Literature update week 33 (2018)

[1] *Behr PEB, Moriguchi EH, Castro I et al.* **Indications of PCSK9 Inhibitors for Patients at High and Very High Cardiovascular Risk**. Arquivos brasileiros de cardiologia 2018; 111:104-108.

PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=30110052

ABSTRACT

[2] *Atarbashi-Moghadam F, Havaei SR, Havaei SA et al.* **Periopathogens in atherosclerotic plaques of patients with both cardiovascular disease and chronic periodontitis**. ARYA atherosclerosis 2018; 14:53-57.

PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=30108636

ABSTRACT

BACKGROUND: Atherosclerosis and periodontitis are both chronic inflammatory diseases. Although a strong relationship between the two has already been established, the underlying mechanism is unknown. The present study was conducted aiming to detect the deoxyribonucleic acid (DNA) of Aggregatibacter actinomycetemcomitans (A.a), Campylobacter rectus (C.r), and Porphyromonas gingivalis (P.g) in subgingival and atherosclerotic plaques of patients with both chronic periodontitis and cardiovascular disease (CVD). METHODS: In this cross sectional study, patients with coronary artery disease (CAD) and moderate to severe periodontitis which were scheduled for coronary artery bypass grafting (CABG) were enrolled in the study. The subgingival plaques were collected before surgery. All samples were examined for the detection of selected periopathogens using polymerase chain reaction (PCR). RESULTS: The subgingival and atherosclerotic plaque samples of 23 patients were examined. The DNA of P.g, A.a, and C.r were found to be positive in 43.47%, 43.47%, and 78.26% of subgingival plaques, and 13.04%, 17.39%, and 8.69% of atherosclerotic plaques, respectively. In all cases, the bacterial species found in atherosclerotic plaques were also found in the subgingival plaques of the same patient. CONCLUSION: This study demonstrated the presence of periopathogens in atherosclerotic plaques of patients with chronic periodontitis. More studies are required to ascertain the exact role of these periopathogens in atherosclerotic plaque formation.

[3] *Vijayaraghavan B, Danabal K, Padmanabhan G, Ramanathan K*. **Study on Regulation of Low Density Lipoprotein Cholesterol Metabolism using PCSK9 Gene Silencing: A computational Approach**. Bioinformation 2018; 14:248-251.

PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=30108423

ABSTRACT

Combating and preventing abnormality in lipid metabolism becomes a pivotal criterion for research. Proprotein convertase subtilisin/kexin type 9 (PCSK9) is a circulating protein; it promotes the degradation of low-density lipoprotein receptors (LDL-R) and hence increases LDL-C levels. Silencing the gene PCSK9 at post-transcriptional level with the help of small interfering Ribo nucleic acid (siRNA) gives a new insight and a novel therapeutic way to regulate LDL-C metabolism. Designing and selecting an efficient siRNA for silencing PCSK9 at post transcriptional level through computational approach. We have designed three siRNAs to silence each mRNA of PCSK9 through computational analysis using software Invivogen. Their minimum free energy of hybridization along with their secondary structure was obtained using bioinformatics tool BIBISERV2-RNAHYBRID. Further factors like GC content, structural linearity and h-b index of mRNA-siRNA complex was calculated to assess their knockdown

efficiency. The minimum free energy of hybridization of the three designed siRNA1, siRNA2 and siRNA3 for target mRNA is as follows -27.1kcal/mol, -25.7kcal/mol and - 28.8 kcal/mol. siRNA1 having the least minimum free energy of hybridization i.e. -27.1 kcal/mol are predicted to be the most efficient towards the PCSK9 gene silencing.

[4] *Hsu RK, Truwit JD, Matthay MA et al.* **Effect of Rosuvastatin on Acute Kidney Injury in Sepsis-Associated Acute Respiratory Distress Syndrome**. Canadian journal of kidney health and disease 2018; 5:2054358118789158.

PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=30116543

ABSTRACT

Background: Acute kidney injury (AKI) commonly occurs in patients with sepsis and acute respiratory distress syndrome (ARDS). Objective: To investigate whether statin treatment is protective against AKI in sepsis-associated ARDS. Design: Secondary analysis of data from Statins for Acutely Injured Lungs in Sepsis (SAILS), a randomized controlled trial that tested the impact of rosuvastatin therapy on mortality in patients with sepsis-associated ARDS. Setting: 44 hospitals in the National Heart, Lung, and Blood Institute ARDS Clinical Trials Network. Patients: 644 of 745 participants in SAILS who had available baseline serum creatinine data and who were not on chronic dialysis. Measurements: Our primary outcome was AKI defined using the Kidney Disease Improving Global Outcomes creatinine criteria. Randomization to rosuvastatin vs placebo was the primary predictor. Additional covariates include demographics, ARDS etiology, and severity of illness. Methods: We used multivariable logistic regression to analyze AKI outcomes in 511 individuals without AKI at randomization, and 93 with stage 1 AKI at randomization. Results: Among individuals without AKI at randomization, rosuvastatin treatment did not change the risk of AKI (adjusted odds ratio: 0.99, 95% confidence interval [CI]: 0.67-1.44). Among those with preexisting stage 1 AKI, rosuvastatin treatment was associated with an increased risk of worsening AKI (adjusted odds ratio: 3.06, 95% CI: 1.14-8.22). When serum creatinine was adjusted for cumulative fluid balance among those with preexisting stage 1 AKI, rosuvastatin was no longer associated worsening AKI (adjusted odds ratio: 1.85, 95% CI: 0.70-4.84). Limitations: Sample size, lack of urine output data, and prehospitalization baseline creatinine. Conclusion: Treatment with rosuvastatin in patients with sepsis-associated ARDS did not protect against de novo AKI or worsening of preexisting AKI.

[5] *Kanikarla-Marie P, Kopetz S, Hawk ET et al.* **Bioactive lipid metabolism in platelet "first responder" and cancer biology**. Cancer metastasis reviews 2018.

PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=30112590

ABSTRACT

Platelets can serve as "first responders" in cancer and metastasis. This is partly due to bioactive lipid metabolism that drives both platelet and cancer biology. The two primary eicosanoid metabolites that maintain platelet rapid response homeostasis are prostacyclin made by endothelial cells that inhibits platelet function, which is counterbalanced by thromboxane produced by platelets during activation, aggregation, and platelet recruitment. Both of these arachidonic acid metabolites are inherently unstable due to their chemical structure. Tumor cells by contrast predominantly make more chemically stable prostaglandin E2, which is the primary bioactive lipid associated with inflammation and oncogenesis. Pharmacological, clinical, and epidemiologic studies demonstrate that non-steroidal anti-

inflammatory drugs (NSAIDs), which target cyclooxygenases, can help prevent cancer. Much of the molecular and biological impact of these drugs is generally accepted in the field. Cyclooxygenases catalyze the rate-limiting production of substrate used by all synthase molecules, including those that produce prostaglandins along with prostacyclin and thromboxane. Additional eicosanoid metabolites include lipoxygenases, leukotrienes, and resolvins that can also influence platelets, inflammation, and carcinogenesis. Our knowledge base and technology are now progressing toward identifying newer molecular and cellular interactions that are leading to revealing additional targets. This review endeavors to summarize new developments in the field.

[6] *Stroes E, Robinson JG, Raal FJ et al.* **Consistent LDL-C response with evolocumab among patient subgroups in PROFICIO: a pooled analysis of 3146 patients from phase 3 studies**. Clinical cardiology 2018.

PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=30120772

ABSTRACT

BACKGROUND: Evolocumab significantly lowers low-density lipoprotein cholesterol (LDL-C) when dosed 140 mg every 2 weeks (Q2W) or 420 mg monthly (QM) subcutaneously. HYPOTHESIS: LDL-C changes are comparable among different patient subgroups in a pooled analysis of data from phase 3 trials. METHODS: A total of 3146 patients received >/=1 dose of evolocumab or control in four 12-week phase 3 studies. Percent change from baseline in LDL-C for evolocumab 140 mg Q2W or 420 mg QM vs control was reported as the average of week 10 and 12 values. Quantitative and qualitative interactions between treatment group and subgroup by dose regimen were tested. RESULTS: In the pooled analysis, treatment differences vs placebo or ezetimibe were similar for both 140 mg Q2W and 420 mg QM doses across ages (<65 years, >/=65 years); gender; race (Asian, black, white, other); ethnicity (Hispanic, non-Hispanic); region (Europe, North America, Asia Pacific); glucose tolerance status (type 2 diabetes mellitus, metabolic syndrome, neither); National Cholesterol Education Program risk categories (high, moderately high, moderate, low); and European Society of Cardiology/European Atherosclerosis Society risk categories (very high, high, moderate, or low). Certain low-magnitude variations in LDL-C lowering among subgroups led to significant quantitative interaction P values that, when tested by qualitative interaction, were not significant. The incidences of adverse events were similar across groups treated with each evolocumab dosing regimen or control. CONCLUSIONS: Consistent reductions in LDL-C were observed in the evolocumab group regardless of demographic and disease characteristics.

[7] *Eljaaly K, Alshehri S, Bhattacharjee S et al.* **Contraindicated drug-drug interactions associated with oral antimicrobial agents prescribed in the ambulatory care setting in the United States**. Clinical microbiology and infection : the official publication of the European Society of Clinical Microbiology and Infectious Diseases 2018.

PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=30107284

ABSTRACT

OBJECTIVE: Antimicrobial agents are commonly used in ambulatory care settings. Our objective was to examine national-level patterns of contraindications between oral antibacterial or antifungal agents and patients' other oral medications in the U.S ambulatory care setting. METHODS: This cross-sectional study included multiple year pooled data (2003-2011) from the National Ambulatory Medical Care

Survey (NAMCS) and the National Hospital Ambulatory Medical Care Survey (NHAMCS Outpatient Department). Visits by adults (age >/= 18 years) in ambulatory settings in US who were prescribed oral antibacterial or antifungal agents were evaluated for potential drug-drug interaction contraindications. Findings with Relative Standard Error > 30% or unweighted sample size < 30 were not reported as these were deemed unreliable estimates. RESULTS: From 2003 to 2011, there were 1,235,000 outpatient visits (proportion = 0.52%, 95% CI 0.29 to 0.74%) in which a patient was prescribed an antimicrobial agent associated with a contraindicated drug-drug interaction. The most prevalent antimicrobials with contraindicated combination among outpatients were simultaneous use of macrolide-containing products (erythromycin or clarithromycin) with statin medication-containing products (simvastatin or lovastatin) (841,864 visits, proportion = 1.91%, 95% CI 0.96 to 2.86%). The next most common combination was use of fluoroquinolones with antiarrhythmic agents (amiodarone, sotalol, quinidine, or procainamide) (365,622 visits, proportion = 0.19%, 95% CI 0.06 to 0.32%). CONCLUSION: Providers should be aware of potential contraindicated drug-drug interactions when prescribing antibiotics, especially macrolides and fluoroquinolones.

[8] *Vincent J*. **Lipid Lowering Therapy for Atherosclerotic Cardiovascular Disease: It Is Not So Simple**. Clinical pharmacology and therapeutics 2018; 104:220-224.

PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=30117592

ABSTRACT

Plasma levels of atherogenic lipoproteins reflect a key risk factor for atherosclerotic cardiovascular disease ASCVD and treatments that lower these lipoproteins improve CV outcomes. Statins and PCSK9 inhibitors reduce LDL-C remarkably to low levels but do not eliminate residual cardiovascular risk as a result of other atherogenic lipoproteins or pathways for ASCVD, including inflammation, that are independent of LDL-C. Statins and PCSK9 inhibitors have complex mechanisms of action which appear to be additive and hence beneficial. Statin-intolerant subjects may benefit from ezetimibe, combination nutraceuticals and other drugs in development, while subjects with low LDL-C levels may benefit from anti-inflammatory drugs that target specific pathways. The future of pharmacotherapy for ASCVD will rely on a combination of drugs that reduce LDL-C and other atherogenic lipoproteins and drugs that target pathways including inflammation, endothelial function, vascular stiffness and anti-oxidant activity.

[9] *Lemoinne S, Pares A, Reig A et al.* **Primary sclerosing cholangitis response to the combination of fibrates with ursodeoxycholic acid: French-Spanish experience**. Clinics and research in hepatology and gastroenterology 2018.

PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=30100231

ABSTRACT

BACKGROUND & AIMS: In patients with primary sclerosing cholangitis (PSC), ursodeoxycholic acid (UDCA) treatment improves serum liver tests and surrogate markers of prognosis but has no proven effect on survival. Additional therapies are obviously needed. Fibrates, PPAR agonists with anti-cholestatic properties, have a beneficial effect in primary biliary cholangitis. The aim of this study was to evaluate the safety and efficacy of fibrates in PSC patients. METHODS: Retrospectively, we investigated PSC patients treated with fibrates (fenofibrate 200mg/day or bezafibrate 400mg/day) for at least 6 months in addition to UDCA, after an incomplete biochemical response (alkaline phosphatase [ALP]

>/=1.5xupper limit of normal) to UDCA. Changes in biochemical parameters and clinical features were assessed. RESULTS: Twenty patients were included (fourteen from Paris and six from Barcelona): median age 43.8 years, median liver stiffness 11kPa (>/=F3). Upon treatment with fibrates (median duration of 1.56 years), liver tests significantly improved, including a reduction of ALP levels by 41% and pruritus significantly decreased. No serious adverse event attributable to fibrates occurred. Discontinuation of fibrates was followed by a clear rebound of ALP. Despite biochemical improvement, liver stiffness significantly increased. CONCLUSIONS: Combining UDCA with fibrates results in a significant biochemical improvement and pruritus decrease in PSC patients with incomplete response to UDCA. These results provide a rationale for larger and prospectively designed studies to establish the efficacy and safety of fibrates in PSC.

[10] *Langlois MR, Nordestgaard BG*. **Which Lipids Should Be Analyzed for Diagnostic Workup and Follow-up of Patients with Hyperlipidemias?** Current cardiology reports 2018; 20:88.

PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=30120626

ABSTRACT

PURPOSE OF REVIEW: To summarize and discuss the clinical use of lipid and apolipoprotein tests in the settings of diagnosis and therapeutic follow-up of hyperlipidemia. RECENT FINDINGS: The joint consensus panel of the European Atherosclerosis Society (EAS) and the European Federation of Clinical Chemistry and Laboratory Medicine (EFLM) recently produced recommendations on the measurement of atherogenic lipoproteins, taking into account the strengths and weaknesses of analytical and clinical performances of the tests. Total cholesterol, triglycerides, HDL cholesterol, LDL cholesterol, and calculated non-HDL cholesterol (= LDL + remnant cholesterol) constitute the primary lipid panel for hyperlipidemia diagnosis and cardiovascular risk estimation. LDL cholesterol is the primary target of lipid-lowering therapies. Non-HDL cholesterol or apolipoprotein B should be used as secondary therapeutic target in patients with mild-to-moderate hypertriglyceridemia, 2-10 mmol/l (175-880 mg/dl). Lipoprotein (a) is included in LDL cholesterol and should be measured at least once in all patients at cardiovascular risk, including to explain poor response to statin treatment.

[11] *Alkhalil M*. **Proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitors, reality or dream in managing patients with cardiovascular disease**. Current drug metabolism 2018.

PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=30112987

ABSTRACT

Statins have been a major keystone in the management of patients with atherosclerotic cardiovascular disease. The benefits of inhibiting HMG CoA reductase, via statins, were translated into reduction in LDL-c (cholesterol) with proportionate decrease in cardiovascular events in response to the magnitude of LDL-c reduction. Despite major advances in pharmacological treatments, including the use of high-dose statins, there are urgent need to further reduce future cardiovascular risk. This is in particularly important since 1 out of 5 high-risk atherosclerotic patients who achieve low LDL-c return with a second cardiovascular event within five years. Although this residual risk post-statin is largely heterogeneous, lowering LDL-c beyond 'normal' or guidelines-recommended level of LDL-c using novel therapies has resulted in further reduction in cardiovascular events. PCSK9 inhibitors are a new class of lipid-lowering drugs that are either fully human monoclonal antibodies (evolocumab and alirocumab) or humanised monoclonal antibodies (bococizumab) that effectively reduce LDL-c to unprecedented level. By blocking

circulating PCSK9, these drugs would preserve LDL receptors and prevent them from cellular degradation. This process promotes recycling of LDL receptors back to hepatocytes surface, leading into further reduction of LDL-c. Combining PCSK9 inhibitors with statin have led into lower LDL-c, reduction in plaque volume and more importantly reduction in future cardiovascular events. While these drugs are very promising, the unselective approach of applying these monoclonal antibodies may not prove to be cost-effective and potentially exposing some patients to unnecessary side effects. The current review will discuss the use of PCSK9 inhibitors in patients with atherosclerotic disease.

[12] *Mast N, Bederman IR, Pikuleva IA*. **Retinal Cholesterol Content is Reduced in Simvastatin-Treated Mice Due to Inhibited Local Biosynthesis Albeit Increased Uptake of Serum Cholesterol**. Drug metabolism and disposition: the biological fate of chemicals 2018.

PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=30115644

ABSTRACT

Statins, a class of cholesterol-lowering drugs, are currently investigated for treatment of age-related macular degeneration, a retinal disease. Herein, retinal and serum concentrations of four statins (atorvastatin, simvastatin, pravastatin, and rosuvastatin) were evaluated after mice were given a single drug dose of 60 mg/kg body weight. All statins, except rosuvastatin, were detected in the retina: atorvastatin and pravastatin at 1.6 pmols and simvastatin at 4.1 pmols. Serum statin concentrations (pmol/ml) were 223 (simvastatin), 1,401 (atorvastatin), 2,792 (pravastatin), and 9,050 (rosuvastatin). Simvastatin was then administered to mice daily for 6 weeks at 60 mg/kg of body weight dose. Simvastatin treatment reduced serum cholesterol levels by 18% and retinal content of cholesterol, lathosterol but not desmosterol by 24% and 21%, respectively. The relative contributions of retinal cholesterol biosynthesis and retinal uptake of serum cholesterol to total retinal cholesterol input were changed as well. These contributions were 79% and 21%, respectively, in vehicle-treated mice and 69% and 31%, respectively, in simvastatin-treated mice. Thus, simvastatin treatment lowered retinal cholesterol because a compensatory upregulation of retinal uptake of serum cholesterol was not sufficient to overcome the effect of inhibited retinal biosynthesis. Simultaneously, simvastatin-treated mice had a 2.9-fold increase in retinal expression of Cd36, the major receptor clearing oxidized low-density lipoproteins from Bruch's membrane. Notably, simvastatin treatment essentially did not affect brain cholesterol homeostasis. Our results reveal the statin effect on the retinal and brain cholesterol input and are of value for future clinical investigations of statins as potential therapeutics for age-related macular degeneration.

[13] *Jia L, Wang L, Liu W et al.* **Fluvastatin inhibits cardiomyocyte apoptosis after myocardial infarction through Toll pathway**. Experimental and therapeutic medicine 2018; 16:1350-1354.

PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=30116385

ABSTRACT

The present study intended to investigate the effect of fluvastatin on cardiomyocyte apoptosis after myocardial infarction in rats. Eighty myocardial infarction rat models were established and randomly divided into 4 groups (n=20): experimental group (n=20) was given fluvastatin treatment; sham operation group (n=20) and normal control group (n=20) were given saline. The dose of fluvastatin was 20 mg/(kg.d), and irrigation gavage was given for 1 week. Western blot analysis and reverse transcription-quantitative PCR (RT-qPCR) were used to detect the expression of TLR4 mRNA and protein

in cardiomyocytes. TUNEL method was used to detect the apoptosis of cardiomyocytes. After fluvastatin treatment for 1 week, RT-qPCR found that compared with myocardial infarction group, the TLR4 mRNA expression of fluvastatin treatment group and normal control group was significantly increased, and the differences between groups were a statistically significant difference (P<0.05). Western blot analysis showed that compared with the myocardial infarction group, the expression of TLR4 protein in normal control group, sham operation group and fluvastatin treatment group were significantly decreased, and they all were statistically significant (P<0.05). TUNEL method found that compared with the myocardial infarction group, the fluvastatin treatment group could significantly reduce the apoptosis of cardiomyocytes (19.2+/-3.8%), and the difference was statistically significant (P<0.05). Fluvastatin can inhibit myocardial infarction and decrease cardiomyocyte apoptosis by increasing the expression of TLR4-like receptor.

[14] *Li M, Liu F, Sang M et al.* **Effects of atorvastatin on p38 phosphorylation and cardiac remodeling after myocardial infarction in rats**. Experimental and therapeutic medicine 2018; 16:751-757.

PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=30116330

ABSTRACT

The aim of the present study was to examine the effects of atorvastatinon p38 phosphorylation and cardiac remodeling after myocardial infarction in rats. A total of 43 rats were randomly divided into the control, sham operation, post-modeling medication (medication) and post-modeling non-medication (non-medication) groups. The control group did not receive any treatment. Anterior descending arteries of the rats in the medication and non-medication groups were ligated, and threading at the anterior descending arteries was conducted for the rats in the sham operation group. Atorvastatin (10 mg/kg) was given daily to the rats in the medication group, and an equivalent amount of normal saline was given daily to the rats in the sham operation group. Four weeks later, the cardiac function, morphological changes in the myocardial cells, and the expression of tumor necrosis factor-alpha (TNF-alpha) and p38 in each group was detected. At 4 weeks after treatment, the myocardial infarction size, fibrosis and myocardial necrosis of the rats in the medication group was examined compared with those in the non-medication group (P<0.05). The cardiac function of the rats in the non-medication group was significantly lower than that of the rats in the control and sham groups (P<0.05), while it was obviously elevated in the medication group compared with that in the non-medication group (P<0.05). The expression of TNF-alpha and phosphorylated p38 of the left ventricle in the non-medication group was higher than that in the control group (P<0.05), while it was obviously reduced in the non-medication group compared with that in the control group (P<0.05). Atorvastatin can improve cardiac remodeling after myocardial infarction in rats, which may be associated with its inhibition of p38 phosphorylation and its decrease of TNF-alpha expression.

[15] *Liu D, Yang G, Zhao X, Yang H*. **Effects of probucol on atherosclerotic plaque and soluble thrombomodulin in patients with coronary heart disease**. Experimental and therapeutic medicine 2018; 16:886-890.

PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=30116341

ABSTRACT

This study explored the effects of probucol on atherosclerotic plaques and soluble thrombomodulin in patients with coronary heart disease (CHD). Five hundred and eighty-three patients with CHD who were

admitted to Jining First People's Hospital from February 2013 to February 2014. A total of 300 of them received conventional treatment, and were assigned to the control group, while the remaining 283 patients were treated with probucol in addition to the conventional treatment, and were assigned to the observation group. A retrospective analysis was performed on the total cholesterol levels, atherosclerotic plaque sizes, and soluble thrombomodulin levels. Probucol was administered at a dose of 500 mg twice a day for a period of 16 weeks. The total cholesterol level decreased gradually over time during the treatment. After 8 weeks of treatment, the total cholesterol level in the observation group was lower than that in the control group (P<0.05). After 8 weeks of treatment, the atherosclerotic plaque area in the observation group decreased compared with that before treatment (P<0.05). After 8 and 16 weeks of treatment, the plaque area in the observation group was smaller than that in the control group (P<0.05). The soluble thrombomodulin level at any time-point after treatment was lower than that before treatment in both groups (P<0.05). At the same time-point, the level in the observation group was lower than that in the control group (P<0.05). The total cholesterol and soluble thrombomodulin levels were positively correlated with the atherosclerotic plaque area (r=0.841, P=0.001; r=0.725, P=0.008). When patients with CHD were treated with probucol in addition to the conventional treatment, a reduction of the atherosclerotic plaque area, as well as a decrease of both the total cholesterol and soluble thrombomodulin levels, was observed. Overall, patients with CHD experienced improved symptoms following treatment with probucol.

[16] *Lu D, Liu Y, Mai H et al.* **Rosuvastatin Reduces Neuroinflammation in the Hemorrhagic Transformation After rt-PA Treatment in a Mouse Model of Experimental Stroke**. Frontiers in cellular neuroscience 2018; 12:225.

PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=30116175

ABSTRACT

Hemorrhagic transformation (HT) is a serious complication that stimulates inflammation during reperfusion therapy after acute ischemic stroke. Rosuvastatin, a 3-hydroxymethyl-3-methylglutaryl coenzyme A (HMG-CoA) reductase inhibitor, might improve the outcome of HT by inhibiting neuroinflammation. This study aimed to explore the protective effects of rosuvastatin against HT after recombinant tissue plasminogen activator (rt-PA) treatment in mice with experimental stroke via the attenuation of inflammation. A total of one hundred sixty-nine male BALB/c mice were used in the experiment. HT was successfully established in 70 mice that were subjected to 3 h of middle cerebral artery occlusion (MCAO) followed by a 10 mg/kg rt-PA injection over 10 min and reperfusion for 24 h. The mice were then administered rosuvastatin (1 mg/kg, 5 mg/kg) or saline (vehicle). The brain water content and neurological deficits (wire hang and adhesive removal somatosensory tests) were assessed at 24 h after rt-PA reperfusion following MCAO surgery. The morphology, blood-brain barrier (BBB) permeability and number of astrocytes and microglia were assessed by immunohistochemistry, electron microscopy and western blotting at 24 h after rt-PA reperfusion following MCAO surgery. Rosuvastatin protected against impaired neurological function and reversed the BBB leakage observed in the HT group. The increased activation of astrocytes and microglia and secretion of inflammatory factors caused by HT damage were significantly attenuated by high-dose rosuvastatin treatment vs. normal-dose rosuvastatin treatment. Related inflammatory pathways, such as the nuclear factor kappa B (NF-kappaB) and mitogen-activated protein kinase (MAPK) pathways, were downregulated in the rosuvastatin-treated groups compared with the HT group. In conclusion, our results indicate that rosuvastatin is a promising therapeutic agent for HT after rt-PA reperfusion following MCAO surgery in

mice, as it attenuates neuroinflammation. Additionally, high-dose rosuvastatin treatment could have a greater anti-inflammatory effect on HT than normal-dose rosuvastatin treatment.

[17] *Antikainen L, Jaaskelainen J, Nordman H et al.* **Prepubertal Children Exposed to Maternal Gestational Diabetes Have Latent Low-Grade Inflammation**. Hormone research in paediatrics 2018:1-7.

PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=30110707

ABSTRACT

BACKGROUND: Maternal gestational diabetes mellitus (GDM) and overweight are associated with an increased risk of obesity and the metabolic syndrome in the adult offspring. We studied the influence of maternal GDM on prepubertal children's height, weight, body mass index (BMI), lipid and glucose metabolism, and low-grade inflammation. METHODS: A cohort of 135 prepubertal Caucasian children (age range 4.4-9.7 years) was studied in a controlled cross-sectional study. Seventy-seven children had been exposed to maternal GDM, and 58 children born after a normal pregnancy served as controls. The outcomes were height, weight, BMI, blood pressure, and biochemical markers of glucose and lipid metabolism and inflammation. RESULTS: There were no differences in height, weight, BMI, fasting serum insulin, plasma glucose, lipids, or blood pressure between the study groups. However, high-sensitivity C-reactive protein (hs-CRP) was significantly higher in the GDM group than in the controls ($p = 0.001$). CONCLUSIONS: Higher hs-CRP as a marker of low-grade inflammation was detected in prepubertal children exposed to maternal GDM, but no differences were seen in height, weight, BMI, or markers of glucose and lipid metabolism compared to control children. This finding may reflect an ongoing process of metabolic changes in children born after a GDM pregnancy.

[18] *Ravi S, Parry TL, Willis MS et al.* **Adverse Effects of Fenofibrate in Mice Deficient in the Protein Quality Control Regulator, CHIP**. Journal of cardiovascular development and disease 2018; 5.

PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=30111698

ABSTRACT

We previously reported how the loss of CHIP expression (Carboxyl terminus of Hsc70-Interacting Protein) during pressure overload resulted in robust cardiac dysfunction, which was accompanied by a failure to maintain ATP levels in the face of increased energy demand. In this study, we analyzed the cardiac metabolome after seven days of pressure overload and found an increase in long-chain and medium-chain fatty acid metabolites in wild-type hearts. This response was attenuated in mice that lack expression of CHIP (CHIP(-/-)). These findings suggest that CHIP may play an essential role in regulating oxidative metabolism pathways that are regulated, in part, by the nuclear receptor PPARalpha (Peroxisome Proliferator-Activated Receptor alpha). Next, we challenged CHIP(-/-) mice with the PPARalpha agonist called fenofibrate. We found that treating CHIP(-/-) mice with fenofibrate for five weeks under non-pressure overload conditions resulted in decreased skeletal muscle mass, compared to wild-type mice, and a marked increase in cardiac fibrosis accompanied by a decrease in cardiac function. Fenofibrate resulted in decreased mitochondrial cristae density in CHIP(-/-) hearts as well as decreased expression of genes involved in the initiation of autophagy and mitophagy, which suggests that a metabolic challenge, in the absence of CHIP expression, impacts pathways that contribute to mitochondrial quality control. In conclusion, in the absence of functional CHIP expression, fenofibrate results in unexpected skeletal muscle and cardiac pathologies. These findings are particularly relevant to

patients harboring loss-of-function mutations in CHIP and are consistent with a prominent role for CHIP in regulating cardiac metabolism.

[19] *Chao Y, Gao S, Wang X et al.* **Untargeted lipidomics based on UPLC-QTOF-MS/MS and structural characterization reveals dramatic compositional changes in serum and renal lipids in mice with glyoxylate-induced nephrolithiasis**. Journal of chromatography. B, Analytical technologies in the biomedical and life sciences 2018; 1095:258-266.

PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=30099286

ABSTRACT

Nephrolithiasis is a systemic metabolic disease with a worldwide incidence that is increasing yearly, as well as a high recurrence rate; however, this disease's pathogenesis has not been thoroughly elucidated to date. Several epidemiological studies have shown that the risk for developing kidney stones increases in people with dyslipidemia. To explore the mechanism of lipid-induced kidney stones, we established a mouse model for renal urolithiasis based on intraperitoneal injections of glyoxylate (120mg/kg/d). Lipidomics based on ultra high performance liquid chromatography coupled with quadrupole-time of flight mass spectrometry (UPLC-QTOF-MS/MS) was performed to determine the changes in lipid metabolism in serum and kidneys. We screened 179 and 196 different lipid metabolites in the kidneys and serum, respectively, including fatty acyls, glycerophospholipids, sphingolipids, glycerolipids and prenol lipids. We found that polyunsaturated fatty acids, such as arachidonic acid, eicosapentaenoic acid, and docosahexoenoic acid, and ceramides and lysophosphocholines mediated inflammatory responses and that the oxidative stress induced by oleylethanolamine and glycerophosphoethanolamine plasmalogens is closely related to the development of kidney stones. These results provide strong evidence for the relationship between lipid metabolism and the development of kidney stones and suggest a clear direction for future research.

[20] *Szabady RL, Louissaint C, Lubben A et al.* **Intestinal P-glycoprotein exports endocannabinoids to prevent inflammation and maintain homeostasis**. J Clin Invest 2018.

PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=30102254

ABSTRACT

Neutrophil influx into the intestinal lumen is a critical response to infectious agents, but is also associated with severe intestinal damage observed in idiopathic inflammatory bowel disease. The chemoattractant hepoxilin A3, an eicosanoid secreted from intestinal epithelial cells by the apically restricted efflux pump multidrug resistance protein 2 (MRP2), mediates this neutrophil influx. Information about a possible counterbalance pathway that could signal the lack of or resolution of an apical inflammatory signal, however, has yet to be described. We now report a system with such hallmarks. Specifically, we identify endocannabinoids as the first known endogenous substrates of the apically restricted multidrug resistance transporter P-glycoprotein (P-gp) and reveal a mechanism, which we believe is novel, for endocannabinoid secretion into the intestinal lumen. Knockdown or inhibition of P-gp reduced luminal secretion levels of N-acyl ethanolamine-type endocannabinoids, which correlated with increased neutrophil transmigration in vitro and in vivo. Additionally, loss of CB2, the peripheral cannabinoid receptor, led to increased pathology and neutrophil influx in models of acute intestinal inflammation. These results define a key role for epithelial cells in balancing the constitutive secretion of antiinflammatory lipids with the stimulated secretion of proinflammatory lipids via surface efflux pumps

in order to control neutrophil infiltration into the intestinal lumen and maintain homeostasis in the healthy intestine.

[21] *Morise AP, Tennant J, Holmes SD, Tacker DH*. **The Effect of Proprotein Convertase Subtilisin/Kexin Type 9 Inhibitors on Nonfasting Remnant Cholesterol in a Real World Population**. Journal of lipids 2018; 2018:9194736.

PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=30105099

ABSTRACT

Background: Proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitors have demonstrated significant effects on low-density lipoprotein (LDL) cholesterol and nonhigh density lipoprotein (HDL) cholesterol. To date, there have been limited reports on the effect of PCSK9 inhibitors on remnant cholesterol. Objectives: Assess the effect of PCSK9 inhibitors on nonfasting remnant cholesterol in a real world population. Identify whether pretreatment triglyceride levels are associated with PCSK9 inhibition success as indicated by changes in remnant cholesterol levels. Methods: Patients in our adult lipid clinic (n = 109) receiving PCSK9 inhibition for atherosclerotic cardiovascular disease or familial hypercholesterolemia who had available pre- and post-PCSK9 inhibition standard nonfasting lipid data were, retrospectively, selected for data analysis. Remnant cholesterol was the difference between non-HDL and LDL cholesterol. LDL cholesterol was measured directly and calculated from Friedewald and Martin/Hopkins methods. Data were analyzed using repeated measures ANOVA and multivariable linear regression for differential effects on remnant and LDL cholesterol based upon pretreatment nonfasting triglyceride levels. Results: Remnant cholesterol as well as total, LDL, non-HDL cholesterol, and triglycerides decreased significantly ($P<0.001$) after PCSK9 inhibition. Patients with higher pretreatment triglyceride levels showed greater decrease in remnant cholesterol after PCSK9 inhibition ($P<0.001$) than those with lower pretreatment triglycerides. Conclusions: In patients receiving PCSK9 inhibitors, remnant cholesterol as determined from nonfasting blood was reduced in proportion to pretreatment triglycerides.

[22] *Disalvo D, Luckett T, Luscombe G et al.* **Potentially Inappropriate Prescribing in Australian Nursing Home Residents with Advanced Dementia: A Substudy of the IDEAL Study**. Journal of palliative medicine 2018.

PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=30106321

ABSTRACT

BACKGROUND: Prescribing medications for nursing home residents with advanced dementia should focus on optimizing function and comfort, reducing unnecessary harms and aligning care goals with a palliative approach. OBJECTIVE: The aim of the study was to estimate the proportion of Australian nursing home residents with advanced dementia receiving potentially inappropriate medications, and identify those most commonly prescribed and factors associated with their use. DESIGN: Data were collected through retrospective audit of medication charts. SETTING/SUBJECTS: Two hundred eighteen nursing home residents with advanced dementia from 20 nursing homes participated in a cluster-randomized controlled trial of case conferencing (the IDEAL Study) from June 2013 to December 2014. MEASUREMENTS: Inappropriate drug use was defined as medications classified as "never appropriate" by the Palliative Excellence in Alzheimer Care Efforts (PEACE) program criteria. Generalized linear mixed models were used to identify variables predicting use of "never" appropriate medications. RESULTS:

Over a quarter (n = 65, 30%) of residents received at least one medication classed as "never" appropriate, the most common being lipid-lowering agents (n = 38, 17.4%), antiplatelet agents (n = 18, 8.3%), and acetylcholinesterase inhibitors (n = 16, 7.3%). Residents who had been at the nursing home for </=10 months (odds ratio [OR] 5.60, 95% confidence interval [CI] 1.74-18.06) and 11-21 months (OR 5.41, 95% CI 1.67-17.75) had significantly greater odds of receiving a never appropriate medication compared with residents who had been at the nursing home for >5 years. CONCLUSIONS: Use of potentially inappropriate medications in Australian nursing home residents with advanced dementia is common. A greater understanding of the rationale that underpins prescribing of medications is required.

[23] *Venardos N, Deng XS, Yao Q et al.* **Simvastatin reduces the TLR4-induced inflammatory response in human aortic valve interstitial cells**. J Surg Res 2018; 230:101-109.

PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=30100024

ABSTRACT

BACKGROUND: Calcific aortic stenosis is a chronic inflammatory disease. Proinflammatory stimulation via toll-like receptor 4 (TLR4) causes the aortic valve interstitial cell (AVIC) to undergo phenotypic change. The AVIC first assumes an inflammatory phenotype characterized by the production of inflammatory mediators such as intercellular adhesion molecule-1 (ICAM-1), interleukin-8 (IL-8), and monocyte chemoattractant protein-1 (MCP-1). This change has been linked with an osteogenic phenotypic response. Statins have recently been shown to have anti-inflammatory properties. We therefore hypothesized that statins may have an anti-inflammatory effect on human AVICs by downregulation of TLR4-stimulated inflammatory responses. Our purposes were (1) to determine the effect of simvastatin on TLR4-induced expression of inflammatory mediators in human AVICs and (2) to determine the mechanism(s) through which simvastatin exert this effect. MATERIALS AND METHODS: Human AVICs were isolated from the explanted hearts of four patients undergoing cardiac transplantation. Cells were treated with simvastatin (50 muM) for 1 h before stimulation with TLR4 agonist lipopolysaccharide (LPS, 0.2 mug/mL). Immunoblotting (IB) was used to analyze cell lysates for ICAM-1 expression, and enzyme-linked immunosorbent assay was used to detect IL-8 and MCP-1 in cell culture media. Likewise, lysates were analyzed for TLR4 and nuclear factor-kappa B activation (IB). After simvastatin treatment, lysates were analyzed for TLR4 levels (IB). Statistics were by analysis of variance ($P < 0.05$). RESULTS: Simvastatin reduced TLR4-induced ICAM-1, IL-8, and MCP-1 expression in AVICs. Simvastatin down-regulated TLR4 levels and suppressed TLR4-induced phosphorylation of nuclear factor-kappa B. CONCLUSIONS: These data demonstrate the potential of a medical therapy (simvastatin) to impact the pathogenesis of aortic stenosis.

[24] *Jiang W, Whellan DJ, Adams KF et al.* **Long-Chain Omega-3 Fatty Acid Supplements in Depressed Heart Failure Patients: Results of the OCEAN Trial**. JACC. Heart failure 2018.

PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=30098961

ABSTRACT

OBJECTIVES: The goal of this study was to test the effects of long-chain omega-3 fatty acid supplementation on omega-3 levels, depressive symptoms, and other psychosocial factors, as well as other chronic heart failure (CHF)-related functional measures. BACKGROUND: Patients with CHF and depression had low blood omega-3 concentrations that were associated with an elevated risk of mortality. METHODS: This study was a randomized, double-blind, placebo-controlled pilot clinical trial

using a 400/200 eicosapentaenoic acid (EPA)/docosahexaenoic acid (DHA) fish oil at 2 g and an almost pure EPA at 2 g, compared with a matched placebo, daily for 12 weeks for patients with CHF and major depressive disorder. Statistical analyses included the intention-to-treat population and "completers" (defined as participants consuming >/=70% of the capsules and completing the final endpoint evaluation between 10 and 14 weeks). RESULTS: A total of 108 patients with CHF and major depressive disorder and a score >/=18 on the Hamilton Depression Scale who were randomized at 1:1:1 to the 3 interventions at 3 enrolling centers from June 12, 2014, to May 19, 2016; 80 (74.1%) qualified as completers. Intention-to-treat analyses revealed that the levels of all omega-3 variables were significantly elevated in the omega-3 groups, whereas the placebo group showed little change; there were no between-group differences with overall depression measurements. Per-protocol exploratory analyses showed that scores on the social functioning measurement of the 36-item Short Form Health Survey improved notably in the 400/200 EPA/DHA (p = 0.040) and EPA (p = 0.10) groups compared with the placebo group. Spearman correlation analysis indicated that increased omega-3 indices were associated with improved cognitive depressive symptoms. CONCLUSIONS: Omega-3 supplementation resulted in significant increases in omega-3 levels in red blood cell counts, corresponding to a particular compound of omega-3. Changes in cognitive depressive symptoms and social function were in favor of the omega-3 supplementation. Further studies with larger sample sizes are necessary to confirm the benefits of omega-3 supplementation on modifying psychosocial factors for patients with CHF. (Omega-3 Supplementation for Co-Morbid Depression and Heart Failure Treatment [OCEAN]; NCT02057406).

[25] *Belov YV, Sinyavin GV, Bredikhina AI et al.* **[Imaging of neoangiogenesis of internal carotid artery's atherosclerotic plaque by contrast-enhanced sonography and histological examination]**. Khirurgiia 2018:90-95.

PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=30113602

ABSTRACT

Previously, atherosclerosis was considered a disease accompanied exclusively by lipids accumulation. At present time success of fundamental and experimental science confirmed that atherosclerotic process is also associated with neovascularization and prolonged inflammatory response at all stages of atherogenesis from initial manifestations to thrombotic complications. The cause of atherosclerotic plaque instability is neovascularization, which is accompanied by intra-plaque hemorrhage and damage. Complications of carotid arteries atherosclerosis are strokes and transient ischemic attacks. The use of a wide range of diagnostic and pathohistological techniques is required for assessing this pathology. The most promising diagnostic technique is Contrast Enhanced Ultrasonography (CEUS) which allows to assess neovascularization degree in atherosclerotic plaque through the injection of a contrast agents.

[26] *Zhang X, Hong S, Yen R et al.* **A system to monitor statin-induced myopathy in individual engineered skeletal muscle myobundles**. Lab on a chip 2018.

PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=30112530

ABSTRACT

Microphysiological tissue engineering models of human skeletal muscle (myobundles) provide a platform to investigate the mechanism of muscle diseases and to study the response to drugs and toxins in vitro. To examine the dynamic response to drugs, which often take several days to induce responses, we developed a system to monitor the contractile force of the same human skeletal muscle myobundles

over time before and after treatment with drugs. Myobundles were formed in series with Ecoflex films (platinum-catalyzed silicones) with embedded microbeads. The displacement of the microbeads in Ecoflex exhibited a linear relation between muscle force production and Ecoflex film stretch. Forces measured with the microbeads embedded in Ecoflex agreed well with simultaneous measurements with a force transducer. Application of the Hill model for the myobundles showed that the Ecoflex affected the magnitude of the response, but not the kinetics. After continuous exposure to 100 nM cerivastatin, both active and passive forces were reduced relative to controls after 2-4 days. The decline in force was associated with a decline in the muscle myofiber organization. The inhibitory effect of cerivastatin was reduced when 0.1-1 mM mevalonate was added with cerivastatin. Although addition of co-enzyme Q10 with cerivastatin inhibited degradation of sarcomeric alpha-actinin (SAA) in myoblasts, the contractile force still declined, suggesting that statin-induced myopathy was related to mevalonate pathway but the addition of co-enzyme Q10 was insufficient to overcome the effect of statins on the mevalonate pathway. Thus, cerivastatin rapidly induces myopathy which can be reversds with mevalonate but not co-enzyme Q10.

[27] *Baker EJ, Yusof MH, Yaqoob P et al.* **Omega-3 fatty acids and leukocyte-endothelium adhesion: Novel anti-atherosclerotic actions**. Molecular aspects of medicine 2018.

PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=30102930

ABSTRACT

Endothelial cells (ECs) play a role in the optimal function of blood vessels. When endothelial function becomes dysregulated, the risk of developing atherosclerosis increases. Specifically, upregulation of adhesion molecule expression on ECs promotes the movement of leukocytes, particularly monocytes, into the vessel wall. Here, monocytes differentiate into macrophages and may become foam cells, contributing to the initiation and progression of an atherosclerotic plaque. The ability of omega-3 (n-3) polyunsaturated fatty acids (PUFAs) to influence the expression of adhesion molecules by ECs and to modulate leukocyte-endothelial adhesion has been studied in cell culture using various types of ECs, in animal feeding studies and in human trials; the latter have tended to evaluate soluble forms of adhesion molecules that circulate in the bloodstream. These studies indicate that n-3 PUFAs (both eicosapentaenoic acid and docosahexaenoic acid) can decrease the expression of key adhesion molecules, such as vascular cell adhesion molecule 1, by ECs and that this results in decreased adhesive interactions between leukocytes and ECs. These findings suggest that n-3 PUFAs may lower leukocyte infiltration into the vascular wall, which could contribute to reduced atherosclerosis and lowered risk of cardiovascular disease.

[28] *Mijailovic N, Selakovic D, Joksimovic J et al.* **The anxiolytic effects of atorvastatin and simvastatin on dietary-induced increase in homocysteine levels in rats**. Molecular and cellular biochemistry 2018.

PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=30120639

ABSTRACT

The aim of this study was to evaluate the effects of atorvastatin and simvastatin on behavioral manifestations that followed hyperhomocysteinemia induced by special dietary protocols enriched in methionine and deficient in B vitamins (B6, B9, B12) by means of alterations in anxiety levels in rats. Simultaneously, we investigated the alterations of oxidative stress markers in rat hippocampus induced by applied dietary protocols. Furthermore, considering the well-known antioxidant properties of statins,

we attempted to assess their impact on major markers of oxidative stress and their possible beneficial role on anxiety-like behavior effect in rats. The 4-week-old male Wistar albino rats were divided (eight per group) according to basic dietary protocols: standard chow, methionine-enriched, and methionine-enriched vitamins B (B6, B9, B12) deficient. Each dietary protocol (30 days) included groups with atorvastatin (3 mg/kg/day i.p.) and simvastatin (5 mg/kg/day i.p.). The behavioral testing was performed in the open field and elevated plus maze tests. Parameters of oxidative stress (index of lipid peroxidation, superoxide dismutase, catalase activity, glutathione) were determined in hippocampal tissue samples following decapitation after anesthesia. Methionine-load dietary protocols induced increased oxidative stress in rat hippocampus, which was accompanied by anxiogenic behavioral manifestations. The methionine-enriched diet with restricted vitamins B intake induced more pronounced anxiogenic effect, as well as increased oxidative stress compared to the methionine-load diet with normal vitamins B content. Simultaneous administration of statins showed beneficial effects by means of both decreased parameters of oxidative stress and attenuation of anxiety. The results obtained with simvastatin were more convincible compared to atorvastatin.

[29] *Monteillet L, Gjorgjieva M, Silva M et al.* **Intracellular lipids are an independent cause of liver injury and chronic kidney disease in non alcoholic fatty liver disease-like context**. Molecular metabolism 2018.

PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=30100243

ABSTRACT

OBJECTIVE: Ectopic lipid accumulation in the liver and kidneys is a hallmark of metabolic diseases leading to non-alcoholic fatty liver disease (NAFLD) and chronic kidney disease (CKD). Moreover, recent data have highlighted a strong correlation between NAFLD and CKD incidences. In this study, we use two mouse models of hepatic steatosis or CKD, each initiated independently of the other upon the suppression of glucose production specifically in the liver or kidneys, to elucidate the mechanisms underlying the development of CKD in the context of NAFLD-like pathology. METHODS: Mice with a deletion of G6pc, encoding glucose-6 phosphatase catalytic subunit, specifically in the liver (L.G6pc(-/-) mice) or the kidneys (K.G6pc(-/-) mice), were fed with either a standard diet or a high fat/high sucrose (HF/HS) diet during 9 months. These mice represent two original models of a rare metabolic disease named Glycogen Storage Disease Type Ia (GSDIa) that is characterized by both NAFLD-like pathology and CKD. Two other groups of L.G6pc(-/-) and K.G6pc(-/-) mice were fed a standard diet for 6 months and then treated with fenofibrate for 3 months. Lipid and glucose metabolisms were characterized, and NAFLD-like and CKD damages were evaluated. RESULTS: Lipid depot exacerbation upon high-calorie diet strongly accelerated hepatic and renal pathologies induced by the G6pc-deficiency. In L.G6pc(-/-) mice, HF/HS diet increased liver injuries, characterized by higher levels of plasmatic transaminases and increased hepatic tumor incidence. In K.G6pc(-/-) mice, HF/HS diet increased urinary albumin and lipocalin 2 excretion and aggravated renal fibrosis. In both cases, the worsening of NAFLD-like injuries and CKD was independent of glycogen content. Furthermore, fenofibrate, via the activation of lipid oxidation significantly decreased the hepatic or renal lipid accumulations and prevented liver or kidney damages in L.G6pc(-/-) and K.G6pc(-/-) mice, respectively. Finally, we show that L.G6pc(-/-) mice and K.G6pc(-/-) mice developed NAFLD-like pathology and CKD independently. CONCLUSIONS: This study highlights the crucial role that lipids play in the independent development of both NAFLD and CKD and demonstrates the importance of lipid-lowering treatments in various metabolic diseases featured by lipid load, from the "rare" GSDIa to the "epidemic" morbid obesity or type 2 diabetes.

Literature update week 33 (2018)

[30] *Jones PJH, Shamloo M, MacKay DS et al.* **Progress and perspectives in plant sterol and plant stanol research**. Nutrition reviews 2018.

PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=30101294

ABSTRACT

Current evidence indicates that foods with added plant sterols or stanols can lower serum levels of low-density lipoprotein cholesterol. This review summarizes the recent findings and deliberations of 31 experts in the field who participated in a scientific meeting in Winnipeg, Canada, on the health effects of plant sterols and stanols. Participants discussed issues including, but not limited to, the health benefits of plant sterols and stanols beyond cholesterol lowering, the role of plant sterols and stanols as adjuncts to diet and drugs, and the challenges involved in measuring plant sterols and stanols in biological samples. Variations in interindividual responses to plant sterols and stanols, as well as the personalization of lipid-lowering therapies, were addressed. Finally, the clinical aspects and treatment of sitosterolemia were reviewed. Although plant sterols and stanols continue to offer an efficacious and convenient dietary approach to cholesterol management, long-term clinical trials investigating the endpoints of cardiovascular disease are still lacking.

[31] *Daenen K, Andries A, Mekahli D et al.* **Oxidative stress in chronic kidney disease**. Pediatric nephrology (Berlin, Germany) 2018.

PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=30105414

ABSTRACT

Oxidative stress (OS), defined as disturbances in the pro-/antioxidant balance, is harmful to cells due to the excessive generation of highly reactive oxygen (ROS) and nitrogen (RNS) species. When the balance is not disturbed, OS has a role in physiological adaptations and signal transduction. However, an excessive amount of ROS and RNS results in the oxidation of biological molecules such as lipids, proteins, and DNA. Oxidative stress has been reported in kidney disease, due to both antioxidant depletions as well as increased ROS production. The kidney is a highly metabolic organ, rich in oxidation reactions in mitochondria, which makes it vulnerable to damage caused by OS, and several studies have shown that OS can accelerate kidney disease progression. Also, in patients at advanced stages of chronic kidney disease (CKD), increased OS is associated with complications such as hypertension, atherosclerosis, inflammation, and anemia. In this review, we aim to describe OS and its influence on CKD progression and its complications. We also discuss the potential role of various antioxidants and pharmacological agents, which may represent potential therapeutic targets to reduce OS in both pediatric and adult CKD patients.

[32] *Soko ND, Chimusa E, Masimirembwa C, Dandara C*. **An African-specific profile of pharmacogene variants for rosuvastatin plasma variability: limited role for SLCO1B1 c.521T>C and ABCG2 c.421A>C**. The pharmacogenomics journal 2018.

PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=30100615

ABSTRACT

Studies in Caucasian and Asian populations consistently associated interindividual and interethnic variability in rosuvastatin pharmacokinetics to the polymorphisms SLCO1B1 c.521T>C (rs4149056 p.

Val174Ala) and ABCG2 c.421C>A (rs2231142, p. Gln141Lys). To investigate the pharmacogenetics of rosuvastatin in African populations, we first screened 785 individuals from nine ethnic African populations for the SLCO1B1 c.521C and ABCG2 c.421CA variants. This was followed by sequencing whole exomes from individuals of African Bantu descent, who participated in a 20 mg rosuvastatin pharmacokinetic trial in Harare Zimbabwe. Frequencies of SLCO1B1 c.521C ranged from 0.0% (San) to 7.0% (Maasai), while ABCG2 c.421A ranged from 0.0% (Shona) to 5.0% (Kikuyu). Variants showing significant association with rosuvastatin exposure were identified in SLCO1B1, ABCC2, SLC10A2, ABCB11, AHR, HNF4A, RXRA and FOXA3, and appear to be African specific. Interindividual differences in the pharmacokinetics of rosuvastatin in this African cohort cannot be explained by the polymorphisms SLCO1B1 c.521T>C and ABCG2 c.421C>A, but appear driven by a different set of variants.

[33] *Al-Ghannami SS, Sedlak E, Hussein IS et al.* **DHA-enriched re-esterified triacylglycerol fish oil supplementation and oily fish consumption enhance red blood n-3 fatty acid index in Omani pre-adolescent schoolchildren**. Prostaglandins, leukotrienes, and essential fatty acids 2018; 135:74-82.

PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=30103936

ABSTRACT

Dietary habits of Omani population particularly of children and young adults have changed significantly. Consumption of imported calorie-dense foods, vegetable oils, milled and polished grains and carbonated beverages have become the norm. Concomitantly, there has been an exponential increase in the prevalence of non-communicable diseases. The impact of the westernisation of eating habits on children has not been evaluated. We have investigated blood fatty acid profile of male (n=125) and female (n=160) children aged 9 and 10 (9.8+/-0.4) years enrolled from three state-funded schools. The schools, which are homogenous with respect to socio-economic background of their pupils, were randomised into fish oil (n=98), oily fish (n=82) or control (n=105) group. Subsequently, the children were given during morning tea break for 12 weeks: 1. DHA-enriched re-esterified triacylglycerol fish oil capsule with cheese/salad sandwich (fish oil group), 2. Lightly grilled oily fish with salad (fish group) or 3. Cheese/salad sandwich (control group). At baseline, the males had higher myristic, palmitic and oleic and lower adrenic acids than the females ($p<0.05$). There was no difference in n-3 fatty acid index (4.86+/-1.95 vs. 5.12+/-1.67, $p>0.05$) or AA (14.6+/-1.9 vs. 14.9+/-1.8, $p>0.05$) between the genders. There was no difference in any of the fatty acids between the three groups at baseline. Post-intervention, the oily fish group had lower n-3 fatty acid index (EPA+DHA, 6.03+/-1.39 vs. 6.60+/-1.63, $p<0.05$) and higher AA (15.2+/-1.8 vs. 13.7+/-2.0, $p=0.0001$) and n-3 DPA (1.40+/-0.27 vs. 1.07+/-0.22, $p=0.0001$) compared with those who received fish oil capsules. In both the fish oil and oily fish groups, fatty acid index correlated positively with AA ($r=0.394$, $p=0.0001$; $r=0.231$, $p=0.038$) and negatively with total saturated ($r=-0.816$, $p=0.0001$; $r=-0.439$, $p=0.0001$) and total mono-unsaturated ($r=-0.431$, $p=0.0001$; $r=-0.231$, $p=0.037$) fatty acids. Although seafood is an integral part of traditional Omani cuisine the children had a low level of n-3 fatty acids index. There is a need to address this nutritional insufficiency through school feeding programme, targeted intervention with n-3 fatty acid enriched food products and/or family education programme.

[34] *Nadjar A*. **Role of metabolic programming in the modulation of microglia phagocytosis by lipids**. Prostaglandins, leukotrienes, and essential fatty acids 2018; 135:63-73.

PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=30103935

ABSTRACT

Literature update week 33 (2018)

Microglia phagocytosis is an essential process to maintain lifelong brain homeostasis and clear potential toxic factors from the neuropil. Microglia can engulf cells or part of cells through the expression of specific receptors at their surface and activation of downstream signaling pathways to engulf material. Microglia phagocytosis is finely regulated and is under the dependence of many factors, including environmental cues such as dietary lipids. Yet, the molecular mechanisms implicated are still largely unknown. The present publication is a 'hypothesis review', assessing the possibility that lipid-mediated modulation of phagocytosis occurs by affecting bioenergetic pathways within microglia. I assess our present knowledge and the elements that allow drawing such hypothesis. I also list some of the important gaps in the literature that need to be filled in. I also consider opportunities for future therapeutic target including nutritional interventions.

[35] *von Schacky C, Harris WS*. **Why docosapentaenoic acid is not included in the Omega-3 Index**. Prostaglandins, leukotrienes, and essential fatty acids 2018; 135:18-21.

PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=30103927

ABSTRACT

As currently defined, the Omega-3 Index comprises eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA), but not docosapentaenoic acid (DPA) in erythrocytes. In fish and many fish oils DPA is detectable (along with EPA and DHA), but sources rich in DPA are scarce. Purified DPA is available, and DPA is a precursor of biologically active molecules, but much remains to be learned about the effects of DPA in humans. In epidemiologic studies, erythrocyte DPA did not predict risk for total mortality, sudden cardiac death, or other relevant cardiovascular events, and, more importantly, did not improve prediction of these events when included along with EPA and DHA, the original Omega-3 Index. We conclude that current scientific evidence does not support including DPA into the Omega-3 Index.

[36] *Puri BK, Derham A, Monro JA*. **Prevention of Infection in Adults Receiving Intravenous Antibiotic Treatment via Indwelling Central Venous Access Devices**. Reviews on recent clinical trials 2018.

PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=30117400

ABSTRACT

Background The use of indwelling central venous access devices (CVADs) is associated with the development of bloodstream infections. When CVADs are used to administer systemic antibiotics, particularly second- or higher-generation cephalosporins, there is a particular risk of developing Clostridium difficile infection. The overall bloodstream infection rate is estimated to be around 1.74 per 1000 central venous catheter (CVC)-days. Objective We hypothesised that daily oral administration of the anion-binding resin colestyramine (cholestyramine) would help prevent infections in those receiving intravenous antibiotic treatment via CVADs. Method A small case series is described of adult patients who received regular intravenous antibiotic treatment (ceftriaxone, daptomycin or vancomycin) for up to 40 weeks via indwelling CVADs; this represented a total of 357 CVC-days. In addition to following well established strategies to prevent C. difficile infection, during the course of the intravenous antibiotic treatment the patients also received daily oral supplementation with 4 g colestyramine. Results There were no untoward infectious events. In particular, none of the patients developed any symptoms or signs of C. difficile infection, whereas approximately one case of a bloodstream infection would have been expected. Conclusion It is suggested that oral colestyramine supplementation may help prevent such infection through its ability to bind C. difficile toxin A (TcdA) and C. difficile toxin B (TcdB); these

toxins are able to gain entry into host cells through receptor-mediated endocytosis, while anti-toxin antibody responses to TcdA and TcdB have been shown to induce protection against C. difficile infection sequelae.

[37] *Aluganti Narasimhulu C, Burge KY, Doomra M et al.* **Primary prevention of atherosclerosis by pretreatment of low-density lipoprotein receptor knockout mice with sesame oil and its aqueous components**. Scientific reports 2018; 8:12270.

PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=30115989

ABSTRACT

Pharmacological intervention using statins and PCSK9 inhibitors have become first-line therapy in the prevention of hypercholesterolemia and atherosclerosis. Currently, no agent is available for the primary prevention of atherosclerosis. However, there is an emerging hypothesis that atherosclerosis could be driven by inflammation. In this study, we tested whether pretreatment with an aqueous extract from sesame oil (SOAE), which showed potent anti-inflammatory properties without hypocholesterolemic actions, would prevent subsequent atherosclerosis development in a mouse model. RAW 264.7 macrophages and female low-density lipoprotein receptor knockout (LDLR(-/-)) mice were used for in vitro and in vivo studies, respectively. Plasma lipids, cytokines and atherosclerotic lesions were quantified at the end of the study. RNA was extracted from the liver and aortic tissues and used for gene analysis. Pre-treatment of SOAE prevented Ox-LDL uptake by RAW macrophages and further inflammation in vitro. SOAE pre-treatment significantly reduced atherosclerotic lesions and pro-inflammatory gene expressions in LDLR(-/-) mice as compared to control mice. No significant change in plasma cholesterol levels was observed. A significant reduction in plasma levels of TNF-alpha, IL-6, MCP-1 and VCAM1 was observed in the SOAE pre-treated animals. This is the first study that demonstrates that pre-treatment with anti-inflammatory agents, could delay/decrease atherosclerosis.

[38] *Sittiwet C, Simonen P, Nissinen MJ et al.* **Serum non-cholesterol sterols in Alzheimer's disease: the Helsinki Businessmen Study**. Translational research : the journal of laboratory and clinical medicine 2018.

PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=30102918

ABSTRACT

Cerebral cholesterol metabolism is perturbed in late-onset Alzheimer's disease (AD), but whether also the extracerebral cholesterol metabolism is perturbed is not known. Thus, we studied whole-body cholesterol synthesis and absorption with serum noncholesterol sterols in men without AD (n=114) or with (n=18) "pure" AD (no concomitant atherosclerotic cardiovascular disease) in a long-term cohort (the Helsinki Businessmen Study) of home-dwelling older men without lipid-lowering drugs and on their habitual home diet. Serum lipids did not differ between AD and controls, but age was higher (78 +/- 1 vs 74 +/- 0.3 years, mean +/- standard error, P < 0.001), age-adjusted plasma glucose concentration was lower (4.8 +/- 0.3 vs 5.7 +/- 0.1 mmol/L, P=0.011), and APOE epsilon4 allele and frailty were more frequent in AD than in controls. Of the age and frailty-adjusted serum noncholesterol sterols desmosterol and lathosterol ratios to cholesterol reflecting cholesterol synthesis were lower in AD than in controls (eg, lathosterol 114 +/- 12 vs 137 +/- 5 10(2) micromol/mmol cholesterol, P=0.004). Cholestanol ratio to cholesterol was higher in AD than in controls suggesting increased cholesterol absorption. Lathosterol and/or sitosterol ratio reflecting cholesterol metabolism was lower in AD than in

controls (0.95 +/- 0.28 vs 1.52 +/- 0.11 10(2) micromol/mmol cholesterol, P=0.027). In AD, plasma glucose correlated negatively with cholesterol synthesis, whereas in controls the correlation was positive. In conclusion, extracerebral cholesterol metabolism was altered in AD. This finding along with the low plasma glucose concentration and its paradoxical interaction with cholesterol synthesis opens new perspectives in the regulation of cholesterol metabolism and glucose homeostasis in AD.