Literature update week 32 (2019)

[1] *Sreedhar R, Kumar VS, Bhaskaran Pillai AK, Mangalathillam S*. **Omega-3 Fatty Acid Based Nanolipid Formulation of Atorvastatin for Treating Hyperlipidemia**. Advanced pharmaceutical bulletin 2019; 9:271-280.

PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=31380253

ABSTRACT

Purpose: In the current study, attempts have been made to formulate an omega-3 fatty acid based nanostructured lipid carriers of atorvastatin (AT), for treating hyperlipidemia; and to evaluate their antihyperlipidemic activity using in vitro and in vivo studies. Methods: Omega-3 fatty acid based AT-loaded nanolipid carriers (NLC) were formulated by the melt emulsification ultrasonication technology. The prepared NLC consist of stearic acid (as solid lipid), omega-3 fatty acid (as liquid lipid), Tween 80, poloxamer 188 (surfactants) and soya-lecithin (co-surfactant). Results: AT loaded NLCs have a particle size of 74.76 +/- 4.266 nm, a zeta potential value of -36.03 +/- 1.504 mV and a high drug entrapment efficiency (EE) of 86.70 % +/- 0.155. The release of AT from NLCs exhibited a sustained behaviour, which made it an ideal vehicle for drug delivery. MTT assay results indicated that NLCs are compatible with L929 (mouse fibroblast) cell lines. Anti-hyperlipidemic study showed a significant reduction in LDL and TG levels in serum with the orally administered Omega-3 fatty acid based AT loaded NLCs when compared to marketed formulation. Conclusion: The results demonstrated that the omega-3 fatty acid based NLC has the potential to be a promising nanomedicine for the treatment of hyperlipidemia.

[2] *Wang Y, Zhang K, Qin X et al.* **Biomimetic Nanotherapies: Red Blood Cell Based Core-Shell Structured Nanocomplexes for Atherosclerosis Management**. Advanced science (Weinheim, Baden-Wurttemberg, Germany) 2019; 6:1900172.

PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=31380165

ABSTRACT

Cardiovascular disease is the leading cause of mortality worldwide. Atherosclerosis, one of the most common forms of the disease, is characterized by a gradual formation of atherosclerotic plaque, hardening, and narrowing of the arteries. Nanomaterials can serve as powerful delivery platforms for atherosclerosis treatment. However, their therapeutic efficacy is substantially limited in vivo due to nonspecific clearance by the mononuclear phagocytic system. In order to address this limitation, rapamycin (RAP)-loaded poly(lactic-co-glycolic acid) (PLGA) nanoparticles are cloaked with the cell membrane of red blood cells (RBCs), creating superior nanocomplexes with a highly complex functionalized bio-interface. The resulting biomimetic nanocomplexes exhibit a well-defined "core-shell" structure with favorable hydrodynamic size and negative surface charge. More importantly, the biomimetic nature of the RBC interface results in less macrophage-mediated phagocytosis in the blood and enhanced accumulation of nanoparticles in the established atherosclerotic plaques, thereby achieving targeted drug release. The biomimetic nanocomplexes significantly attenuate the progression of atherosclerosis. Additionally, the biomimetic nanotherapy approach also displays favorable safety properties. Overall, this study demonstrates the therapeutic advantages of biomimetic nanotherapy for atherosclerosis treatment, which holds considerable promise as a new generation of drug delivery system for safe and efficient management of atherosclerosis.

Literature update week 32 (2019)

[3] *Cannon CP, Khan I, Klimchak AC et al.* **Simulation of impact on cardiovascular events due to lipid-lowering therapy intensification in a population with atherosclerotic cardiovascular disease**. American heart journal 2019; 216:30-41.

PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=31386936

ABSTRACT

In patients with atherosclerotic cardiovascular disease (ASCVD), guidelines recommend statins as first-line lipid-lowering therapy (LLT) with addition of nonstatin agents in those with persistently elevated low-density lipoprotein cholesterol levels. METHODS: To estimate the cardiovascular (CV) risk reduction implications of treatment intensification, we used a previously reported simulation model with enhancements. An ASCVD cohort was developed from a US claims database. A Cox model was used to estimate baseline risk of CV events: myocardial infarction, ischemic stroke, unstable angina hospitalization, elective coronary revascularization, or cardiovascular death. Patients were sampled with replacement (bootstrapping) and entered the simulation model, which applied stepwise LLT intensification logic, with a goal of achieving low-density lipoprotein cholesterol less than 70mg/dL at each step. CV risk reduction assumptions were based on published data. Two treatment intensification scenarios were investigated: ideal and real-world (which accounted for statin intolerance, nonadherence, and payer restrictions). RESULTS: In a cohort of 1,000 patients with ASCVD, approximately 813 (809-818) would require treatment intensification with LLT under an ideal treatment intensification scenario. Before treatment intensification, 183 (179-187) events would be expected to occur over 5years. With treatment intensification, 40 (34-45) of these events could be avoided. In a real-world scenario, about 818 (813-823) patients require treatment intensification with LLT, resulting in 29 (24-34) events avoided over 5years. CONCLUSIONS: Intensification of LLT in an ASCVD population translates into a substantial number of CV events avoided. This simulation-based model could assist in assessing the potential benefits of various types of population-level LLT interventions.

[4] *Bethancourt HJ, Kratz M, O'Connor K*. **A short-term religious "fast" from animal products has a minimal impact on cardiometabolic health biomarkers irrespective of concurrent shifts in distinct plant-based food groups**. The American journal of clinical nutrition 2019.

PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=31380559

ABSTRACT

BACKGROUND: Plant-based diets may help improve measures of body fat, blood cholesterol, glucose metabolism, and inflammation. However, limited evidence suggests that the health effects of reducing animal products may depend on the quality of plant-based foods consumed as caloric replacements. OBJECTIVE: This study examined how temporarily restricting consumption of meat, dairy, and egg (MDE) products for religious purposes influences cardiometabolic health biomarkers and whether any effects of MDE restriction on biomarkers are modified by concurrent shifts in calories, fish, and distinct plant-based foods. DESIGN: This study followed a sample of 99 individuals in the United States with varying degrees of adherence to Orthodox Christian (OC) guidance to abstain from MDE products during Lent, the 48-d period prior to Easter. Dietary composition was estimated from FFQs and 7-d food records; measures of body fat, blood lipids, glucose metabolism, and inflammation were collected prior to and at the end of Lent. RESULTS: Each serving decrease in MDE products was associated with an average -3.7% (95% CI: -5.5%, -2.0%; $P < 0.0001$) and -3.6% (95% CI: -5.8%, -1.3%; $P = 0.003$) change in fasting total and LDL blood cholesterol, respectively, which were partly explained by minor weight loss. However, the total/HDL cholesterol ratio did not significantly decrease due to an average -3.2% (95% CI: -5.8%, -0.6%;

P = 0.02) change in HDL cholesterol. No associations between MDE restrictions and shifts in measures of body fat, glucose, insulin, or C-reactive protein were observed. The data could not provide evidence that changes in cardiometabolic health biomarkers in relation to MDE restriction were modified by concurrent shifts in calories, fish, or plant-based foods. CONCLUSION: Temporary MDE restrictions practiced by this sample of OCs in the United States during Lent had minimal effects on cardiometabolic disease risk factors. Further research among larger samples of OCs is needed to understand how nutritionally distinct and complex combinations of plant-based foods may modify the health effects of religious fasting from MDE products.

[5] *Tian XQ, Yang YJ, Li Q et al.* **Combined therapy with atorvastatin and atorvastatin-pretreated mesenchymal stem cells enhances cardiac performance after acute myocardial infarction by activating SDF-1/CXCR4 axis**. American journal of translational research 2019; 11:4214-4231.

PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=31396330

ABSTRACT

The SDF-1/CXCR4 signaling plays a critical role in the trafficking of mesenchymal stem cells (MSCs) to the sites of tissue damage. Our recent study demonstrated that atorvastatin (ATV) treatment improved the survival of MSCs, and ATV pretreated MSCs ((ATV-)MSCs) exhibited enhanced engraftment to injured myocardium. In this study, we investigated whether combined treatment with ATV and (ATV-)MSCs enhances cardiac repair and regeneration by activating SDF-1/CXCR4 signaling in a rat model of acute myocardial infarction. Rats were randomized into eight groups: the Sham, AMI control and 6 other groups that were subjected to AMI followed by treatment with MSCs, ATV, ATV+MSCs, (ATV-)MSCs, ATV+(ATV-)MSCs, ATV+(ATV-)MSCs+AMD3100 (SDF-1/CXCR4 antagonist), respectively. ATV+(ATV-)MSCs significantly potentiated targeted recruitment of MSCs to peri-infarct myocardium and resulted in further improvements in cardiac function and reduction in scar size compared with MSCs treatment alone at 4-week after AMI. More importantly, the cardioprotective effects conferred by ATV+(ATV-)MSCs were almost completely abolished by AMD3100 treatment. Together, our study demonstrated that ATV+(ATV-)MSCs significantly enhanced the targeted recruitment and survival of transplanted MSCs, and resulted in subsequent cardiac function improvement by augmenting SDF-1/CXCR4 signaling.

[6] *Shi N, Zhang S, Silverman G et al.* **Protective effect of hydroxychloroquine on rheumatoid arthritis-associated atherosclerosis**. Animal models and experimental medicine 2019; 2:98-106.

PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=31392302

ABSTRACT

Background: Patients with rheumatoid arthritis (RA) have an increased risk for cardiovascular disease. We examined the effect of gut microbiota in a mouse model of RA that develops atherosclerosis. Methods: We created three groups of K/BxN female mice that were positive for the anti-glucose-6-phosphate isomerase (GPI) antibody: control diet (CD), high fat diet (HFD), and HFD with hydroxychloroquine (HFD + HCQ). Serological tests were used to detect the serum levels of total cholesterol (TCHO), low-density lipoprotein cholesterol (LDL-C), triglyceride (TG), high-density lipoprotein cholesterol (HDL-C), anti-GPI antibody titers, and serum cytokines. Atherosclerotic plaque was determined by histological analysis, and gut microbiota were determined by 16sV4 sequencing. Results: Relative to mice given the CD, those receiving the HFD had increased serum levels of LDL-C, TCHO, and TG, decreased serum levels of HDL-C, increased atherosclerotic lesions in the aortic root, and

altered gut microbiota. Addition of HCQ to HFD decreased the serum levels of LDL-C, TCHO, and TG, increased serum levels of HDL-C, and decreased the atherosclerotic lesions in the aortic root. Mice receiving HFD + HCQ also had the greatest bacterial diversity among the three experimental groups. Moreover, HCQ treatment significantly increased the abundance of Akkermansia and Parabacteroides, and decreased the abundance of Clostridium sensu stricto cluster 1, and therefore may be responsible for the reduced RA-associated atherosclerosis and dyslipidemia. Conclusion: Our mouse model of RA indicated that HFD increased ankle width and aggravated atherosclerosis and dyslipidemia, and that HCQ alleviated the dyslipidemia and atherosclerosis, but had no effect on ankle width.

[7] *Piplani H, Marek-Iannucci S, Sin J et al.* **Simvastatin induces autophagic flux to restore cerulein-impaired phagosome-lysosome fusion in acute pancreatitis**. Biochimica et biophysica acta. Molecular basis of disease 2019; 1865:165530.

PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=31398467

ABSTRACT

BACKGROUND: During pancreatitis, autophagy is activated, but lysosomal degradation of dysfunctional organelles including mitochondria is impaired, resulting in acinar cell death. Retrospective cohort analyses demonstrated an association between simvastatin use and decreased acute pancreatitis incidence. METHODS: We examined whether simvastatin can protect cell death induced by cerulein and the mechanisms involved during acute pancreatitis. Mice were pretreated with DMSO or simvastatin (20mg/kg) for 24h followed by 7 hourly cerulein injections and sacrificed 1h after last injection to harvest blood and tissue for analysis. RESULTS: Pancreatic histopathology revealed that simvastatin reduced necrotic cell death, inflammatory cell infiltration and edema. We found that cerulein triggered mitophagy with autophagosome formation in acinar cells. However, autophagosome-lysosome fusion was impaired due to altered levels of LAMP-1, AMPK and ULK-1, resulting in autophagosome accumulation (incomplete autophagy). Simvastatin abrogated these effects by upregulating LAMP-1 and activating AMPK which phosphorylated ULK-1, resulting in increased formation of functional autolysosomes. In contrast, autophagosomes accumulated in control group during pancreatitis. The effects of simvastatin to promote autophagic flux were inhibited by chloroquine. Mitochondria from simvastatin-treated mice were resistant to calcium overload compared to control, suggesting that simvastatin induced mitochondrial quality control to eliminate susceptible mitochondria. Clinical specimens showed a significant increase in cell-free mtDNA in plasma during pancreatitis compared to normal controls. Furthermore, genetic deletion of parkin abrogated the benefits of simvastatin. CONCLUSION: Our findings reveal the novel role of simvastatin in enhancing autophagic flux to prevent pancreatic cell injury and pancreatitis.

[8] *Righolt CH, Bisewski R, Mahmud SM*. **Statin use and prostate cancer incidence in Manitoba, Canada: A population-based nested case control study**. Cancer Epidemiol Biomarkers Prev 2019.

PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=31387966

ABSTRACT

BACKGROUND: A link between statin use and prostate cancer (PC) risk has been proposed. Epidemiological evidence is, however, inconclusive and data for specific statin types as well as for period, duration, and dose of use is lacking. METHODS: We conducted a population-based nested case-control study using administrative data in Manitoba, Canada. PC cases were matched to cancer-free

controls and their statin use (including period, duration, and dose of use) was assessed (with adjustment for PC screening) for statins as a class and for each specific statin. RESULTS: We matched 9,384 PC cases to 46,749 cancer-free controls. Ever-use of any statin was not associated with PC risk, odds ratio 0.96 (95% confidence interval 0.90-1.03). Except for pravastatin, 0.82 (0.71-0.96), individual statins were not associated with PC risk. There was no dose- or duration-response for pravastatin (or any other statin). CONCLUSIONS: We found limited evidence of an association between statin use and PC risk. The association between pravastatin and PC risk may be due to chance. IMPACT: We show that statin use is not associated with PC risk after adjustment for screening for a large population with data going back to the mid-1990s.

[9] *Kalogirou TE, Meditskou S, Davidopoulou S et al.* **Investigating the Possible Protective Role of Direct Intra-arterial Administration of Mannitol and N-Acetylcysteine and Per Os Administration of Simvastatin Against Contrast-Induced Nephropathy: An Experimental Study in a Rabbit Model**. Cardiovascular and interventional radiology 2019.

PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=31392490

ABSTRACT

PURPOSE: Contrast-induced nephropathy (CIN) is one of the leading causes of hospital-acquired acute kidney injury due to the use of iodinated contrast media in various interventional procedures like endovascular aneurysm repair. Its pathophysiology remains mostly unclear. The purpose of the present study was to comparatively study the possible protective role of direct intra-arterial administration of mannitol and acetylcysteine and per os administration of simvastatin in a histopathological level. MATERIALS AND METHODS: In the present study, we administered iopromide directly in the infrarenal aorta of 24 New Zealand white rabbits after laparotomy. Animals were divided in four groups of six: G1 received iopromide with no protection, G2 iopromide with mannitol, G3 iopromide with acetylcysteine, and G4 iopromide with simvastatin. Renal function blood parameters were assessed prior to the administration, and in 48 h; histopathological evaluation of the kidneys was performed. RESULTS: CIN was evident only in the no protection group G1. Moreover, G1 demonstrated significantly more severe lesions than groups G2, G3, and G4 regarding histopathological findings in glomeruli, vacuolization of tubular epithelial cells, tubular proteinaceous casts, and tubular necrosis. According to our results, intra-arterial administration of mannitol seems to be effective in protection against tubular necrosis. CONCLUSION: In general, all three agents demonstrated a protective role in preventing the development of CIN, although it seems that there are various pathways that remain to be investigated further.

[10] *Cucchi D, Camacho-Munoz D, Certo M et al.* **Omega-3 polyunsaturated fatty acids impinge on CD4+ T cell motility and adipose tissue distribution via direct and lipid mediator-dependent effects**. Cardiovascular research 2019.

PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=31399738

ABSTRACT

AIMS: Adaptive immunity contributes to the pathogenesis of cardiovascular metabolic disorders (CVMD). The omega-3 polyunsaturated fatty acids (n-3PUFA) are beneficial for cardiovascular health, with potential to improve the dysregulated adaptive immune responses associated with metabolic imbalance. We aimed to explore the mechanisms through which n-3PUFA may alter T cell motility and

tissue distribution to promote a less inflammatory environment and improve lymphocyte function in CVMD. METHODS AND RESULTS: Using mass spectrometry lipidomics, cellular, biochemical, and in vivo and ex vivo analyses, we investigated how eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA), the main n-3PUFA, modify the trafficking patterns of activated CD4+ T cells. In mice subjected to allogeneic immunization, a 3-week n-3PUFA-enriched diet reduced the number of effector memory CD4+ T cells found in adipose tissue, and changed the profiles of eicosanoids, octadecanoids, docosanoids, endocannabinoids, 2-monoacylglycerols, N-acyl ethanolamines and ceramides, in plasma, lymphoid organs and fat tissues. These bioactive lipids exhibited differing chemotactic properties when tested in chemotaxis assays with activated CD4+ T cells in vitro. Furthermore, CD4+ T cells treated with EPA and DHA showed a significant reduction in chemokinesis, as assessed by trans-endothelial migration assays, and, when implanted in recipient mice, demonstrated less efficient migration to the inflamed peritoneum. Finally, EPA and DHA treatments reduced the number of polarised CD4+ T cells in vitro, altered the phospholipid composition of membrane microdomains and decreased the activity of small Rho GTPases, Rhoalpha and Rac1 instrumental in cytoskeletal dynamics. CONCLUSIONS: Our findings suggest that EPA and DHA affect the motility of CD4+ T cells and modify their ability to reach target tissues by interfering with the cytoskeletal rearrangements required for cell migration. This can explain, at least in part, the anti-inflammatory effects of n-3PUFA supporting their potential use in interventions aiming to address adipocyte low grade inflammation associated with cardiovascular metabolic disease.

[11] *Fasolo F, Gregoli KD, Maegdefessel L, Johnson JL*. **Non-coding RNAs in cardiovascular cell biology and atherosclerosis**. Cardiovascular research 2019.

PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=31389987

ABSTRACT

Atherosclerosis underlies the predominant number of cardiovascular diseases and remains a leading cause of morbidity and mortality worldwide. The development, progression and formation of clinically relevant atherosclerotic plaques involves the interaction of distinct and over-lapping mechanisms which dictate the roles and actions of multiple resident and recruited cell types including endothelial cells, vascular smooth muscle cells, and monocyte/macrophages. The discovery of non-coding RNAs including microRNAs, long non-coding RNAs, and circular RNAs, and their identification as key mechanistic regulators of mRNA and protein expression has piqued interest in their potential contribution to atherosclerosis. Accruing evidence has revealed non-coding RNAs regulate pivotal cellular and molecular processes during all stages of atherosclerosis, including; cell invasion, growth, and survival; cellular uptake and efflux of lipids, expression and release of pro- and anti-inflammatory intermediaries, and proteolytic balance. The expression profile of non-coding RNAs within atherosclerotic lesions and the circulation have been determined with the aim of identifying individual or clusters of non-coding RNAs which may be viable therapeutic targets alongside deployment as biomarkers of atherosclerotic plaque progression. Consequently, numerous in vivo studies have been convened to determine the effects of moderating the function or expression of select non-coding RNAs in well-characterised animal models of atherosclerosis. Together, clinicopathological findings and studies in animal models have elucidated the multifaceted and frequently divergent effects non-coding RNAs impose both directly and indirectly on the formation and progression of atherosclerosis. From these findings' potential novel therapeutic targets and strategies have been discovered which may pave the way for further translational studies and possibly taken forward for clinical application.

Literature update week 32 (2019)

[12] *Moss AJ, Doris MK, Andrews JPM et al.* **Molecular Coronary Plaque Imaging Using (18)F-Fluoride**. Circulation. Cardiovascular imaging 2019; 12:e008574.

PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=31382765

ABSTRACT

BACKGROUND: Coronary (18)F-fluoride positron emission tomography identifies ruptured and high-risk atherosclerotic plaque. The optimal method to identify, to quantify, and to categorize increased coronary (18)F-fluoride uptake and determine its reproducibility has yet to be established. This study aimed to optimize the identification, quantification, categorization, and scan-rescan reproducibility of increased (18)F-fluoride activity in coronary atherosclerotic plaque. METHODS: In a prospective observational study, patients with multi-vessel coronary artery disease underwent serial (18)F-fluoride positron emission tomography. Coronary (18)F-fluoride activity was visually assessed, quantified, and categorized with reference to maximal tissue to background ratios. Levels of agreement for both visual and quantitative methods were determined between scans and observers. RESULTS: Thirty patients (90% male, 20 patients with stable coronary artery disease, and 10 with recent type 1 myocardial infarction) underwent paired serial positron emission tomography-coronary computed tomography angiography imaging within an interval of 12+/-5 days. A mean of 3.7+/-1.8 (18)F-fluoride positive plaques per patient was identified after recent acute coronary syndrome, compared with 2.4+/-2.3 positive plaques per patient in stable coronary artery disease. The bias in agreement in maximum tissue to background ratio measurements in visually positive plaques was low between observers (mean difference, -0.01; 95% limits of agreement, -0.32 to 0.30) or between scans (mean difference, 0.06; 95% limits of agreement, -0.49 to 0.61). Good agreement in the categorization of focal (18)F-fluoride uptake was achieved using visual assessment alone (kappa=0.66) and further improved at higher maximum tissue to background ratio values. CONCLUSIONS: Coronary (18)F-fluoride activity is a precise and reproducible metric in the coronary vasculature. The analytical performance of (18)F-fluoride is sufficient to assess the prognostic utility of this radiotracer as a noninvasive imaging biomarker of plaque vulnerability. CLINICAL TRIAL REGISTRATION: URL: http://www.clinicaltrials.gov. Unique identifiers: NCT02110303 and NCT02278211.

[13] *Xu L, Wang YR, Li PC, Feng B*. **Atorvastatin Blocks Advanced Glycation End Products Induced Reduction in Macrophage Cholesterol Efflux Mediated With ATP-Binding Cassette Transporters G 1**. Circulation journal : official journal of the Japanese Circulation Society 2019.

PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=31378770

ABSTRACT

BACKGROUND: There is accumulating evidence that the AGEs-RAGE interaction plays an important role in accelerated atherosclerosis in diabetes. Our previous study showed that the AGEs-RAGE axis can reduce the cholesterol efflux of THP-1 macrophages through suppression of the expression of ABCG1 and that statins can inhibit the expression of RAGE. However, the role of statins in recovering the cholesterol efflux of macrophages reduced by AGEs has not been assessed.Methods and Results:ApoE(-/-)mice and THP-1 macrophages were both treated by AGEs or AGEs combined with anti-RAGE antibody (only in THP-1 cells), ALT711 and atorvastatin separately. Cholesterol efflux of THP-1 macrophages and murine peritoneal macrophages was tested by fluorescence microplate technique. RT-PCR and western blot analysis were used to measure the expression of RAGE and molecules included in cholesterol efflux. After co-incubating with atorvastatin and AGEs, reduction in lipid accumulation in THP-1 macrophages and improvement of lesions complexity occurred compared with treating by AGEs only. Atorvastatin

increased cholesterol efflux and ABCG1 expression of macrophages, which were reduced by AGEs, and decreased the expression of RAGE at the same time. CONCLUSIONS: This study demonstrated that atorvastatin can recover the deleterious ABCG1-mediated cholesterol efflux induced by AGEs in THP-1 macrophages and murine peritoneal macrophages by downregulating RAGE expression. It may contribute to the protective action of atorvastatin in diabetic subjects with atherosclerosis.

[14] *Yang Z, Edwards D, Massou E et al.* **Statin use and high-dose statin use after ischemic stroke in the UK: a retrospective cohort study**. Clinical epidemiology 2019; 11:495-508.

PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=31388316

ABSTRACT

Background: Trial evidence supports statin use after ischemic stroke and recent American, European and British guidelines recommend high-intensity statins for this indication. Limited data are available describing current statin use among these patients in unselected settings. We conducted a cohort study to examine secular trends and factors associated with statin use and dose following ischemic stroke. Methods: A retrospective cohort study of patients with first ischemic stroke between 2000 and 2014 was conducted using the Clinical Practice Research Datalink (CPRD). Proportions of statin users and high-intensity statin users within 2 years after stroke were estimated for each calendar year. We used Cox regression models to explore potential factors associated with statin use and Poisson regression models to calculate risk ratios for the use of a high-intensity statin. Results: A total of 80,442 patients with first stroke were analyzed. The proportion using statins within 2 years after stroke increased from 25% in 2000 to 70% in 2006 and remained at about 75% through 2014. Among post-stroke statin users, high-intensity use accounted for approximately 15% between 2004 and 2011 and then increased to almost 35% in 2014. Older patients (aged >/=75 years), younger patients (<45 years), patients with no prior statin treatment, dementia, underweight, or absence of cardiovascular factors (coronary heart disease, smoking, obesity, diabetes, hypertension, or transient ischemic attack) were less likely to use statins and less likely to receive a high-intensity statin. Conclusion: There has been an increase over time in both statin use and dose, but many patients with ischemic stroke continue to be under-treated. Clinical trials and policy interventions to improve appropriate post-stroke statin use should focus on younger and older patients, patients with no pre-stroke statin treatment, and patients without additional cardiovascular risk factors.

[15] *Mohammadalipour A, Hashemnia M, Goudarzi F, Pouyandeh Ravan A*. **Increasing the effectiveness of tyrosine kinase inhibitor (TKI) in combination with a statin in reducing liver fibrosis**. Clinical and experimental pharmacology & physiology 2019.

PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=31396972

ABSTRACT

It has been shown that nilotinib as a tyrosine kinase inhibitor, and atorvastatin as a Rho-kinase inhibitor, both have anti-fibrotic effects. Therefore, considering the relationship between these two pathways, this study aimed to investigate the effects of their co-treatment against hepatic stellate cells (HSCs) activation and liver fibrosis. For this purpose, the activation of HSCs coincided with these therapies. Also, liver fibrosis by carbon tetrachloride (CCl4) was induced in male Wistar rats and treated simultaneously with these compounds. The expression of alpha-smooth muscle actin (alpha-SMA), connective tissue growth factor (CTGF), Ras homolog gene family, and member A (RhoA)/Rho-associated protein kinase

(ROCK) in HSCs were measured. The expression of transforming growth factor beta-1 (TGF-beta1), its receptor (TbetaRII), CTGF, and platelets derived growth factor (PDGF), in the livers, were also investigated, all by real-time PCR and western blot analysis. Also, histopathologic and immunohistochemical evaluations were performed to evaluate changes in liver fibrosis during treatment. The results indicated the downregulation of RhoA/ROCK, CTGF, and alpha-SMA, and inhibition of the HSCs activation toward myofibroblasts. The results also showed that the combined use of atorvastatin and nilotinib has significantly higher inhibitory effects. The anti-fibrotic effects of atorvastatin and nilotinib co-administration were also observed by histopathologic and immunohistochemical observations, and inhibiting the expression of TGF-beta1, TbetaRII, CTGF, and PDGF. Taken together, this study revealed that co-administration of nilotinib-atorvastatin has novel anti-fibrotic effects, by inhibiting RhoA/ROCK, and CTGF pathway. Therefore, the importance of the common pathway of RhoA/ROCK and CTGF, in reducing fibrosis may almost be concluded.

[16] *Markossian TW, Kramer HJ, Burge NJ et al.* **Low statin use in nondialysis-dependent chronic kidney disease in the absence of clinical atherosclerotic cardiovascular disease or diabetes**. Clinical kidney journal 2019; 12:530-537.

PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=31384445

ABSTRACT

Background: Both reduced glomerular filtration rate and increased urine albumin excretion, markers of chronic kidney disease (CKD), are associated with increased risk of atherosclerotic cardiovascular disease (ASCVD). However, CKD is not recognized as an ASCVD risk equivalent by most lipid guidelines. Statin medications, especially when combined with ezetimibe, significantly reduce ASCVD risk in patients with nondialysis-dependent CKD. Unless physicians recognize the heightened ASCVD risk in this population, statins may not be prescribed in the absence of clinical cardiovascular disease or diabetes, a recognized ASCVD risk equivalent. We examined statin use in adults with nondialysis-dependent CKD and examined whether the use differed in the presence of clinical ASCVD and diabetes. Methods: This study ascertained statin use from pharmacy dispensing records during fiscal years 2012 and 2013 from the US Department of Veterans Affairs Healthcare System. The study included 581 344 veterans aged >/=50 years with nondialysis-dependent CKD Stages 3-5 with no history of kidney transplantation or dialysis. The 10-year predicted ASCVD risk was calculated with the pooled risk equation. Results: Of veterans with CKD, 62.1% used statins in 2012 and 55.4% used statins continuously over 2 years (2012-13). Statin use in 2012 was 76.2 and 75.5% among veterans with CKD and ASCVD or diabetes, respectively, but in the absence of ASCVD, diabetes or a diagnosis of hyperlipidemia, statin use was 21.8% ($P < 0.001$). The 10-year predicted ASCVD risk was >/=7.5% in 95.1% of veterans with CKD, regardless of diabetes status. Conclusions: Statin use is low in veterans with nondialysis-dependent CKD in the absence of ASCVD or diabetes despite high-predicted ASCVD risk. Future studies should examine other populations.

[17] *Berman AN, Blankstein R*. **Optimizing Dyslipidemia Management for the Prevention of Cardiovascular Disease: a Focus on Risk Assessment and Therapeutic Options**. Current cardiology reports 2019; 21:110.

PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=31378838

ABSTRACT

Literature update week 32 (2019)

Primary prevention of incident atherosclerotic cardiovascular disease (ASCVD) as well as decreasing the risk of future events in those with established atherosclerosis is critical from a public health perspective. Management of dyslipidemias constitutes a key target in decreasing the risk of developing ASCVD events. While there have been great strides in the treatment of dyslipidemia over the last three decades, there are important recent developments and ongoing research that will expand the available therapeutic options and enable further cardiovascular risk reduction. PURPOSE OF REVIEW: The purpose of this paper is to review new developments relating to the primary prevention and management of ASCVD with a specific focus on optimizing the treatment of dyslipidemias. RECENT FINDINGS: In the realm of ASCVD risk prediction, mounting evidence over the last decade has demonstrated that coronary artery calcium testing is superior to any serum biomarker in the prediction of future ASCVD events and in discriminating future cardiovascular risk. As such, it has been incorporated into the most recent ACC/AHA primary prevention guideline to help guide management decisions in select patients. In terms of the management of dyslipidemias, PCSK9 inhibitors lower LDL-C by 50-70% and provide an additional 15% reduction in key cardiovascular events in high-risk patients with known ASCVD, as demonstrated in the ODYSSEY and FOURIER trials. Cholesteryl ester transfer protein (CETP) inhibitors, which significantly increase HDL-C levels, demonstrated mixed results in large clinical trials and have helped reframe HDL-C as a risk marker rather than a modifiable risk factor. In regard to the management of triglycerides, the REDUCE-IT trial demonstrated a nearly 5% absolute reduction in key cardiovascular events with a highly purified fish-oil derivative named icosapent ethyl in high-risk patients already on statin therapy. Finally, in regard to lipoprotein(a)-which is a strong risk factor for ASCVD-there are exciting developments in the therapeutic pipeline which reduce circulating lipoprotein(a) levels by nearly 90%. The management of dyslipidemias continues to be an exciting field with several ongoing cardiovascular outcomes trials, improvement in risk prediction models, and new therapeutic agents in the pipeline that will further mitigate residual cardiovascular risk in both primary and secondary prevention patients.

[18] *Santos RD*. **Screening and management of familial hypercholesterolemia**. Current opinion in cardiology 2019; 34:526-530.

PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=31393421

ABSTRACT

PURPOSE OF REVIEW: To discuss recent findings related to epidemiology, diagnosis, natural history, atherosclerotic cardiovascular disease (ASCVD) risk heterogeneity and stratification, and treatment of familial hypercholesterolemia. RECENT FINDINGS: Familial hypercholesterolemia persists subdiagnosed, inadequately treated and social disparities aggravate this scenario. Molecular diagnosis is recommended but still not widely available and reimbursed, also recent reclassification of genetic variants associated with familial hypercholesterolemia limits its routine use. New familial hypercholesterolemia clinical diagnostic criteria like FAMCAT are being tested and are apparently more accurate than the classical ones. Genetic traits for familial hypercholesterolemia and high lipoprotein(a) concentrations apparently co-exist and are associated with a higher ASVCD risk than each alone. Indeed, ASCVD risk is heterogenous in heterozygous familial hypercholesterolemia and prospective studies show that it is influenced not only by high LDL-C but also by other risk features like smoking, hypertension, or diabetes. Coronary artery calcification might indicate a higher risk familial hypercholesterolemia population that could benefit from further LDL-C lowering with PCSK9 inhibitors. The latter medications may reduce ASCVD risk in familial hypercholesterolemia individuals similarly to their impact on the general population as shown in a randomized prospective development program (SPIRE). SUMMARY: Knowledge

about familial hypercholesterolemia has improved but there are still many challenges for its optimal management.

[19] *Chen B, Zhao P, Shi X et al.* **A Review of PCSK9 Inhibitors and their effects on cardiovascular disease**. Current topics in medicinal chemistry 2019.

PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=31400268

ABSTRACT

BACKGROUND: Cardiovascular disease remains the leading cause of morbidity and mortality in the world, with elevated low density lipoprotein-cholesterol (LDL-C) levels as a major risk factor. Lower levels of LDL-C can effectively reduce the risk of cardiovascular disease. Proprotein convertase subtilisin/kexin type 9 (PCSK9) plays an important role in regulating the degradation of hepatic LDL receptors that remove LDL-C from the circulation. PCSK9 inhibitors are a new class of agents that are becoming increasingly important as treatments to reduce LDL-C levels. Two PCSK9 inhibitors, alirocumab and evolocumab, have been approved to treat hypercholesterolemia and are available in the United States and European Union. Through inhibition of PCSK9 and increased recycling of LDL receptors, they can significantly reduce serum LDL-C levels. OBJECTIVE: This review will describe the chemistry, pharmacokinetics, and pharmacodynamics of PCSK9 inhibitors and their clinical effects.

[20] *Mantovani A, Bonapace S, Lunardi G et al.* **Associations between specific plasma ceramides and severity of coronary-artery stenosis assessed by coronary angiography**. Diabetes Metab 2019.

PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=31386900

ABSTRACT

AIM: Recent prospective studies have identified distinct plasma ceramides as strong predictors of major adverse cardiovascular events in patients with established or suspected coronary artery disease (CAD). Currently, it is uncertain whether higher levels of distinct plasma ceramides are associated with greater angiographic severity of coronary-artery stenoses in this patient population. METHODS: We measured six previously identified high-risk plasma ceramide species [Cer(d18:1/16:0), Cer(d18:1/18:0), Cer(d18:1/20:0), Cer(d18:1/22:0), Cer(d18:1/24:0) and Cer(d18:1/24:1)] in 167 consecutive patients with established or suspected CAD, who underwent urgent or elective coronary angiography. RESULTS: Approximately 77% of patients had a significant stenosis (>/=50%) in one or more of the main coronary arteries, the majority of whom (approximately 60%) had a significant stenosis in the left anterior descending (LAD) artery. Of the six measured plasma ceramides, higher levels of plasma Cer(d18:1/20:0) (adjusted-odds ratio 1.39, 95%CI 1.0-1.99), Cer(d18:1/22:0) (adjusted-odds ratio 1.57, 95%CI 1.08-2.29) and Cer(d18:1/24:0) (adjusted-odds ratio 1.59, 95%CI 1.08-2.32) were significantly associated with the presence of LAD stenosis>/=50%, after adjustment for age, sex, smoking, pre-existing CAD, hypertension, diabetes, dyslipidaemia, lipid-lowering therapy, estimated glomerular filtration rate and plasma C-reactive protein levels. Almost identical results were found even after excluding patients (n=15) with acute ST-elevation myocardial infarction. Similar results were also found when patients were categorized according to the Gensini severity score. CONCLUSION: Our cross-sectional study shows for the first time that higher levels of specific plasma ceramides are independently associated with a greater severity of coronary-artery stenoses in the LAD artery in patients who had suspected or established CAD.

Literature update week 32 (2019)

[21] *Hareedy MS, Ahmed EA, Ali MF*. **Montelukast modifies simvastatin-induced myopathy and hepatotoxicity**. Drug development research 2019.

PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=31389048

ABSTRACT

Montelukast (MNK) has prominent anti-inflammatory and antioxidant activities. It can protect the liver in different hepatotoxic models in animals. Simvastatin (SMV) is one of commonly used lipid lowering drugs for treatment of dyslipidemia in order to reduce cardiovascular disease. It has severe side effects such as myopathy and hepatotoxicity. The aim of the present study is to investigate the possible effect of MNK on SMV-induced myopathy and hepatotoxicity. Four groups of male rats: control group which received saline via stomach tube, MNK treated group (received 10 mg/kg/day MNK via stomach tube), SMV treated group (received 30 mg/kg/day SMV via stomach tube), and MNK + SMV (combination) group which received both MNK and SMV. All animals were treated for 14 days before obtaining blood and tissue samples. SMV has both hepatotoxic effects and myopathy. SMV caused a significant increase in myoglobin, creatinine kinase, ALT, AST, ALP, and bilirubin but, it decreased total proteins, globulin and albumin levels. Co-treatment of SMV and MNK increased the antioxidant activity significantly. MNK modifies partially the myopathic changes and hepatotoxic effect of SMV. Co-administration of MNK and SMV decreased their toxic potentials on the liver, skeletal muscles, and kidney. They have antioxidant activities when given together that produce muscle and hepatic protective effects.

[22] *Rago D, Rasmussen MA, Lee-Sarwar KA et al.* **Fish-oil supplementation in pregnancy, child metabolomics and asthma risk**. EBioMedicine 2019; 46:399-410.

PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=31399385

ABSTRACT

BACKGROUND: We recently demonstrated that maternal dietary supplementation with fish oil-derived n-3 long-chain polyunsaturated fatty acids (n-3 LCPUFAs) during pregnancy reduces the risk of asthma in the offspring but the mechanisms involved are unknown. METHODS: Here we investigated potential metabolic mechanisms using untargeted liquid chromatography-mass spectrometry-based metabolomics on 577 plasma samples collected at age 6months in the offspring of mothers participating in the n-3 LCPUFA randomized controlled trial. First, associations between the n-3 LCPUFA supplementation groups and child metabolite levels were investigated using univariate regression models and data-driven partial least square discriminant analyses (PLS-DA). Second, we analyzed the association between the n-3 LCPUFA metabolomic profile and asthma development using Cox-regression. Third, we conducted mediation analyses to investigate whether the protective effect of n-3 LCPUFA on asthma was mediated via the metabolome. FINDINGS: The univariate analyses and the PLS-DA showed that maternal fish oil supplementation affected the child's metabolome, especially with lower levels of the n-6 LCPUFA pathway-related metabolites and saturated and monounsaturated long-chain fatty acids-containing compounds, lower levels of metabolites of the tryptophan pathway, and higher levels of metabolites in the tyrosine and glutamic acid pathway. This fish oil-related metabolic profile at age 6months was significantly associated with a reduced risk of asthma by age 5 and the metabolic profile explained 24% of the observed asthma-protective effect in the mediation analysis. INTERPRETATION: Several of the observed pathways may be involved in the asthma-protective effect of maternal n-3 LCPUFA supplementation and act as mediators between the intervention and disease

development. FUNDING: COPSAC is funded by private and public research funds all listed on www.copsac.com.

[23] *Kumar A, Shariff M, Doshi R*. **Impact of rosuvastatin versus atorvastatin on coronary atherosclerotic plaque volume - a systematic review and meta-analysis with trial sequential analysis of randomized control trials**. European journal of preventive cardiology 2019:2047487319868035.

PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=31382809

ABSTRACT

[24] *Gong B, Chen X, Lin R et al.* **Safety and Efficacy of the C-117 Formula for Vulnerable Carotid Artery Plaques (Spchim): A Randomized Double-Blind Controlled Pilot Study**. Evidence-based complementary and alternative medicine : eCAM 2019; 2019:9746492.

PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=31391862

ABSTRACT

Objective: To investigate the safety and efficacy of the Herbal Medicine C-117 (C-117) formula in the treatment of carotid atherosclerotic vulnerable plaques. Methods: This was a prospective, single-centre, randomized, double-blind study. A total of 120 eligible patients were randomly divided into two groups to receive the C-117 formula or placebo. As the basic treatment, both groups were treated according to the Guidelines for Secondary Prevention of Ischemic Stroke/Transient Ischemic Stroke in China using statins to regulate blood lipids, blood pressure lowering drugs, drugs for controlling blood sugar, and antiplatelet drugs according to the indications. The primary outcomes were the change in stability, the mean change of the plaque Crouse score, and the area and number of bilateral carotid artery plaques before and after 6 months of treatment. The secondary outcomes were the total number of cardiocerebrovascular events during the treatment and follow-up and the mean changes of lipid levels. Result: After 180 days of treatment, the plaque Crouse score(95% CI, 0.39 (0.01-0.77), P=0.046) and plaque area (95% CI, 2.14 (-10.10-14.39), P=0.727) were lower in the C-117 formula group than that before treatment. The plaque Crouse score of the control group (95% CI, 0.17 (-0.24-0.57), P=0.417) was lower than that before treatment, while the plaque area (95% CI, -0.35 (-9.35-8.65), P=0.938) increased, but without statistical significance. There was no significant difference in the reduction of the intima-media thickness (IMT), plaque Crouse score, or plaque area between the two groups after treatment (P>0.05). Subgroup analysis of patients whose Lipitor medication time >/= 20% of the 6-month treatment showed that the levels of total cholesterol, triglycerides, and low-density lipoprotein were lower in the two groups after treatment than before, and the low-density lipoprotein levels in the C-117 formula group significantly decreased (95% CI, 2.99 (-0.08-0.39), P=0.005), but there was no statistical difference between the two groups after treatment (P>0.05). No serious adverse events occurred in the two groups after 180 days of treatment. Conclusion: The C-117 formula may be antiatherosclerotic by strengthening statins to reduce the low-density lipoprotein levels and reducing the carotid plaque Crouse scores. Clinical trials with large sample sizes, long-term interventions, and follow-up are needed to investigate the efficacy of the C-117 formula. Clinical Trials Registration: This trial is registered with clinicaltrials.gov identifier: NCT03072225 (registered retrospectively on 1st March 2017).

Literature update week 32 (2019)

[25] *Preston KJ, Rom I, Vrakas C et al.* **Postprandial activation of leukocyte-endothelium interaction by fatty acids in the visceral adipose tissue microcirculation**. FASEB journal : official publication of the Federation of American Societies for Experimental Biology 2019:fj201802637RR.

PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=31393790

ABSTRACT

High-fat diet (HFD)-induced obesity is associated with accumulation of inflammatory cells predominantly in visceral adipose depots [visceral adipose tissue (VAT)] rather than in subcutaneous ones [subcutaneous adipose tissue (SAT)]. The cellular and molecular mechanisms responsible for this phenotypic difference remain poorly understood. Controversy also exists on the overall impact that adipose tissue inflammation has on metabolic health in diet-induced obesity. The endothelium of the microcirculation regulates both the transport of lipids and the trafficking of leukocytes into organ tissue. We hypothesized that the VAT and SAT microcirculations respond differently to postprandial processing of dietary fat. We also tested whether inhibition of endothelial postprandial responses to high-fat meals (HFMs) preserves metabolic health in chronic obesity. We demonstrate that administration of a single HFM or ad libitum access to a HFD for 24 h quickly induces a transient P-selectin-dependent inflammatory phenotype in the VAT but not the SAT microcirculation of lean wild-type mice. Studies in P-selectin-deficient mice confirmed a mechanistic role for P-selectin in the initiation of leukocyte trafficking, myeloperoxidase accumulation, and acute reduction in adiponectin mRNA expression by HFMs. Despite reduced VAT inflammation in response to HFMs, P-selectin-deficient mice still developed glucose intolerance and insulin resistance when chronically fed an HFD. Our data uncover a novel nutrient-sensing role of the vascular endothelium that instigates postprandial VAT inflammation. They also demonstrate that inhibition of this transient postprandial inflammatory response fails to correct metabolic dysfunction in diet-induced obesity.-Preston, K. J., Rom, I., Vrakas, C., Landesberg, G., Etwebe, Z., Muraoka, S., Autieri, M., Eguchi, S., Scalia, R. Postprandial activation of leukocyte-endothelium interaction by fatty acids in the visceral adipose tissue microcirculation.

[26] *Mikaeeli S, Susan-Resiga D, Girard E et al.* **Functional analysis of natural PCSK9 mutants in modern and archaic humans**. The FEBS journal 2019.

PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=31386798

ABSTRACT

PCSK9 is the last member of the proprotein convertases (PCs) family and its gene is mutated in ~2-3% of individuals with familial hypercholesterolemia (FH). This protein enhances the degradation of the low-density lipoprotein receptor (LDLR) and hence increases the levels of circulating LDL-cholesterol (LDLc). Studies of the underlying mechanism(s) regulating the activity of different mutations in the PCSK9 gene are ongoing as they enhance our understanding of the biology and clinical relevance of PCSK9 and its partners. In an attempt to unravel the regulation of PCSK9 transcription and possibly identify mutation "hot spot" regions with alterations in CpG methylation, we present for the first time the complete methylome profile of the PCSK9 gene in modern and archaic humanoids. Our data showed that the genomes of modern humans and archaic PCSK9 exhibit a similar methylation pattern. Next, we defined the mechanistic consequences of three PCSK9 natural mutations (PCSK9-R96L, -R105W and -P174S) and one archaic Denisovan mutation (PCSK9-H449L) using various complementary cellular and in vitro binding assays. Our results showed that the PCSK9-H449L is a loss-of-function (LOF) mutation, likely due to its lower binding affinity to the LDLR. Similarly, PCSK9-R96L and -R105W are LOF mutations, even though they have been identified in FH patients. The PCSK9-R105W mutation leads to a significantly

lower autocatalytic processing of proPCSK9. PCSK9-P174S resulted in a LOF in both extracellular and intracellular pathways. In conclusion our extensive analyses revealed that all studied mutations result in PCSK9 LOF, via various mechanisms, leading to lower levels of LDLc.

[27] *Weinstock A, Brown EJ, Garabedian ML et al.* **Single-Cell RNA Sequencing of Visceral Adipose Tissue Leukocytes Reveals that Caloric Restriction Following Obesity Promotes the Accumulation of a Distinct Macrophage Population with Features of Phagocytic Cells**. Immunometabolism 2019; 1.

PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=31396408

ABSTRACT

Obesity can lead to type 2 diabetes and is an epidemic. A major contributor to its adverse effects is inflammation of the visceral adipose tissue (VAT). Life-long caloric restriction (CR), in contrast, results in extended lifespan, enhanced glucose tolerance/insulin sensitivity, and other favorable phenotypes. The effects of CR following obesity are incompletely established, but studies show multiple benefits. Many leukocyte types, macrophages predominantly, reside in VAT in homeostatic and pathological states. CR following obesity transiently increases VAT macrophage content prior to resolution of inflammation and obesity, suggesting that macrophage content and phenotype play critical roles. Here, we examined the heterogeneity of VAT leukocytes and the effects of obesity and CR. In general, our single-cell RNA-sequencing data demonstrate that macrophages are the most abundant and diverse subpopulation of leukocytes in VAT. Obesity induced significant transcriptional changes in all 15 leukocyte subpopulations, with many genes showing coordinated changes in expression across the leukocyte subpopulations. Additionally, obese VAT displayed expansion of one major macrophage subpopulation, which, in silico, was enriched in lipid binding and metabolic processes. This subpopulation returned from dominance in obesity to lean proportions after only 2 weeks of CR, although the pattern of gene expression overall remained similar. Surprisingly, CR VAT is dominated by a different macrophage subpopulation, which is absent in lean conditions. This subpopulation is enriched in genes related to phagocytosis and we postulate that its function includes clearance of dead cells, as well as excess lipids, contributing to limiting VAT inflammation and restoration of the homeostatic state.

[28] *Marathe A, Ganaraja B, Ashwin Shenoy K et al.* **Effect of Atorvastatin on Serum Para-Oxonase-1 and C-Reactive Protein in Wistar Rats**. Indian journal of clinical biochemistry : IJCB 2019; 34:312-317.

PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=31391721

ABSTRACT

Statins have been widely used in the treatment of hypercholesterolemia and atherosclerotic disease. Atherosclerosis is an ongoing inflammatory response which is involved in mediating all stages of this multifactorial disease. The present study focuses on the long term effect of atorvastatin on the anti-atherogenic and anti-inflammatory properties with reference to para-oxonase and C-reactive protein levels in rats. Thirty six Wistar albino rats obtained from the central animal house were divided into 6 groups with 6 rats in each group. Group I and IV served as the control for male and female rats respectively. Group II and V comprised of male and female rats that received low dose of atorvastatin (10 mg/kg body weight). Group III and VI comprised of male and female rats that received high dose of atorvastatin (40 mg/kg body weight) for period of 45 days. Blood was collected by cardiac puncture. The plasma was analysed for total cholesterol, HDL cholesterol, C-reactive protein (CRP) and Paraoxonase-1,

both basal Paraoxonase (BPON) & Salt stimulated Paraoxonase (SPON) by standard procedures. Results of the present study showed a reduction in TC and increase in HDL-C in both groups of rats receiving low and high dose of Atorvastatin. Both male and female rats responded similarly. The levels of CRP decreased in the male rats receiving either low or high dose of atorvastatin. Activity of SPON and BPON was increased only in the group receiving high dose of atorvastatin in both male and female rats.

[29] *Di Cara F, Andreoletti P, Trompier D et al.* **Peroxisomes in Immune Response and Inflammation**. International journal of molecular sciences 2019; 20.

PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=31398943

ABSTRACT

The immune response is essential to protect organisms from infection and an altered self. An organism's overall metabolic status is now recognized as an important and long-overlooked mediator of immunity and has spurred new explorations of immune-related metabolic abnormalities. Peroxisomes are essential metabolic organelles with a central role in the synthesis and turnover of complex lipids and reactive species. Peroxisomes have recently been identified as pivotal regulators of immune functions and inflammation in the development and during infection, defining a new branch of immunometabolism. This review summarizes the current evidence that has helped to identify peroxisomes as central regulators of immunity and highlights the peroxisomal proteins and metabolites that have acquired relevance in human pathologies for their link to the development of inflammation, neuropathies, aging and cancer. This review then describes how peroxisomes govern immune signaling strategies such as phagocytosis and cytokine production and their relevance in fighting bacterial and viral infections. The mechanisms by which peroxisomes either control the activation of the immune response or trigger cellular metabolic changes that activate and resolve immune responses are also described.

[30] *Muscogiuri G, Cantone E, Cassarano S et al.* **Gut microbiota: a new path to treat obesity**. International journal of obesity supplements 2019; 9:10-19.

PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=31391921

ABSTRACT

Obesity is a multifactorial disease resulting in excessive accumulation of adipose tissue. Over the last decade, growing evidence has identified the gut microbiota as a potential factor in the pathophysiology of both obesity and the related metabolic disorders. The gut microbiota is known to protect gastrointestinal mucosa permeability and to regulate the fermentation and absorption of dietary polysaccharides, perhaps explaining its importance in the regulation of fat accumulation and the resultant obesity. The proposed mechanisms by which the gut microbiota could contribute to the pathogenesis of obesity and the related metabolic diseases include: (a) a high abundance of bacteria that ferment carbohydrates, leading to increased rates of short-chain fatty acid (SCFA) biosynthesis, providing an extra source of energy for the host, that is eventually stored as lipids or glucose; (b) increased intestinal permeability to bacterial lipopolysaccharides (LPS), resulting in elevated systemic LPS levels that aggravate low-grade inflammation and insulin resistance; (c) increased activity of the gut endocannabinoid system. Fecal transplantation studies in germ-free mice have provided crucial insights into the potential causative role of the gut microbiota in the development of obesity and obesity-related disorders. Diet +/- bariatric surgery have been reported to modulate the gut microbiota, leading to lean

host phenotype body composition. This review aims to report clinical evidence for a link of the gut microbiota with human obesity and obesity-related diseases, to provide molecular insights into these associations, and to address the effect of diet and bariatric surgery on the gut microbiota, including colonic microbiota, as a potential mechanism for promoting weight loss.

[31] *Arashi H, Yamaguchi J, Kawada-Watanabe E et al.* **Polyunsaturated Fatty Acid Impact on Clinical Outcomes in Acute Coronary Syndrome Patients With Dyslipidemia: Subanalysis of HIJ-PROPER**. Journal of the American Heart Association 2019; 8:e012953.

PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=31390907

ABSTRACT

Background This study aimed to examine the impact of baseline eicosapentaenoic acid (EPA) to arachidonic acid (AA) ratio on clinical outcomes of patients with acute coronary syndrome. Methods and Results In the HIJ-PROPER (Heart Institute of Japan Proper Level of Lipid Lowering With Pitavastatin and Ezetimibe in Acute Coronary Syndrome) study, 1734 patients with acute coronary syndrome and dyslipidemia were randomly assigned to pitavastatin+ezetimibe therapy or pitavastatin monotherapy. We divided the patients into 2 groups based on EPA/AA ratio on admission (cutoff 0.34 mug/mL as median of baseline EPA/AA ratio) and examined their clinical outcomes. The primary end point comprised all-cause death, nonfatal myocardial infarction, nonfatal stroke, unstable angina pectoris, or ischemia-driven revascularization. Percentage reduction of low-density lipoprotein cholesterol and triglyceride from baseline to follow-up was similar regardless of baseline EPA/AA ratio. Despite the mean low-density lipoprotein cholesterol level during follow-up being similar between the low- and high-EPA/AA groups, the mean triglyceride levels during follow-up were significantly higher in the low- than in the high-EPA/AA group. After 3 years of follow-up, the cumulative incidence of the primary end point in patients with low EPA/AA was 27.2% in the pitavastatin+ezetimibe group compared with 36.6% in the pitavastatin-monotherapy group (hazard ratio 0.69; 95% CI, 0.52-0.93; P=0.015). However, there was no effect of pitavastatin+ezetimibe therapy on the primary end point in patients with high EPA/AA (hazard ratio 0.92; 95% CI, 0.70-1.20; P=0.52). Conclusions Among acute coronary syndrome patients who have dyslipidemia and low EPA/AA ratio, adding ezetimibe to statin decreases the risk of cardiovascular events compared with statin monotherapy. Clinical Trial Registration URL: http://www.umin.ac.jp/ctr. Unique identifier: UMIN000002742.

[32] *Shi R, Mei Z, Zhang Z, Zhu Z*. **Effects of Statins on Relative Risk of Fractures for Older Adults: An Updated Systematic Review With Meta-Analysis**. Journal of the American Medical Directors Association 2019.

PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=31395495

ABSTRACT

OBJECTIVES: Basic and translational studies have found statin treatment may have beneficial effects on bone metabolism; however, whether statins reduce the risk of fractures in older adults is still in debate. Therefore, we aimed to summarize the up-to-date evidence on risk of fracture among older individuals with statin use. DESIGN: Systematic literature review and meta-analysis. SETTING AND PARTICIPANTS: Twenty-one observational studies and 2 randomized controlled trials (RCTs) comprising 1,783,123 participants aged at least 50 years were retrieved from PubMed, Embase, and the Cochrane Library. MEASURES: We estimated summary relative risks (RRs) with 95% confidence intervals (CIs) using the

random-effects model. Subgroup analysis was performed to explore the potential source of heterogeneity. RESULTS: Meta-analysis of observational studies suggested that statin treatment was significantly associated with reduced risk of all fractures (RR 0.80, 95% CI 0.72-0.88), among which hip fracture (RR 0.73, 95% CI 0.64-0.82) and lower extremity fracture (RR 0.69, 95% CI 0.54-0.88) showed consistent results, whereas no significant decreased risk was observed with respect to other fracture sites. Subgroup analyses showed that among the statin users, fracture risk was reduced in both genders, older adults >/=50 years old, those with short drug duration (< year) or medium to high statin dose (>90 defined daily dose), those taking atorvastatin, and in Europeans and Americans. Meta-analysis of RCTs revealed no significant effect of statin treatment on the risk of fractures (RR 1.00, 95% CI 0.87-1.15). CONCLUSIONS AND IMPLICATIONS: Overall, the findings of this updated meta-analysis indicated no solid evidence supporting that statins have a beneficial effect associated with reduced risk of fractures for older adults. Our findings should be further confirmed in future larger population-based prospective cohort studies or well-designed RCTs.

[33] *Raal FJ, Tuomilehto J, Sposito AC et al.* **Treatment effect of alirocumab according to age group, smoking status, and hypertension: Pooled analysis from 10 randomized ODYSSEY studies**. Journal of clinical lipidology 2019.

PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=31377052

ABSTRACT

BACKGROUND: Age, smoking, hypercholesterolemia, and hypertension are major risk factors for atherosclerotic cardiovascular disease. OBJECTIVE: We examined whether the effects of alirocumab on low-density lipoprotein cholesterol (LDL-C) differed according to age, hypertension, or smoking status. METHODS: Data were pooled from 10 Phase 3 ODYSSEY randomized trials (24-104 weeks' duration) in 4983 people with heterozygous familial hypercholesterolemia (FH) or non-familial hypercholesterolemia (3188 on alirocumab, 1795 on control [620 on ezetimibe and 1175 on placebo]). Most participants received concomitant maximum tolerated statin therapy. In 8 trials, the alirocumab dose was increased from 75 mg every 2 weeks (Q2W) to 150 mg Q2W at Week 12 if predefined risk-based LDL-C goals were not achieved at Week 8 (>/=70 mg/dL in very high cardiovascular risk; >/=100 mg/dL in moderate or high cardiovascular risk). Two trials compared alirocumab 150 mg Q2W vs placebo. The efficacy and safety of alirocumab were assessed post hoc in subgroups stratified by age (<65, >/=65 to <75, >/=75 years) and baseline hypertension or smoking status. RESULTS: Alirocumab reduced LDL-C by 23.7% (75/150 mg vs ezetimibe + statin) to 65.4% (150 mg vs placebo + statin) from baseline to Week 24 vs control. Subgroup analyses confirmed no significant interactions in response to alirocumab between age group, hypertension, or smoking status. Overall rates of treatment-emergent adverse events were similar between alirocumab and control groups. CONCLUSIONS: In this pooled analysis from 10 trials, alirocumab led to substantial LDL-C reductions vs control in every age group and regardless of hypertension or smoking status. Alirocumab was well tolerated in all subgroups.

[34] *Esparza MI, Li X, Adams-Huet B et al.* **Very Severe Hypertriglyceridemia in a Large US County Health Care System: Associated Conditions and Management**. Journal of the Endocrine Society 2019; 3:1595-1607.

PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=31384720

ABSTRACT

Context: Patients with very severe hypertriglyceridemia (triglyceride levels >/=2000 mg/dL; 22.6 mmol/L) require aggressive treatment. However, little research exists on the underlying etiologies and management of very severe hypertriglyceridemia. Objective: We hypothesized (i) very severe hypertriglyceridemia in adults is mostly associated with secondary causes and (ii) most patients with very severe hypertriglyceridemia lack appropriate follow-up and treatment. Design: We queried electronic medical records at Parkland Health and Hospital Systems for lipid measurements in the year 2016 and identified patients with serum triglyceride levels >/=2000 mg/dL (22.6 mmol/L). We extracted data on demographics, underlying causes, lipid-lowering therapy, and follow-up. Results: One hundred sixty-four serum triglyceride measurements were >/=2000 mg/dL (22.6 mmol/L) in 103 unique patients. Of these, 60 patients were admitted to the hospital (39 for acute pancreatitis). Most were Hispanic (79%). The major conditions associated with very severe hypertriglyceridemia included uncontrolled diabetes mellitus (74%), heavy alcohol use (10%), medication use (7%), and hypothyroidism (2%). Two patients were known to have monogenic causes of hypertriglyceridemia. After the index measurement of triglycerides >/=2000 mg/dL (22.6 mmol/L), the use of triglyceride-lowering drugs increased, most prominently the use of fish oil supplements, which increased by 80%. However, in follow-up visits, hypertriglyceridemia was addressed in only 50% of encounters, and serum triglycerides were remeasured in only 18%. Conclusion: In summary, very severe hypertriglyceridemia was quite prevalent (approximately 0.1% of all lipid measurements) in our large county health care system, especially in Hispanic men. Most cases were related to uncontrolled diabetes mellitus, and follow-up monitoring was inadequate.

[35] *Pirazzi C, Tavaglione F, Tivesten A, Romeo S*. **PCSK9 Inhibitors in a Statin-Intolerant Transgender Man With Heterozygous Familial Hypercholesterolemia: A Case Report**. Journal of the Endocrine Society 2019; 3:1461-1464.

PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=31380502

ABSTRACT

In female-to-male transgender individuals, testosterone is used to induce masculinization. Sex steroid therapy may increase circulating triglyceride and low-density lipoprotein cholesterol (LDL-C) levels and may decrease high-density lipoprotein cholesterol (HDL-C) levels, resulting in a more atherogenic lipid profile. These potentially adverse effects of androgen therapy may be exacerbated by the presence of familial hypercholesterolemia (FH). We describe the case of a transgender man with genetically diagnosed FH who was intolerant to statins and was started on a proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitor to control his lipoproteins more effectively. The 35-year-old female-to-male transgender individual was referred to our center with a history of elevated LDL-C levels. Despite treatment with high doses of high-potency statins and ezetimibe, he had never achieved a sustained reduction in LDL-C; his levels of LDL-C were fluctuating between 170 and 344 mg/dL (4.4 and 8.9 mmol/L). Moreover, he developed side effects to statins in the form of myalgia and discontinued statin treatment. At the Sahlgrenska Lipid Clinic, a genetic diagnosis of heterozygous FH was established, and PCSK9 inhibitor therapy was started. The patient's LDL-C level has been reduced by approximately 40% for 23 months, and no adverse events have been reported.

[36] *Winther M, Shpitzen S, Yaacov O et al.* **In search for genetic explanation for LDLc variabily in an FH family: Common SNPs and a rare mutation in microsomal triglyceride transfer protein explain only part of LDL variability in an FH family**. Journal of lipid research 2019.

PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=31387896

ABSTRACT

BACKGROUND: We previously identified a highly consanguineous FH family demonstrating segregation of the JD Bari mutation in the LDL receptor as well as a putative cholesterol-lowering trait. We aimed to identify genes related to the latter effect. METHODS: LDLc values were normalized for FH affectation status, age, and gender. Using genome-wide SNP data, we examined whether known SNPs gleaned from a GWAS could explain the variation observed in LDLc. Four individuals with markedly reduced LDL levels underwent whole-exome sequencing. After prioritizing all potential mutations, we identified the most promising candidate genes and tested them for segregation with the lowering trait. We transfected a plasmid carrying the top candidate mutation, MTTP R634C, into COS-7 cells, to test enzymatic activity. RESULTS: The SNP score explained 3% of the observed variability. MTTP R634C showed reduced activity (49.1 nmol/mL) compared to wild-type allele (185.8 nmol/mL) (p=0.0012) and was marginally associated with reduced LDLc in FH patients (P=0.05). CONCLUSIONS: Phenotypic variability in an FH pedigree can only patrialy be explained by a combination of common SNPs and rare mutation and a rare variant in the MTTP gene. LDLc varianiily in FH patients may have non genetic causes.

[37] *Chong M, Yoon G, Susan-Resiga D et al.* **Hypolipidaemia among patients with PMM2-CDG is associated with low circulating PCSK9 levels: a case report followed by observational and experimental studies**. Journal of medical genetics 2019.

PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=31391289

ABSTRACT

BACKGROUND: Proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitors are novel therapeutics for reducing low-density lipoprotein cholesterol (LDLc). While serious side-effects have not been observed in short-term clinical trials, there remain concerns that long-term PCSK9 inhibition may cause neurocognitive side-effects. METHODS AND RESULTS: An adult male with childhood-onset global developmental delay, cerebellar atrophy and severe hypolipidaemia underwent extensive biochemical and genetic investigations. Initial testing revealed low circulating PCSK9 levels and a common loss-of-function PCSK9 polymorphism, but these findings did not fully account for severe hypolipidaemia. Whole-exome sequencing was subsequently performed and identified two pathogenic phosphomannose mutase 2 (PMM2) variants (p.Arg141His and p.Pro69Ser) known to cause PMM2-associated congenital disorder of glycosylation (PMM2-CDG). A diagnosis of PMM2-CDG was consistent with the proband's neurological symptoms and severe hypolipidaemia. Given that PMM2-CDG is characterised by defective protein N-glycosylation and that PCSK9 is a negative regulator of LDLc, we postulated that loss of PCSK9 N-glycosylation mediates hypolipidaemia among patients with PMM2-CDG. First, in an independent cohort of patients with PMM2-CDG (N=8), we verified that circulating PCSK9 levels were significantly lower in patients than controls (p=0.0006). Second, we conducted in vitro experiments in hepatocyte-derived cells to evaluate the effects of PCSK9 N-glycosylation loss on LDL receptor (LDLR) activity. Experimental results suggest that defective PCSK9 N-glycosylation reduces the ability of circulating PCSK9 to degrade LDLR. CONCLUSION: Life-long exposure to genetically lower PCSK9 per se is unlikely to cause neurocognitive impairment. Both observational and experimental findings suggest that hypolipidaemia in PMM2-CDG may be partially mediated by loss of PCSK9 N-glycosylation and/or its regulators.

[38] *Giraud C, Tournadre A, Pereira B et al.* **Alterations of HDL particle phospholipid composition and role of inflammation in rheumatoid arthritis**. Journal of physiology and biochemistry 2019.

PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=31392628

ABSTRACT

The increased cardiovascular risk in RA (rheumatoid arthritis) cannot be explained by common quantitative circulating lipid parameters. The objective of the study was to characterize the modifications in HDL phosphosphingolipidome in patients with RA to identify qualitative modifications which could better predict the risk for CVD. Nineteen patients with RA were compared to control subjects paired for age, sex, BMI, and criteria of metabolic syndrome. The characterization of total HDL phosphosphingolipidome was performed by LC-MS/MS. RA was associated with an increased HDL content of lysophosphatidylcholine and a decreased content of PC (phosphatidylcholine), respectively, positively and negatively associated with cardiovascular risk. A discriminant molecular signature composed of 18 lipids was obtained in the HDL from RA patients. The detailed analysis of phospholipid species showed that molecules carrying omega-3 FA (fatty acids), notably docosahexaenoic acid (C22:6 n-3), were depleted in HDL isolated from RA patients. By contrast, two PE (phosphatidylethanolamine) species carrying arachidonic acid (C20:4 n-6) were increased in HDL from RA patients. Furthermore, disease activity and severity indexes were associated with altered HDL content of 4 PE and 2 PC species. In conclusion, the composition of HDL phosphosphingolipidome is altered during RA. Identification of a lipidomic signature could therefore represent a promising biomarker for CVD risk. Although a causal link remains to be demonstrated, pharmacological and nutritional interventions targeting the normalization of the FA composition of altered phospholipids could help to fight against RA-related inflammation and CVD risk.

[39] *Veit L, Allegri Machado G, Burer C et al.* **Sitosterolemia-10 years observation in two sisters**. JIMD reports 2019; 48:4-10.

PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=31392106

ABSTRACT

Familial hypercholesterolemia due to heterozygous low-density lipoprotein-receptor mutations is a common inborn errors of metabolism. Secondary hypercholesterolemia due to a defect in phytosterol metabolism is far less common and may escape diagnosis during the work-up of patients with dyslipidemias. Here we report on two sisters with the rare, autosomal recessive condition, sitosterolemia. This disease is caused by mutations in a defective adenosine triphosphate-binding cassette sterol excretion transporter, leading to highly elevated plant sterol concentrations in tissues and to a wide range of symptoms. After a delayed diagnosis, treatment with a diet low in plant lipids plus ezetimibe to block the absorption of sterols corrected most of the clinical and biochemical signs of the disease. We followed the two patients for over 10 years and report their initial presentation and long-term response to treatment.

[40] *Gonzalez-Cantero A, Gonzalez-Cantero J, Sanchez-Moya AI et al.* **Is intima-media thickness a predictor for cardiovascular risk?** Lancet 2019; 394:380-381.

PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=31379328

ABSTRACT

Literature update week 32 (2019)

[41] *Naslund U, Lundgren A, Vanoli D, Norberg M*. **Is intima-media thickness a predictor for cardiovascular risk? - Authors' reply**. Lancet 2019; 394:381.

PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=31379329

ABSTRACT

[42] *Huang TY, Goldsmith FR, Fuller SE et al.* **Response of Liver Metabolic Pathways to Ketogenic Diet and Exercise Are Not Additive**. Med Sci Sports Exerc 2019.

PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=31389908

ABSTRACT

PURPOSE: Studies suggest ketogenic diets (KDs) produce favorable outcomes (health and exercise performance); however, most rodent studies have used a low protein KD, which does not reflect the normal-to-high protein KDs used by humans. Liver has an important role in ketoadaptation due to its involvement in gluconeogenesis and ketogenesis. This study was designed to test the hypothesis that exercise training (ExTr) while consuming a normal protein KD (NPKD) would induce additive/synergistic responses in liver metabolic pathways. METHODS: Lean, healthy male C57BL/6J mice were fed a low-fat control diet (15.9% kcal protein, 11.9% kcal fat, 72.2% kcal carbohydrate) or carbohydrate-deficient NPKD (16.1% protein, 83.9% kcal fat) for 6 weeks. After 3 weeks on the diet, half were subjected to 3-week treadmill ExTr (5day/week, 60min/day, moderate-vigorous intensity). Upon conclusion, metabolic and endocrine outcomes related to substrate metabolism were tested in liver and pancreas. RESULTS: NPKD-fed mice had higher circulating beta-hydroxybutyrate and maintained glucose at rest and during exercise. Liver of NPKD-fed mice had lower pyruvate utilization and greater ketogenic potential as evidenced by higher oxidative rates to catabolize lipids (mitochondrial and peroxisomal) and ketogenic amino acids (leucine). ExTr had higher expression of the gluconeogenic gene, Pck1, but lower hepatic glycogen, pyruvate oxidation, incomplete fat oxidation, and total pancreas area. Interaction effects between the NPKD and ExTr were observed for intrahepatic triglycerides, as well as genes involved in gluconeogenesis, ketogenesis, mitochondrial fat oxidation, and peroxisomal markers; however, none were additive/synergistic. Rather, in each instance the interaction effects showed the NPKD and ExTr opposed each other. CONCLUSIONS: A NPKD and ExTr independently induce shifts in hepatic metabolic pathways, but changes do not seem to be additive/synergistic in healthy mice.

[43] *Zanetti HR, Goncalves A, Paranhos Lopes LT et al.* **Effects of Exercise Training and Statin Use in People Living with HIV with Dyslipidemia**. Med Sci Sports Exerc 2019.

PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=31389909

ABSTRACT

PURPOSE: To evaluate the effects of the combination of ET and statins in people living with HIV. METHODS: This was a randomized, double-blind, placebo-controlled clinical trial. Eighty-three people living with HIV were assigned to either placebo (PL), statins (STA), placebo + ET (PLET) or statins + ET (STAET) groups. Volunteers assigned to STA and STAET groups were administered 10 mg of rosuvastatin, whereas the PL and PLET groups were administered a placebo. PLET and STAET groups performed ET three times a week. Before and after the 12-week follow-up, the volunteers underwent to anthropometric assessment and blood collection to evaluate lipid profile, cardiovascular markers,

inflammatory profile; a Doppler ultrasound examination, muscle strength (MS) and cardiorespiratory fitness (CF) tests were performed. RESULTS: There was a decrease in total cholesterol (TC), triglycerides (TG), low-density lipoprotein (LDL-c), C-reactive protein, fibrinogen, interleukin (IL)-1beta and right carotid intima-media thickness (cIMT) in the STA, PLET, and STAET groups compared to PL group ($p<0.001$). Furthermore, there was a decrease in TC, TG, LDL, IL-1beta, IL-6, and IL-8 levels and in left and right cIMT and an increase in HDL-c levels in the STAET groups compared to the STA ($p<0.001$) and PLET groups ($p<0.001$). There was an increase in IL-10 levels, peak-systolic velocity, end-diastolic velocity, wall shear rate in the PLET and STAET groups compared to the PL ($p<0.001$) and STA groups ($p<0.001$). The PLET and STAET groups reduced body fat mass, body fat percentage and increased lean body mass, MS and CF compared to PL ($p<0.001$) and STA ($p<0.001$) groups. CONCLUSION: The combination of ET and statins is useful to enhance lipid and inflammatory profiles, reduce CVD markers, and improve Doppler ultrasound findings, MS and CF in people living with HIV.

[44] *Espano E, Nam JH, Song EJ et al.* **Lipophilic statins inhibit Zika virus production in Vero cells**. Scientific reports 2019; 9:11461.

PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=31391514

ABSTRACT

Zika virus (ZIKV) is a mosquito-borne member of the Flaviviridae family. ZIKV infection has been associated with neurological complications such as microcephaly in newborns and Guillain-Barre syndrome in adults; thus, therapeutic agents are urgently needed. Statins are clinically approved for lowering cholesterol levels to prevent cardiovascular disease but have shown potential as antiviral drugs. In this study, we explored the possibility of utilizing statins as anti-ZIKV drugs. We found that, generally, lipophilic statins (atorvastatin, cerivastatin, fluvastatin, lovastatin, mevastatin, and simvastatin) could reduce ZIKV production in vitro and result in smaller foci of infection. Time-of-drug-addition assay revealed that early treatment with statins is more beneficial than late treatment; however, statins could not completely inhibit the entry stage of ZIKV infection. Furthermore, individual lipophilic statins differed in anti-ZIKV capacity, with fluvastatin being the most efficient at low concentrations. Taken together, this study shows that statins or their derivatives have the potential to be used as anti-ZIKV therapeutic agents.

[45] *Diehl P, Nienaber F, Zaldivia MTK et al.* **Lysophosphatidylcholine is a Major Component of Platelet Microvesicles Promoting Platelet Activation and Reporting Atherosclerotic Plaque Instability**. Thrombosis and haemostasis 2019; 119:1295-1310.

PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=31378855

ABSTRACT

BACKGROUND: Microvesicles (MVs) are small cell-derived vesicles, which are mainly released by activated cells. They are part of a communication network delivering biomolecules, for example, inflammatory molecules, via the blood circulation to remote cells in the body. Platelet-derived MVs are known to induce vascular inflammation. Research on the mediators and mechanisms of their inflammatory effects has attracted major interest. We hypothesize that specific lipids are the mediators of vascular inflammation caused by platelet-derived MVs. METHODS AND RESULTS: Liquid chromatography electrospray ionization-tandem mass spectrometry was used for lipid profiling of platelet-derived MVs. Lysophosphatidylcholine (LPC) was found to be a major component of platelet-

derived MVs. Investigating the direct effects of LPC, we found that it induces platelet activation, spreading, migration and aggregation as well as formation of inflammatory platelet-monocyte aggregates. We show for the first time that platelets express the LPC receptor G2AR, which mediates LPC-induced platelet activation. In a mouse model of atherosclerotic plaque instability/rupture, circulating LPC was detected as a surrogate marker of plaque instability. These findings were confirmed by matrix-assisted laser desorption ionization imaging, which showed that the LPC concentration of human plaques was highest in vulnerable plaque regions. CONCLUSION: LPC is a major component of platelet-derived MVs and via its interaction with G2AR on platelets contributes to platelet activation, spreading, migration and aggregation and ultimately to vascular inflammation. Circulating LPC reports on atherosclerotic plaque instability in mice and is significantly increased in unstable areas of atherosclerotic plaques in both mice and humans, linking LPC to plaque instability.

[46] *Tajbakhsh A, Bianconi V, Pirro M et al.* **Efferocytosis and Atherosclerosis: Regulation of Phagocyte Function by MicroRNAs**. Trends in endocrinology and metabolism: TEM 2019.

PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=31383556

ABSTRACT

There is evidence of the critical role of efferocytosis, the clearance of apoptotic cells (ACs) by phagocytes, in vascular cell homeostasis and protection against atherosclerosis. Specific microRNAs (miRs) can regulate atherogenesis by controlling the accumulation of professional phagocytes (e.g., macrophages) and nonprofessional phagocytes (i.e., neighboring tissue cells with the ability to acquire a macrophage-like phenotype) within the arterial wall, the differentiation of phagocytes into foam cells, the efferocytosis of apoptotic foam cells by phagocytes, and the phagocyte-mediated inflammatory response. A better understanding of the mechanisms involved in miR-regulated phagocyte function might lead to novel therapeutic antiatherosclerotic strategies. In this review, we try to shed light on the relationship between miRs and cellular players in the process of efferocytosis in the context of atherosclerotic plaque and their potential as molecular targets for novel antiatherosclerotic therapies.