. Objective: To investigate the association between statin therapy and the development of diabetic retinopathy in patients with diabetes and dyslipidemia. Design, Setting, and Participants: This population-based cohort study, conducted among 37894 Taiwanese patients between January 1, 1998, and December 31, 2013, used the National Health Insurance Research Database to identify patients with type 2 diabetes and dyslipidemia. Outcomes were compared between those taking statins and those not taking statins. Statistical analysis was performed from May 1 to 31, 2018. Exposure: Statin therapy with a medication possession rate of 80% or more with no other lipid-lowering medications. Main Outcomes and Measures: Any stage of diabetic retinopathy and treatments for vision-threatening diabetic retinopathy. Results: Of 1648305 patients with type 2 diabetes, 219359 were eligible for analysis over the study period, including 199760 patients taking statins and 19599 patients not taking statins. After propensity score matching, there were 18947 patients in the statin group (10 436 women and 8511 men; mean [SD] age, 61.5 [10.8] years) and 18947 patients in the nonstatin group (10 430 women and 8517 men; mean [SD] age, 61.0 [11.0] years), with a mean follow-up of 7.6 years for the statin group and 7.3 years for the nonstatin group. During the study period, 2004 patients in the statin group (10.6%) and 2269 patients in the nonstatin group (12.0%) developed diabetic retinopathy. Patients in the statin group had a significantly lower rate of diabetic retinopathy (hazard ratio [HR], 0.86; 95% CI, 0.81-0.91), nonproliferative diabetic retinopathy (HR, 0.92; 95% CI, 0.86-0.99), proliferative diabetic retinopathy (HR, 0.64; 95% CI, 0.58-0.70), vitreous hemorrhage (HR, 0.62; 95% CI, 0.54-0.71), tractional retinal

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detachment (HR, 0.61; 95% CI, 0.47-0.79), and macular edema (HR, 0.60; 95% CI, 0.46-0.79) than the nonstatin group, as well as lower rates of interventions such as retinal laser treatment (HR, 0.71; 95% CI, 0.65-0.77), intravitreal injection (HR, 0.74; 95% CI, 0.61-0.89), and vitrectomy (HR, 0.58; 95% CI, 0.48-0.69), along with a smaller number of the interventions (retinal lasers: rate ratio, 0.61; 95% CI, 0.59-0.64; intravitreal injections: rate ratio, 0.68; 95% CI, 0.61-0.76; and vitrectomies: rate ratio, 0.54; 95% CI, 0.46-0.63). Statin therapy was also associated with lower risks of major adverse cardiovascular events (HR, 0.81; 95% CI, 0.77-0.85), new-onset diabetic neuropathy (HR, 0.85; 95% CI, 0.82-0.89), and new-onset diabetic foot ulcers (HR, 0.73; 95% CI, 0.68-0.78). Conclusions and Relevance: Statin therapy was associated with a decreased risk of diabetic retinopathy and need for treatments for vision-threatening diabetic retinopathy in Taiwanese patients with type 2 diabetes and dyslipidemia.

[37] *Titov VN, Rozhkova TA, Samokhodskaya LM. [The disturbance of unification of coupled biochemical reactions in synthesis of endogenous omega-9 oleic acid. The resistance to insulin, stearic triglycerides and pathogenesis of eruptive xanthomata]. Klinicheskaia laboratornaia diagnostika 2017; 62:68-77.*

PM: <http://www.ncbi.nlm.nih.gov/pubmed/?term=30615382>

ABSTRACT

The eruptive xanthomata are formed in vivo under realization of biological function of endoecology. The xanthomata are formed in tissues by early in phylogenesis resident macrophages at absorption of secreted by hepatocytes aphysiological stearic lipoproteins of very low density with high content of the same name triglycerides down to tristearate. In these lipoproteins of very low density, by force of aphysiologically high hydrophobicity, stearic triglycerides are not hydrolyzed by post-heparin lipoproteinlipase. They both do not associate apoE and form apoE/B-J00 ligands. The formation of stearic lipoproteins of very low density occurred at impairment of function of coupled biochemical reactions in synthesis of physiological omega-9 oleic mono unsaturated fatty acid in hepatocytes. To synthesize endogenous oleic mono unsaturated fatty acid the late in phylogenesis insulin expresses two enzymes of coupled biochemical reactions: palmitoyl-KoA-elongase andstearyl-KoA-desaturase, activating synthesis of fatty acids following the path glucose-endogenous palmitic unsaturated fatty acid-stearic unsaturated fatty acid-oleic mono unsaturated fatty acid. The uncoupling of enzymes of coupling synthesis forms in hepatocytes surplus of stearic mono unsaturated fatty acid, stearic triglycerides and of the same name aphysiologic lipoproteins of very low density. During inhibition of the second enzyme the first one continues to actively produce stearic unsaturated fatty acid which the second enzyme, already uncoupled, does not convert into oleic unsaturated fatty acid. By absorbing aphysiologic ligand-free stearic lipoproteins of very low density in biologic reaction of endoecology, phylogenetically early macrophages convert into foam cells initiating aphysiologic biological reaction of transcytosis, biologic reaction of inflammation, biologic reaction of apoptosis and formation of eruptive xanthomata. The lipids of eruptive xanthomata: such endogenous stearic triglycerides as tristearate, tripalmitate, exogenous carotenoids, phospholipids and unesterified cholesterol.

[38] *Bigagli E, Toti S, Lodovici M et al. Dietary Extra-Virgin Olive Oil Polyphenols Do Not Attenuate Colon Inflammation in Transgenic HLAB-27 Rats but Exert Hypocholesterolemic Effects through the Modulation of HMGCR and PPAR-alpha Gene Expression in the Liver. Lifestyle genomics 2019:1-10.*

PM: <http://www.ncbi.nlm.nih.gov/pubmed/?term=30630166>

ABSTRACT

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BACKGROUND: Human studies have demonstrated that olive oil phenolic compounds reduce inflammatory markers associated with chronic diseases. **OBJECTIVES:** To explore the anti-inflammatory effects of extra-virgin olive oil polyphenols in an experimental model of inflammatory bowel disease (IBD). **METHODS:** HLA-B27 transgenic rats were fed an AIN-76 diet containing 10% corn oil (CO) or extra-virgin olive oil with high (EVOO) or low phenolic content (ROO) for 3 months. Wild-type rats (WT) were fed the CO diet. **RESULTS:** CO-fed HLA-B27 animals developed intestinal inflammation characterized by diarrhea, increased myeloperoxidase activity, and mucosal injury. None of these parameters were influenced by EVOO. Gene expression profiling indicated that proinflammatory pathways were upregulated in the colon mucosa of CO-fed HLA-B27 rats compared to WT, and this was further confirmed by RT-PCR for the iNOS, TNFalpha, and IL1beta genes. EVOO significantly reduced TNFalpha gene expression in the colon mucosa and decreased total cholesterol blood levels compared to CO HLA-B27 rats (89.43 +/- 3.66 vs. 111.5 +/- 8.10 mg/dL, $p < 0.05$). This latter effect with EVOO was associated with reduced HMGCR and increased PPAR-alpha hepatic gene expression, compared to ROO. **CONCLUSION:** These data indicate that olive oil polyphenols do not control colon inflammation in HLA-B27 transgenic rats but exert a positive effect on blood lipids by reducing total cholesterol levels. This preliminary result suggests the need to explore the efficacy of EVOO rich in polyphenols as a complementary strategy for managing hypercholesterolemia and to potentially limit statin-associated myotoxicity.

[39] Fang T, Guo B, Xue L, Wang L. **Atorvastatin Prevents Myocardial Fibrosis in Spontaneous Hypertension via Interleukin-6 (IL-6)/Signal Transducer and Activator of Transcription 3 (STAT3)/Endothelin-1 (ET-1) Pathway.** Medical science monitor : international medical journal of experimental and clinical research 2019; 25:318-323.

PM: <http://www.ncbi.nlm.nih.gov/pubmed/?term=30631031>

ABSTRACT

BACKGROUND Hypertension is a leading global disease, and myocardial fibrosis is an important adverse effect of hypertension, seriously threatening human health. The IL-6/STAT3 pathway and endothelin-1 (ET-1) were previously suggested to play a part in myocardial fibrosis. **MATERIAL AND METHODS** To investigate the role of Atorvastatin (Ato) in spontaneous hypertension, systolic blood pressure (SBP) and left ventricular mass index (LVMI) were measured, and Masson trichrome staining was performed. Furthermore, the relative protein levels of the IL-6/STAT3/ET-1 pathway were tested. **RESULTS** Ato prevented myocardial fibrosis in spontaneous hypertension rats, especially at the dosage of 50 mg/kg/d. The IL-6/STAT3 pathway was observed to be suppressed by Ato, and ET-1 level in myocardial tissues was also downregulated by Ato. The phosphorylation status of STAT3 was tested after Ato treatment, showing that Ato mainly stimulated the tyr-705 phosphorylation of STAT3. **CONCLUSIONS** Results of this study may help promote myocardial fibrosis therapy and provide insights into the IL-6/STAT3/ET-1-mediated mechanism in Ato-induced myocardial fibrosis inhibition.

[40] Cho AR, Moon JY, Kim S et al. **Effects of alternate day fasting and exercise on cholesterol metabolism in overweight or obese adults: a pilot randomized controlled trial.** Metabolism 2019.

PM: <http://www.ncbi.nlm.nih.gov/pubmed/?term=30615947>

ABSTRACT

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BACKGROUND AND PURPOSE: The objective of this pilot randomized controlled trial was to investigate the effect of alternate day fasting (ADF) and exercise on serum sterol signatures, which are surrogate markers of cholesterol absorption and biosynthesis. **METHODS:** We randomly assigned 112 overweight or obese participants to four groups: 1) ADF and exercise (E-ADF); 2) ADF; 3) exercise; and 4) control. We studied 31 completers in this exploratory analysis and measured their serum sterol signatures using gas chromatography-mass spectrometry. **RESULTS:** After intervention, most serum sterol signatures that correspond to cholesterol metabolism were significantly different between groups ($p < 0.05$ by analysis of covariance [ANCOVA]). We found no differences in plant sterols, which are markers of cholesterol absorption. In the exercise group, desmosterol, cholesteryl esters, and oxysterols decreased significantly. Furthermore, only changes in physical activity levels negatively correlated with changes in the metabolic ratios of desmosterol and 7-dehydrocholesterol to cholesterol, which reflect cholesterol biosynthesis ($r = -0.411$; $p = 0.030$, and $r = -0.540$; $p = 0.003$, respectively). **CONCLUSION:** These findings suggest that exercise with or without ADF improves cholesterol metabolism as measured by serum sterol signatures, and increased physical activity has a greater effect on cholesterol biosynthesis than weight reduction or calorie restriction.

[41] *de Faria CA, Zanette DL, Silva WA, Jr., Ribeiro-Paes JT. PAI-1 inhibition by simvastatin as a positive adjuvant in cell therapy. Molecular biology reports 2019.*

PM: <http://www.ncbi.nlm.nih.gov/pubmed/?term=30612281>

ABSTRACT

Cell therapy (CT) can be briefly described as the use of cells or cell components in the treatment of diseases. One of the main challenges in establishing new cell types for therapy is the low survival rates of homing cells. Glycoprotein plasminogen activator inhibitor 1 (PAI-1) is a key regulator of the plasminogen activation system, and also an essential mediator of mesenchymal stem cell (MSC) post-transplant survival rate in the target tissue. It was previously observed that the survival of cells infused into the transplanted tissue increase in the presence of PAI-1 neutralizing antibodies. Simvastatin acts at several levels in the protein cascade regulating PAI-1 levels. Thus, simvastatin-induced reduction of PAI-1 levels has a therapeutic potential by modulating the main processes involved in the creation of an inhospitable environment during the process of injury (fibrosis and cell migration). In this way, simvastatin modulates process such as migration, that plays a key role in homing and engraftment of cells after cell therapy. Due to this modulatory effect, research groups proposed the use of simvastatin as an adjuvant in different cell therapy approaches. These observations allow the proposition of the potential use of simvastatin, and possibly other statins, as an adjuvant in cell therapy, due to a mechanism of action that acts in the tissue microenvironment, promoting a better efficiency of the homing and, as a consequence, an enhancement of the paracrine effects of the stem cells in the process of tissue regeneration.

[42] *Zhao WB, Fu H, Chang F et al. Effects of various doses of atorvastatin on vascular endothelial cell apoptosis and autophagy in vitro. Molecular medicine reports 2019.*

PM: <http://www.ncbi.nlm.nih.gov/pubmed/?term=30628690>

ABSTRACT

Atorvastatin (Lipitor) is a lipidlowering agent that is widely used in the treatment of cardiovascular diseases. Previous research has largely focused on its cholesterollowering effects; however, a limited

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number of studies have investigated the actions of atorvastatin on vascular endothelial cells. In the present study, the effects of various doses of atorvastatin were investigated on human umbilical vein endothelial cells (HUVECs). HUVECs were treated with various concentrations of atorvastatin in serumfree or serumcontaining medium, and alterations in HUVEC morphology were observed. Cell survival and necrosis rates were evaluated using sulforhodamine B and lactate dehydrogenase assays, respectively. In addition, the protein expression levels of cellular apoptosis and autophagy markers were detected using western blot analysis. The results revealed that HUVEC morphology was altered following treatment with various concentrations of atorvastatin. In addition, autophagy was demonstrated to be induced by atorvastatin treatment at all concentrations, whereas high concentrations appeared to induce apoptosis and suppress the survival of HUVECs. In conclusion, the results of the present study suggested that various doses of atorvastatin may exert differential effects on HUVECs, and high doses may suppress angiogenesis. Therefore, atorvastatin may present a novel potential antitumor therapeutic strategy. However, further studies are required to fully elucidate the association between the dose of atorvastatin and its clinical outcome.

[43] *Zheng XF, Liu KX, Wang XM et al. MicroRNA192 acts as a tumor suppressor in colon cancer and simvastatin activates miR192 to inhibit cancer cell growth. Molecular medicine reports* 2019.

PM: <http://www.ncbi.nlm.nih.gov/pubmed/?term=30628692>

ABSTRACT

Colon cancer is one of the most common malignant tumors worldwide. Understanding the underlying molecular mechanisms is crucial for the development of therapeutic strategies for the treatment of patients with colon cancer. In the present study, a novel tumor suppressive microRNA, miR192, was demonstrated to be markedly downregulated in colon cancer cells compared with normal colon cells. By overexpressing miR192 in colon cancer HCT116 cells, the results of the present study revealed that miR192 inhibits cell proliferation, migration and invasion. Bioinformatics were used to determine the target gene of miR192 and Rasrelated protein Rab2A (RAB2A) was identified as a downstream target of miR192. Following the determination of the role of the miR192RAB2A pathway in colon cancer, small molecules that may regulate miR192 were screened and the results demonstrated that simvastatin is an activator of miR192. Furthermore, simvastatin upregulated miR192 and inhibited the expression of downstream targets of miR192, which subsequently led to suppressed proliferation, migration and invasion of colon cancer cells. In conclusion, the present study identified a novel colon cancer cell suppressor, as well as a smallmolecule activator of the tumor suppressor miR192, which may represent a therapeutic strategy for the treatment of patients with colon cancer.

[44] *Milard M, Laugerette F, Durand A et al. Milk Polar Lipids in a High-Fat Diet Can Prevent Body Weight Gain: Modulated Abundance of Gut Bacteria in Relation with Fecal Loss of Specific Fatty Acids. Molecular nutrition & food research* 2019:e1801078.

PM: <http://www.ncbi.nlm.nih.gov/pubmed/?term=30628158>

ABSTRACT

SCOPE: Enhanced adiposity and metabolic inflammation are major features of obesity associated with altered gut microbiota and intestinal barrier. We investigated in mice fed a mixed high-fat (HF) diet how these metabolic outcomes could be impacted by milk polar lipids (MPL), naturally containing 25% of sphingomyelin. METHODS AND RESULTS: Male C57Bl/6 mice received for 8 weeks a HF-diet devoid of

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MPL (21% fat, mainly palm oil, in chow), or supplemented with 1.1% or 1.6% of MPL (HF-MPL1; HF-MPL2) via a total-lipid extract from butterserum concentrate. HF-MPL2 mice gained less weight vs HF ($p < 0.01$). Diets did not impact plasma markers of inflammation but in the liver HF-MPL2 tended to decrease hepatic gene expression of macrophage marker F4/80 vs HF-MPL1 ($p = 0.06$). Colonic crypt depth was greatest in HF-MPL2 ($p < 0.05$). In caecal microbiota, HF-MPL1 increased *Bifidobacterium animalis*, vs HF ($p < 0.05$). HF-MPL2 decreased *Lactobacillus reuteri* ($p < 0.05$), which correlated negatively with the fecal loss of milk sphingomyelin-specific fatty acids ($p < 0.05$). **CONCLUSION:** In mice fed a mixed HF diet, MPL can limit HF-induced body weight gain and modulate gut physiology and the abundance of beneficial bacteria of the microbiota. This supports further exploration of how residual unabsorbed lipids reaching the colon could impact HF-induced metabolic disorders. This article is protected by copyright. All rights reserved.

[45] *Oliveira TE, Castro E, Belchior T et al. Fish Oil Protects Wild Type and Uncoupling Protein 1 Deficient Mice from Obesity and Glucose Intolerance by Increasing Energy Expenditure. Molecular nutrition & food research* 2019:e1800813.

PM: <http://www.ncbi.nlm.nih.gov/pubmed/?term=30632684>

ABSTRACT

SCOPE: We investigated the mechanisms and involvement of uncoupling protein 1 (UCP1) in the protection from obesity and insulin resistance induced by intake of high-fat diet rich in omega 3 (n-3) fatty acids. **METHODS AND RESULTS:** C57BL/6J mice were fed either a low-fat (control group) or one of two isocaloric high-fat diets containing either lard (HFD) or fish oil (HFN3) as fat source and evaluated for body weight, adiposity, energy expenditure, glucose homeostasis and inguinal white and interscapular brown adipose tissues (iWAT and iBAT, respectively) gene expression, lipidome and mitochondrial bioenergetics. HFN3 intake protected from obesity, glucose and insulin intolerances and hyperinsulinemia. This was associated with increased energy expenditure, iWAT UCP1 expression and incorporation of n-3 eicosapentaenoic and docosahexaenoic fatty acids in iWAT and iBAT triacylglycerol. Importantly, HFN3 was equally effective in reducing body weight gain, adiposity and glucose intolerance and increasing energy expenditure in wild type and UCP1-deficient mice without recruiting other thermogenic processes in iWAT and iBAT such as mitochondrial uncoupling, SERCA-mediated calcium and creatine-driven substrate cyclings. **CONCLUSION:** Intake of a high-fat diet rich in omega 3 fatty acids protects both wild type and UCP1-deficient mice from obesity and insulin resistance by increasing energy expenditure through unknown mechanisms. This article is protected by copyright. All rights reserved.

[46] *Lanzillo R, Moccia M, Russo CV et al. Therapeutic lag in reducing disability progression in relapsing-remitting multiple sclerosis: 8-year follow-up of two randomized add-on trials with atorvastatin. Multiple sclerosis and related disorders* 2019; 28:193-196.

PM: <http://www.ncbi.nlm.nih.gov/pubmed/?term=30623857>

ABSTRACT

BACKGROUND: Current treatments for relapsing remitting multiple sclerosis (RRMS) reduce inflammation, but have a partial or modest effect on disability. This effect may require a much longer follow-up than standard trial design, in particular in RRMS with relatively-preserved functional reserve. We aimed to assess the long-term clinical evolution of RRMS patients exposed to atorvastatin in two

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trials (ACTIVE and ARIANNA). METHODS: We retrospectively looked at 69 participants randomized with atorvastatin or placebo as add-on therapy to interferon-beta for 24 months at a single MS centre. We recorded relapses, 1-point EDSS progression and progression to EDSS 4.0. Cox regression was performed for these three questions. A Poisson regression model was used to evaluate the association between atorvastatin treatment and annualized relapse rate (ARR). RESULTS: After 8.4+/-2.3 (3.7-11.9) years from trial, the use of atorvastatin was associated with reduced risk of 1-point EDSS progression (HR=0.440; 95%CI=0.225-0.861; p=0.017), and of EDSS 4.0 (HR=0.310; 95%CI=0.123-0.784; p=0.013). We found no significant association between atorvastatin and relapses. DISCUSSION: These data suggest that a delayed treatment effect may be seen with atorvastatin added to interferon-beta, eight years after entering the clinical trials. Long-term follow-up of trial cohorts should be mandated.

[47] *Mashnafi S, Plat J, Mensink RP, Baumgartner S. Non-Cholesterol Sterol Concentrations as Biomarkers for Cholesterol Absorption and Synthesis in Different Metabolic Disorders: A Systematic Review. Nutrients* 2019; 11.

PM: <http://www.ncbi.nlm.nih.gov/pubmed/?term=30634478>

ABSTRACT

Non-cholesterol sterols are validated biomarkers for intestinal cholesterol absorption and endogenous cholesterol synthesis. However, their use in metabolic disturbances has not been systematically explored. Therefore, we conducted a systematic review to provide an overview of non-cholesterol sterols as markers for cholesterol metabolism in different metabolic disorders. Potentially relevant studies were retrieved by a systematic search of three databases in July 2018 and ninety-four human studies were included. Cholesterol-standardized levels of campesterol, sitosterol and cholestanol were collected to reflect cholesterol absorption and those of lathosterol and desmosterol to reflect cholesterol synthesis. Their use as biomarkers was examined in the following metabolic disorders: overweight/obesity (n = 16), diabetes mellitus (n = 15), metabolic syndrome (n = 5), hyperlipidemia (n = 11), cardiovascular disease (n = 17), and diseases related to intestine (n = 16), liver (n = 22) or kidney (n = 2). In general, markers for cholesterol absorption and synthesis displayed reciprocal patterns, showing that cholesterol metabolism is tightly regulated by the interplay of intestinal absorption and endogenous synthesis. Distinctive patterns for cholesterol absorption or cholesterol synthesis could be identified, suggesting that metabolic disorders can be classified as 'cholesterol absorbers or cholesterol synthesizers'. Future studies should be performed to confirm or refute these findings and to examine whether this information can be used for targeted (dietary) interventions.

[48] *Plat J, Baumgartner S, Vreugdenhil ACE et al. Modifying Serum Plant Sterol Concentrations: Effects on Markers for Whole Body Cholesterol Metabolism in Children Receiving Parenteral Nutrition and Intravenous Lipids. Nutrients* 2019; 11.

PM: <http://www.ncbi.nlm.nih.gov/pubmed/?term=30626159>

ABSTRACT

BACKGROUND: Non-cholesterol sterols are validated markers for fractional intestinal cholesterol absorption (cholestanol) and endogenous cholesterol synthesis (lathosterol). This study's objective was to evaluate markers for cholesterol synthesis and absorption in children exposed to two different intravenous lipid emulsions that rapidly change serum plant sterol concentrations as part of their parenteral nutrition (PN). METHODS: Serum samples from two different studies were used: (1) nine PN-

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dependent children with intestinal failure associated liver disease (IFALD) whose soy-based, plant sterol-rich lipid (SO) was replaced with a fish-based, plant sterol-poor (FO) lipid; and (2) five neonates prescribed SO after birth. In the first study, samples were collected at baseline (prior to FO initiation) and after 3 and 6 months of FO. In study 2, samples were collected at 1 and 3 weeks of age. RESULTS: In study 1, a 7-fold reduction in campesterol, a 12-fold reduction in sitosterol, and a 15-fold reduction in stigmasterol was observed 6 months after switching to FO. Serum cholesterol concentrations did not change, but cholesterol-standardized lathosterol increased (3-fold) and cholesterol-standardized cholestanol decreased (2-fold). In study 2, after 3 weeks of SO, sitosterol and campesterol concentrations increased 4-5 fold. At the same time, cholesterol-standardized lathosterol increased 69% and cholesterol-standardized cholestanol decreased by 29%. CONCLUSION: Based on these findings we conclude that changes in serum plant sterol concentrations might have direct effects on endogenous cholesterol synthesis, although this needs to be confirmed in future studies. Moreover, we speculate that this changed synthesis subsequently affects intestinal cholesterol absorption.

[49] Wisniewski PJ, Dowden RA, Campbell SC. **Role of Dietary Lipids in Modulating Inflammation through the Gut Microbiota.** *Nutrients* 2019; 11.

PM: <http://www.ncbi.nlm.nih.gov/pubmed/?term=30626117>

ABSTRACT

Inflammation and its resolution is a tenuous balance that is under constant contest. Though several regulatory mechanisms are employed to maintain homeostasis, disruptions in the regulation of inflammation can lead to detrimental effects for the host. Of note, the gut and microbial dysbiosis are implicated in the pathology of systemic chronic low-grade inflammation which has been linked to several metabolic diseases. What remains to be described is the extent to which dietary fat and concomitant changes in the gut microbiota contribute to, or arise from, the onset of metabolic disorders. The present review will highlight the role of microorganisms in host energy regulation and several mechanisms that contribute to inflammatory pathways. This review will also discuss the immunomodulatory effects of the endocannabinoid system and its link with the gut microbiota. Finally, a brief discussion arguing for improved taxonomic resolution (at the species and strain level) is needed to deepen our current knowledge of the microbiota and host inflammatory state.

[50] Nicholls SJ, Nelson AJ. **HDL and cardiovascular disease.** *Pathology* 2019.

PM: <http://www.ncbi.nlm.nih.gov/pubmed/?term=30612759>

ABSTRACT

High-density lipoprotein (HDL) has received increasing interest due to observations of an inverse relationship between its systemic levels and cardiovascular risk and targeted interventions in animal models that have had favourable effects on atherosclerotic plaque. In addition to its pivotal role in reverse cholesterol transport, HDL has been reported to possess a range of functional properties, which may exert a protective influence on inflammation, oxidation, angiogenesis and glucose homeostasis. This has led to the development of a range of HDL targeted therapeutics, which have undergone evaluation in clinical trials. The current state of HDL in cardiovascular prevention will be reviewed.

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[51] *Waldmann E, Parhofer KG. Apheresis for severe hypercholesterolaemia and elevated lipoprotein(a). Pathology 2019.*

PM: <http://www.ncbi.nlm.nih.gov/pubmed/?term=30611543>

ABSTRACT

Low-density lipoprotein (LDL)-cholesterol (LDL-c) and lipoprotein(a) [Lp(a)] are independent cardiovascular risk factors. Reduction of LDL-c leads to reduction in cardiovascular events, regardless of the method of reducing LDL-c levels. Lifestyle modification and drugs are first line treatment options. However, many patients do not reach treatment goals, as defined in guidelines worldwide, through standard medication. So far, drugs are not efficient in lowering Lp(a) levels, or the reduction of plasma levels does not result in clinical benefit. In these two groups of patients lipoprotein apheresis is very efficient in decreasing LDL-c and Lp(a) levels. A single apheresis session can decrease LDL-c and Lp(a) by approximately 65%, and apheresis performed weekly or biweekly results in considerably decreased mean interval concentrations (approximately 30% reduction). Most apheresis systems (HELP, heparin induced extracorporeal LDL precipitation; DALI, direct adsorption of lipoproteins; lipoprotein apheresis with dextran sulfate; lipid filtration; immunoabsorption) decrease LDL-c and Lp(a). Lipopac is a specific form of immunoadsorption and only decreases Lp(a). Lipoprotein apheresis is a well-tolerated treatment option but it is expensive and time consuming. The evidence for clinical benefit through regular apheresis comes from observational data. Adequate, randomised, controlled trials are lacking.

[52] *Chen YT, Kuo SC, Chao PW, Chang YY. Use of lipid-lowering agents is not associated with improved outcomes for tuberculosis patients on standard-course therapy: A population-based cohort study. PloS one 2019; 14:e0210479.*

PM: <http://www.ncbi.nlm.nih.gov/pubmed/?term=30633771>

ABSTRACT

OBJECTIVES: Animal and ex vitro studies suggested lipid-lowering agents (LLAs) may be used as an adjunct to standard anti-tuberculosis (TB) treatment. No human study has been conducted to date. Using the Taiwan National Health Insurance Research Database (NHIRD), the current population-based cohort study sought to examine the association between use of LLAs and outcomes of patients with pulmonary TB receiving anti-TB treatment. METHODS: Using a NHIRD from 2003 to 2010, this population-based cohort study retrospectively examined the association between LLAs (statins or fibrates) and the outcomes of patients with pulmonary TB receiving anti-TB treatment. RESULTS: A total of 1452 adult patients newly diagnosed with pulmonary TB during the study period were identified and compared with 5808 matched patients. In the LAA cohort, 1258 received statin, and 295 received fibrate. Compared with patients who did not take LLA, patients who took oral LLAs had similar incidence of treatment completion at 9, 12, and 24 months. CONCLUSIONS: Neither statins nor fibrates provide clinical benefit superior to that achieved with standard anti-tuberculosis treatment. Future clinical trials should investigate the effects of statins and fibrates on short-course standard anti-TB therapy.

[53] *Ghanem AM, Hamimi AH, Matta JR et al. Automatic Coronary Wall and Atherosclerotic Plaque Segmentation from 3D Coronary CT Angiography. Scientific reports 2019; 9:47.*

PM: <http://www.ncbi.nlm.nih.gov/pubmed/?term=30631101>

ABSTRACT

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Coronary plaque burden measured by coronary computerized tomography angiography (CCTA), independent of stenosis, is a significant independent predictor of coronary heart disease (CHD) events and mortality. Hence, it is essential to develop comprehensive CCTA plaque quantification beyond existing subjective plaque volume or stenosis scoring methods. The purpose of this study is to develop a framework for automated 3D segmentation of CCTA vessel wall and quantification of atherosclerotic plaque, independent of the amount of stenosis, along with overcoming challenges caused by poor contrast, motion artifacts, severe stenosis, and degradation of image quality. Vesselness, region growing, and two sequential level sets are employed for segmenting the inner and outer wall to prevent artifact-defective segmentation. Lumen and vessel boundaries are joined to create the coronary wall. Curved multiplanar reformation is used to straighten the segmented lumen and wall using lumen centerline. In-vivo evaluation included CCTA stenotic and non-stenotic plaques from 41 asymptomatic subjects with 122 plaques of different characteristics against the individual and consensus of expert readers. Results demonstrate that the framework segmentation performed robustly by providing a reliable working platform for accelerated, objective, and reproducible atherosclerotic plaque characterization beyond subjective assessment of stenosis; can be potentially applicable for monitoring response to therapy.

[54] *Vethe NT, Munkhaugen J, Andersen AM et al. A Method for Direct Monitoring of Atorvastatin Adherence in Cardiovascular Disease Prevention: Quantification of the Total Exposure to Parent Drug and Major Metabolites Using 2-Channel Chromatography and Tandem Mass Spectrometry. Therapeutic drug monitoring 2019; 41:19-28.*

PM: <http://www.ncbi.nlm.nih.gov/pubmed/?term=30633723>

ABSTRACT

BACKGROUND: Low adherence to statin therapy remains a public health concern associated with poor prognosis in cardiovascular disease patients. A feasible method for statin adherence monitoring in clinical practice has yet to be developed. In this article, we describe a novel method designed for the direct monitoring of atorvastatin adherence based on the sum of parent drug and major metabolites in blood samples. **METHODS:** Acid and lactone forms of atorvastatin, 2-OH-atorvastatin, and 4-OH-atorvastatin were assayed. Plasma proteins were precipitated with an acidified mixture of methanol, acetonitrile, and aqueous zinc sulfate, and the supernatant was analyzed with 2-channel reversed-phase chromatography coupled to tandem mass spectrometry. Assay validation was performed according to the guidelines provided by the European Medicines Agency and the US Food and Drug Administration. **RESULTS:** The effective run time was 1 minute and 45 seconds per sample. Mean accuracy ranged from 92% to 110%, and coefficients of variation were $\leq 8.1\%$ over the measurement ranges for individual compounds. The sum of acids and corresponding lactones was stable in clinical plasma samples kept at ambient temperature for up to 6 days after blood sampling (mean sum within 96.6%-101% of baseline). **CONCLUSIONS:** A fast and reliable assay for the quantification of atorvastatin and its 5 major metabolites in clinical blood samples is reported. Limitations of preanalytical stability were solved using the sum of the acid and lactone forms. The assay is feasible for implementation in clinical practice, and the sum of parent drug and metabolites may be used for direct monitoring of atorvastatin adherence.