

Literature update week 02 (2018)

[1] Zakrajsek J, Bevc-Cernilec K, Bohanec S, Urleb U. **Optimization of UPLC Method for Simultaneous Determination of Rosuvastatin and Rosuvastatin Degradation Products.** *Acta chimica Slovenica* 2017; 64:968-979.

PM: <http://www.ncbi.nlm.nih.gov/pubmed/?term=29318320>

ABSTRACT

An ultra-performance liquid chromatographic method for simultaneous determination of rosuvastatin and rosuvastatin degradation products was developed and optimized by using fractional factorial experimental design. Optimized method is capable to accurately determine all potential degradation products of rosuvastatin. During the optimization the effect of four chosen chromatographic factors was evaluated. The analytical method operational design region was modeled using Umetrics MODDE software and optimal chromatographic conditions were predicted. The results of the model show that the most important factors to reach good separation between the peaks of rosuvastatin impurities are the pH of buffer solution and the amount of ACN and THF in the mobile phase. The final optimized method using QbD approach was validated for linearity, accuracy and precision for determination of rosuvastatin and rosuvastatin degradation products in rosuvastatin pharmaceutical dosage forms. Limit of detection and quantification were determined for two known specified impurities. The use of experimental designs enabled us to obtain the maximum amount of information about the analytical method design region. Optimization of the method was done without additional experiments, only weighing the responses and rebuilding the statistical model. This approach is very cost-effective when evaluating a variety of different factors and their interactions.

[2] Clausen M, Jonasson K, Keil T et al. **Fish oil in infancy protects against food allergy in Iceland - results from a birth cohort study.** *Allergy* 2018.

PM: <http://www.ncbi.nlm.nih.gov/pubmed/?term=29318622>

ABSTRACT

BACKGROUND: Consumption of oily fish or fish oil during pregnancy, lactation, and infancy has been linked to a reduction in the development of allergic diseases in childhood. METHODS: In an observational study, Icelandic children (n = 1304) were prospectively followed from birth to 2.5 years with detailed questionnaires administered at birth and at one and two years of age, including questions about fish oil supplementation. Children with suspected food allergy were invited for physical examinations, allergic sensitization tests, and a double-blind, placebo-controlled food challenge if the allergy testing or clinical history indicated food allergy. The study investigated the development of sensitization to food and confirmed food allergy according to age and frequency of postnatal fish oil supplementation using proportional hazards modelling. RESULTS: The incidence of diagnosed food sensitization was significantly lower in children who received regular fish oil supplementation (relative risk 0.51, 95% confidence interval 0.32-0.82). The incidence of challenge-confirmed food allergy was also reduced, although not statistically significantly (0.57, 0.30-1.12). Children who began to receive fish oil in their first half year of life were significantly more protected than those who began later (p = 0.045 for sensitization, p = 0.018 for allergy). Indicators of allergy severity decreased with increased fish oil consumption (p = 0.013). Adjusting for parent education and allergic family history did not change the results. CONCLUSION: Postnatal fish oil consumption is associated with decreased food sensitization and food allergies in infants and may provide an

Literature update week 02 (2018)

intervention strategy for allergy prevention. This article is protected by copyright. All rights reserved.

[3] Jones HM, Fang Z, Sun W et al. **Atorvastatin exhibits anti-tumorigenic and anti-metastatic effects in ovarian cancer in vitro.** American journal of cancer research 2017; 7:2478-2490.

PM: <http://www.ncbi.nlm.nih.gov/pubmed/?term=29312801>

ABSTRACT

Ovarian cancer is the 8th most common cancer in women, and the 5th leading cause of cancer-related deaths among women in the United States. Statins have been shown to have promising anti-tumorigenic activity in many types of cancers. We sought to determine the effects of atorvastatin (ATO) on cell proliferation in ovarian cancer and identify the mechanisms by which ATO inhibits cell growth in this disease. ATO inhibited cell proliferation of both the Hey and SKOV3 ovarian cancer cells in a dose-dependent manner. The anti-proliferative activity of ATO in the ovarian cancer cell lines was associated with induction of apoptosis, autophagy, cellular stress and cell cycle G1 arrest via inhibition of AKT/mTOR and activation of the MAPK pathways. Moreover, ATO inhibited cell adhesion and invasion as well as decreased expression of VEGF and MMP9. c-Myc was downregulated in ovarian cancer cells exposed to ATO. Inhibition of c-Myc by JQ1 synergistically increased the sensitivity of ovarian cancer cells to ATO. This data suggests that ATO may have a therapeutic role in the treatment of ovarian cancer and warrant further exploration in clinical trials.

[4] Levy C, Lindor KD. **Editorial: Itching to Know: Role of Fibrates in PBC.** Am J Gastroenterol 2018; 113:56-57.

PM: <http://www.ncbi.nlm.nih.gov/pubmed/?term=29311728>

ABSTRACT

Approximately one-third of patients with primary biliary cholangitis (PBC) fail to respond to ursodeoxycholic acid (UDCA) and are at risk for progression to biliary cirrhosis and end-stage liver disease. In this paper by Pares et al., the authors evaluate the effect of long-term use of bezafibrate in patients with primary biliary cholangitis (PBC) and inadequate response to UDCA. They found that addition of bezafibrate led to normalization of serum alkaline phosphatase in half of the study subjects and major improvement in pruritus. Here we discuss these findings and place them in context with current knowledge about fibrates in PBC.

[5] Braza MS, Conde P, Garcia M et al. **Neutrophil derived CSF1 induces macrophage polarization and promotes transplantation tolerance.** American journal of transplantation : official journal of the American Society of Transplantation and the American Society of Transplant Surgeons 2018.

PM: <http://www.ncbi.nlm.nih.gov/pubmed/?term=29314558>

ABSTRACT

The colony-stimulating factor 1 (CSF1) regulates the differentiation and function of tissue macrophages and determines the outcome of the immune response. The molecular mechanisms behind CSF1-mediated macrophage development remain to be elucidated. Here we demonstrate that neutrophil-derived CSF1 controls macrophage polarization and proliferation, which is necessary for the induction of tolerance. Inhibiting neutrophil production

Literature update week 02 (2018)

of CSF1 or preventing macrophage proliferation, using targeted nanoparticles loaded with the cell cycle inhibitor simvastatin, abrogates the induction of tolerance. These results provide new mechanistic insights into the developmental requirements of tolerogenic macrophages and identify CSF1 producing neutrophils as critical regulators of the immunological response. This article is protected by copyright. All rights reserved.

[6] *Kiezel-Tsugunova M, Kendall AC, Nicolaou A. Fatty acids and related lipid mediators in the regulation of cutaneous inflammation. Biochemical Society transactions 2018.*

PM: <http://www.ncbi.nlm.nih.gov/pubmed/?term=29330355>

ABSTRACT

Human skin has a distinct profile of fatty acids and related bioactive lipid mediators that regulate many aspects of epidermal and dermal homeostasis, including immune and inflammatory reactions. Sebum lipids act as effective antimicrobial agents, shape immune cell communications and contribute to the epidermal lipidome. The essential fatty acid linoleic acid is crucial for the structure of the epidermal barrier, while polyunsaturated fatty acids act as precursors to eicosanoids, octadecanoids and docosanoids through cyclooxygenase, lipoxygenase and cytochrome P450 monooxygenase-mediated reactions, and endocannabinoids and N-acyl ethanolamines. Cross-communication between these families of bioactive lipids suggests that their cutaneous activities should be considered as part of a wider metabolic network that can be targeted to maintain skin health, control inflammation and improve skin pathologies.

[7] *Yamanashi Y, Takada T, Suzuki H. Associations between Lifestyle-Related Diseases and Transporters Involved in Intestinal Absorption and Biliary Excretion of Cholesterol. Biological & pharmaceutical bulletin 2018; 41:1-10.*

PM: <http://www.ncbi.nlm.nih.gov/pubmed/?term=29311470>

ABSTRACT

Westernization of dietary habits leads to an increase in lipid intake and is thought to be responsible for an increase in patients with dyslipidemia. It is a well-known fact that the impaired cholesterol homeostasis is closely related to the development of various lifestyle-related diseases such as fatty liver, diabetes, and gallstone as well as dyslipidemia leading to atherosclerosis and cardiovascular diseases such as heart attack and stroke. Therefore, appropriate management of cholesterol levels in the body is considered important in prevention and treatments of these lifestyle-related diseases and in addition, molecular mechanisms controlling plasma (and/or hepatic) cholesterol levels have been intensively studied. Due to its hydrophobicity, cholesterol was long believed to pass through cell membranes by passive diffusion. However, recent studies have identified a number of plasma membrane transporters that are responsible for the cellular uptake or efflux of cholesterol and involved in developments of lifestyle-related diseases. In this review, we focus on Niemann-Pick C1 Like 1 (NPC1L1) and a heterodimer of ATP-binding cassette transporter G5 and G8 (ABCG5/G8), both of which are responsible for intestinal cholesterol absorption and biliary cholesterol secretion, and discuss the relationship between these cholesterol transporters and lifestyle-related diseases. In addition, we also discuss the related uncertainties that need to be explored in future studies.

[8] *Beires MT, Silva-Pinto A, Santos AC et al. Visceral adipose tissue and carotid intima-media thickness in HIV-infected patients undergoing cART: a prospective cohort study. BMC infectious diseases* 2018; 18:32.

PM: <http://www.ncbi.nlm.nih.gov/pubmed/?term=29325542>

ABSTRACT

BACKGROUND: Combined antiretroviral therapy (cART) in HIV-infected patients has been associated with lipodystrophy, metabolic abnormalities, and an increased risk of cardiovascular disease. Ultrasound measures of carotid artery intima-media thickness (cIMT) have been used as a valid measure of subclinical atherosclerosis and as a tool to predict the risk of cardiovascular events. Our aim was to evaluate the progression of cIMT in HIV-infected patients subjected to cART, with and without lipodystrophy, over a one-year period. METHODS: We performed a one-year prospective cohort study to compare changes in cIMT, metabolic and inflammation markers in HIV-infected patients undergoing cART. Body composition was assessed by dual-energy X-ray absorptiometry (DXA) and abdominal computed tomography (CT). Levels of blood pressure, lipids and inflammatory markers were evaluated, as well as ultrasound measures of cIMT. Lipodystrophy defined by Fat Mass Ratio (L-FMR) is measured as the ratio of the percentage of trunk fat mass to the percentage of lower limb fat mass by DXA. Categorical variables were compared, using the chi-square or Fisher's exact test. Wilcoxon ranks tests and the McNemar chi-square tests were used to compare results of selected variables, from the first to the second year of evaluation. Means of cIMT, adjusted for age, glucose, triglycerides levels, systolic blood pressure (SBP), and waist to hip ratio were calculated, using generalised linear models for repeated measures. RESULTS: L-FMR was present in 44.3% of patients, and the mean of cIMT increased significantly in this group [0.82 (0.26) vs 0.92 (0.33); $p = 0.037$], as well as in patients without lipodystrophy [0.73 (0.20) vs 0.84 (0.30); $p = 0.012$]. In the overall sample, the progression of cIMT was statistically significant after the adjustment for age, glucose, triglycerides, and SBP, but the significance of the progression ceased after the adjustment for waist/hip ratio [0.770 (0.737-0.803) vs 0.874 (0.815-0.933); $p = 0.514$]. CONCLUSIONS: Carotid IMT progressed significantly in both groups of this HIV-infected cohort, however no association between the progression of cIMT and the presence of lipodystrophy defined by FMR was found. Visceral adipose tissue had an impact on the increment of cIMT, both in patients with, and without lipodystrophy defined by FMR.

[9] *Luymes CH, Poortvliet RKE, van Geloven N et al. Deprescribing preventive cardiovascular medication in patients with predicted low cardiovascular disease risk in general practice - the ECSTATIC study: a cluster randomised non-inferiority trial. BMC medicine* 2018; 16:5.

PM: <http://www.ncbi.nlm.nih.gov/pubmed/?term=29321031>

ABSTRACT

BACKGROUND: The use of cardiovascular medication for the primary prevention of cardiovascular disease (CVD) is potentially inappropriate when potential risks outweigh the potential benefits. It is unknown whether deprescribing preventive cardiovascular medication in patients without a strict indication for such medication is safe and cost-effective in general practice. METHODS: In this pragmatic cluster randomised controlled non-inferiority trial, we recruited 46 general practices in the Netherlands. Patients aged 40-70 years who were using

Literature update week 02 (2018)

antihypertensive and/or lipid-lowering drugs without CVD and with low risk of future CVD were followed for 2 years. The intervention was an attempt to deprescribe preventive cardiovascular medication. The primary outcome was the difference in the increase in predicted (10-year) CVD risk in the per-protocol (PP) population with a non-inferiority margin of 2.5 percentage points. An economic evaluation was performed in the intention-to-treat (ITT) population. We used multilevel (generalised) linear regression with multiple imputation of missing data. RESULTS: Of 1067 participants recruited between 7 November 2012 and 18 February 2014, 72% were female. Overall, their mean age was 55 years and their mean predicted CVD risk at baseline was 5%. Of 492 participants in the ITT intervention group, 319 (65%) quit the medication (PP intervention group); 135 (27%) of those participants were still not taking medication after 2 years. The predicted CVD risk increased by 2.0 percentage points in the PP intervention group compared to 1.9 percentage points in the usual care group. The difference of 0.1 (95% CI -0.3 to 0.6) fell within the non-inferiority margin. After 2 years, compared to the usual care group, for the PP intervention group, systolic blood pressure was 6 mmHg higher, diastolic blood pressure was 4 mmHg higher and total cholesterol and low-density lipoprotein-cholesterol levels were both 7 mg/dl higher (all $P < 0.05$). Cost and quality-adjusted life years did not differ between the groups. CONCLUSIONS: The results of the ECSTATIC study show that an attempt to deprescribe preventive cardiovascular medication in low-CVD-risk patients is safe in the short term when blood pressure and cholesterol levels are monitored after stopping. An attempt to deprescribe medication can be considered, taking patient preferences into consideration. TRIAL REGISTRATION: This study was registered with Dutch trial register on 20 June 2012 (NTR3493).

[10] *Nguyen T, Nguyen HQ, Widyakusuma NN et al. Enhancing prescribing of guideline-recommended medications for ischaemic heart diseases: a systematic review and meta-analysis of interventions targeted at healthcare professionals. BMJ open* 2018; 8:e018271.

PM: <http://www.ncbi.nlm.nih.gov/pubmed/?term=29326185>

ABSTRACT

OBJECTIVES: Ischaemic heart diseases (IHDs) are a leading cause of death worldwide. Although prescribing according to guidelines improves health outcomes, it remains suboptimal. We determined whether interventions targeted at healthcare professionals are effective to enhance prescribing and health outcomes in patients with IHDs. METHODS: We systematically searched PubMed and EMBASE for studies published between 1 January 2000 and 31 August 2017. We included original studies of interventions targeted at healthcare professionals to enhance prescribing guideline-recommended medications for IHDs. We only included randomised controlled trials (RCTs). Main outcomes were the proportion of eligible patients receiving guideline-recommended medications, the proportion of patients achieving target blood pressure and target low-density lipoprotein-cholesterol (LDL-C)/cholesterol level and mortality rate. Meta-analyses were performed using the inverse-variance method and the random effects model. The quality of evidence was assessed using the Grading of Recommendations, Assessment, Development, and Evaluation approach. RESULTS: We included 13 studies, 4 RCTs (1869 patients) and 9 cluster RCTs (15 224 patients). 11 out of 13 studies were performed in North America and Europe. Interventions were of organisational or professional nature. The interventions significantly enhanced prescribing of statins/lipid-lowering agents (OR 1.23; 95% CI 1.07 to 1.42, $P=0.004$), but not other medications

Literature update week 02 (2018)

(aspirin/antiplatelet agents, beta-blockers, ACE inhibitors/angiotensin II receptor blockers and the composite of medications). There was no significant association between the interventions and improved health outcomes (target LDL-C and mortality) except for target blood pressure (OR 1.46; 95% CI 1.11 to 1.93; P=0.008). The evidence was of moderate or high quality for all outcomes. CONCLUSIONS: Organisational and professional interventions improved prescribing of statins/lipid-lowering agents and target blood pressure in patients with IHDs but there was little evidence of change in other outcomes. PROSPERO REGISTRATION NUMBER: CRD42016039188.

[11] Jha A, Ryu MH, Ojo OO et al. **Prophylactic benefits of systemically delivered simvastatin treatment in a house dust mite challenged murine model of allergic asthma.** *Br J Pharmacol* 2018.

PM: <http://www.ncbi.nlm.nih.gov/pubmed/?term=29318574>

ABSTRACT

BACKGROUND AND PURPOSE: Systemically delivered statins can blunt airway inflammation in ovalbumin-challenged mice; however, in asthma clinical trials the beneficial effects of introducing oral statins are not compelling. We aim to reconcile this discrepancy using a clinically relevant murine model of allergic asthma, and by including a prophylactic study arm. **EXPERIMENTAL APPROACH:** Adult mice were: 1) challenged with house dust mite (HDM) alone or with subcutaneous (s.c.) simvastatin for two weeks; or 2) also treated with simvastatin for one week prior to HDM challenge. We assayed lung function, inflammatory cell influx and cytokine profile, goblet cell abundance, and simvastatin concentration in serum, lung lavage and tissue. **KEY RESULTS:** Ultrahigh performance liquid chromatography-tandem mass spectrometry revealed that pharmacologically active simvastatin reached peak serum concentration after 8h, but declined rapidly. Prophylactic treatment doubled peak serum simvastatin and repeated s.c. delivery established stable serum levels, but simvastatin was undetectable in the lungs. Both simvastatin treatment arms suppressed indices of HDM-induced airway inflammation and goblet cell hyperplasia, but this was significantly greater with prophylactic therapy, in particular to inhibit neutrophil and eosinophil influx, and cytokine accumulation. Conversely, neither acute nor prophylactic delivery of simvastatin prevented HDM challenge-induced airway hyperreactivity. **CONCLUSION AND IMPLICATIONS:** Systemically administered simvastatin accumulates in the blood, but not in lung tissues, and reduces leukocyte influx and associated lung inflammation. Prophylactic therapy has the greatest anti-inflammatory effects, but as observed in human clinical trials, systemic simvastatin therapy does not prevent allergic airway hyperreactivity.

[12] Kang J, Kim YC, Park JJ et al. **Increased epicardial adipose tissue thickness is a predictor of new-onset diabetes mellitus in patients with coronary artery disease treated with high-intensity statins.** *Cardiovascular diabetology* 2018; 17:10.

PM: <http://www.ncbi.nlm.nih.gov/pubmed/?term=29325562>

ABSTRACT

BACKGROUND: Statins are widely used for lipid lowering in patients with coronary artery disease (CAD), but increasing evidence indicates an association between statin use and new-onset of diabetes mellitus (NODM). Epicardial adipose tissue (EAT) refers to the visceral fat

Literature update week 02 (2018)

surrounding the heart, which is associated with metabolic diseases. We sought to determine the association between EAT thickness and NODM in CAD patients treated with high-intensity statins. **METHODS:** We conducted a retrospective medical record review of CAD patients treated with high-intensity statins for at least 6 months after percutaneous coronary intervention performed between January 2009 and June 2013 at Seoul National University Bundang Hospital. EAT thickness was measured by echocardiography using standardized methods. **RESULTS:** A total of 321 patients were enrolled, who received high-intensity statins for a mean of 952 days; atorvastatin 40 mg in 204 patients (63.6%), atorvastatin 80 mg in 57 patients (17.8%), and rosuvastatin 20 mg in 60 patients (18.7%). During the follow-up period of 3.9 +/- 1.7 years, NODM occurred in 40 patients (12.5%). On Cox proportional-hazard regression analysis, EAT thickness at systole [for each 1 mm: hazard ratio (HR) 1.580; 95% confidence interval (CI) 1.346-1.854; $P < 0.001$] and prediabetes at baseline (HR 4.321; 95% CI 1.998-9.349; $P < 0.001$) were the only independent predictors of NODM. Using binary cutoff values derived from the receiver operating characteristic curve analysis, EAT thickness at systole larger than 5.0 mm had an HR of 3.402 (95% CI 1.751-6.611, $P < 0.001$), sensitivity of 52.5%, and specificity of 80.8% for predicting NODM. Also, patients with EAT thickness ≥ 5 mm and prediabetes at baseline had a 12.0-times higher risk of developing NODM compared to the risk noted in patients with EAT thickness < 5 mm and normal glucose tolerance at baseline. **CONCLUSION:** Epicardial adipose tissue thickness at systole is a consistent independent predictor of NODM in patients with CAD treated with high-intensity statins. Such predictors may help physicians plan adequate surveillance for early detection of NODM.

[13] Patel V, Joharapurkar A, Kshirsagar S et al. **Coagonist of GLP-1 and glucagon decreases liver inflammation and atherosclerosis in dyslipidemic condition.** Chemico-biological interactions 2018; 282:13-21.

PM: <http://www.ncbi.nlm.nih.gov/pubmed/?term=29325849>

ABSTRACT

Dyslipidemia enhances progression of atherosclerosis. Coagonist of GLP-1 and glucagon are under clinical investigation for the treatment of obesity and diabetes. Earlier, we have observed that coagonist reduced circulating and hepatic lipids, independent of its anorexic effects. Here, we investigated the role of coagonist of GLP-1 and glucagon receptors in complications of diet-induced dyslipidemia in hamsters and humanized double transgenic mice. Hamsters fed on high fat high cholesterol diet were treated for 8 weeks with coagonist of GLP-1 and glucagon receptors (75 and 150 μ g/kg). Pair-fed control was maintained. Cholesterol fed transgenic mice overexpressing hApoB100 and hCETP with coagonist (300 μ g/kg) for 4 weeks. After the completion of treatment, biochemical estimations were done. Coagonist treatment reduced triglycerides in plasma, liver and aorta, plasma cholesterol and hepatic triglyceride secretion rate. Expressions of HMG-CoA reductase and SBREBP-1C were reduced and expressions of LDLR, CYP7A1, ABCA1 and ABCB11 were increased in liver, due to coagonist treatment. Coagonist treatment increased bile flow rate and biliary cholesterol excretion. IL-6 and TNF- α were reduced in plasma and expression of TNF- α , MCP-1, MMP-9 and TIMP-1 decreased in liver. Treatment with coagonist reduced oxidative stress in liver and aorta. Energy expenditure was increased and respiratory quotient was reduced by coagonist treatment. These changes were correlated with reduced hepatic inflammation and lipids in liver and aorta

Literature update week 02 (2018)

in coagonist treated hamsters. Coagonist treatment also reduced lipids in cholesterol-fed transgenic mice. These changes were independent of glycaemia and anorexia observed after coagonist treatment. Long term treatment with coagonist of GLP-1 and glucagon receptor ameliorated diet-induced dyslipidemia and atherosclerosis by regulating bile homeostasis, liver inflammation and energy expenditure.

[14] *Doshi JA, Puckett JT, Parmacek MS, Rader DJ. Prior Authorization Requirements for Proprotein Convertase Subtilisin/Kexin Type 9 Inhibitors Across US Private and Public Payers. Circulation. Cardiovascular quality and outcomes* 2018; 11:e003939.

PM: <http://www.ncbi.nlm.nih.gov/pubmed/?term=29326146>

ABSTRACT

BACKGROUND: Proprotein convertase subtilisin/kexin type 9 inhibitors (PCSK9is) are an innovative treatment option for patients with familial hypercholesterolemia or clinical atherosclerotic cardiovascular disease who require further lowering of low-density lipoprotein cholesterol. However, the high costs of these agents have spurred payers to implement utilization management policies to ensure appropriate use. We examined prior authorization (PA) requirements for PCSK9is across private and public US payers. METHODS AND RESULTS: We conducted an analysis of 2016 formulary coverage and PA data from a large, proprietary database with information on policies governing >95% of Americans with prescription drug coverage (275.3 million lives) within 3872 plans across the 4 major insurance segments (commercial, health insurance exchange, Medicare, and Medicaid). The key measures included administrative PA criteria (prescriber specialty, number of criteria in PA policy or number of fields on PA form, requirements for medical record submission, reauthorization requirements) and clinical/diagnostic PA criteria (approved conditions, required laboratories or other tests, required concomitant therapy, step therapy requirements, continuation criteria) for each of 2 Food and Drug Administration-approved PCSK9is. Select measures (eg, number of PA criteria/fields, medical record submission requirements) were obtained for 2 comparator cardiometabolic drugs (ezetimibe and liraglutide). Between 82% and 97% of individuals were enrolled in plans implementing PA for PCSK9is (depending on insurance segment), and one third to two thirds of these enrollees faced PAs restricting PCSK9i prescribing to a specialist. For patients with familial hypercholesterolemia, diagnostic confirmation via genetic testing or meeting minimum clinical scores/criteria was also required. PA requirements were more extensive for PCSK9is as compared with the other cardiometabolic drugs (ie, contained 3x-11x the number of PA criteria or fields on PA forms and more frequently involved the submission of medical records as supporting documentation). CONCLUSIONS: PA requirements for PCSK9is are greater than for selected other drugs within the cardiometabolic disease area, raising concerns about whether payer policies to discourage inappropriate use may also be restricting access to these drugs in patients who need them.

[15] *Liu WH, Xu XH, Luo Q et al. Inhibition of the RhoA/Rho-associated, coiled-coil-containing protein kinase-1 pathway is involved in the therapeutic effects of simvastatin on pulmonary arterial hypertension. Clinical and experimental hypertension (New York, N.Y. : 1993)* 2018:1-7.

PM: <http://www.ncbi.nlm.nih.gov/pubmed/?term=29319354>

ABSTRACT

Literature update week 02 (2018)

BACKGROUND: Recent research has shown that statins improve pulmonary arterial hypertension (PAH), but their mechanisms of action are not fully understood. This study aimed to investigate the role of RhoA/ROCK1 regulation in the therapeutic effects of simvastatin on PAH. **METHODS:** For in vivo experiments, rats (N = 40) were randomly assigned to four groups: control, simvastatin, monocrotaline (MCT), and MCT + simvastatin. The MCT group and MCT + simvastatin groups received proline dithiocarbamate (50 mg/kg, i.p.) on the first day of the study. The MCT + simvastatin group received simvastatin (2 mg/kg) daily for 4 weeks, after which pulmonary arterial pressure was measured by right heart catheterization. The protein and mRNA levels of Rho and ROCK1 were measured by immunohistochemistry, Western blot, and PCR. For in vitro experiments, human pulmonary endothelial cells were divided into seven groups: control, simvastatin, monocrotaline pyrrole (MCTP), MCTP + simvastatin, MCTP + simvastatin + mevalonate, MCTP + simvastatin + farnesyl pyrophosphate (FPP), and MCTP + simvastatin + FPP + geranylgeranyl pyrophosphate (GGPP). After 72 h exposed to the drugs, the protein and mRNA levels of RhoA and ROCK1 were measured by Western blot and PCR. **RESULTS:** The MCT group showed increased mean pulmonary arterial pressure, marked vascular remodeling, and increased protein and mRNA levels of RhoA and ROCK1 compared to the other groups ($P < 0.05$). In vitro, the MCTP group showed a marked proliferation of vascular endothelial cells, as well as increased protein and mRNA levels of RhoA and ROCK1 compared to the MCTP + simvastatin group. The MCTP + simvastatin + mevalonate group, MCTP + simvastatin + FPP group, and MCTP + simvastatin + FPP + GGPP group showed increased mRNA levels of RhoA and ROCK1, as well as increased protein levels of RhoA, compared to the MCTP + simvastatin group. **CONCLUSIONS:** Simvastatin improved vascular remodeling and inhibited the development of PAH. The effects of simvastatin were mediated by inhibition of RhoA/ROCK1. Simvastatin decreased RhoA/ROCK1 overexpression by inhibition of mevalonate, FPP, and GGPP synthesis.

[16] *Steinarsson AO, Rawshani A, Gudbjornsdottir S et al. Short-term progression of cardiometabolic risk factors in relation to age at type 2 diabetes diagnosis: a longitudinal observational study of 100,606 individuals from the Swedish National Diabetes Register. Diabetologia* 2018.

PM: <http://www.ncbi.nlm.nih.gov/pubmed/?term=29318343>

ABSTRACT

AIMS/HYPOTHESIS: The reasons underlying a greater association of premature mortality with early-onset type 2 diabetes relative to late-onset disease are unclear. We evaluated the clinical characteristics at type 2 diabetes diagnosis and the broad trajectories in cardiometabolic risk factors over the initial years following diagnosis in relation to age at diagnosis. **METHODS:** Our cohort consisted of 100,606 individuals with newly diagnosed type 2 diabetes enrolled in the Swedish National Diabetes Register from 2002 to 2012. The average follow-up time was 2.8 years. Analyses were performed using a linear mixed-effects model for continuous risk factors and a mixed generalised linear model with a logistic link function for dichotomous risk factors. **RESULTS:** The individuals diagnosed at the youngest age (18-44 years) were more often male and had the highest BMI (mean of 33.4 kg/m²) at diagnosis and during follow-up compared with all other groups (those diagnosed at 45-59 years, 60-74 years and ≥ 75 years; $p < 0.05$), being ~ 5 kg/m² higher than the oldest group. Although HbA1c patterns were similar between

Literature update week 02 (2018)

all age groups, there was a difference of about 5 mmol/mol (0.45%) between the two groups at 8 years post-diagnosis ($p < 0.05$). Additionally, individuals diagnosed younger had ~ 0.7 mmol/l higher triacylglycerol, and ~ 0.2 mmol/l lower HDL-cholesterol levels at diagnosis relative to the oldest group. Such differences continued for several years post diagnosis. Yet, although more of these younger individuals were receiving oral glucose-lowering agents, other cardioprotective therapies were prescribed less often in this group. Differences in BMI, blood glucose and lipid levels remained with adjustment for potential confounders, including marital status, education and country of birth, and, where relevant, differential treatments by age, and in those with at least 5 years of follow-up. **CONCLUSIONS/INTERPRETATION:** Individuals who develop type 2 diabetes at a younger age are more frequently obese, display a more adverse lipid profile, have higher HbA1c and a faster deterioration in glycaemic control compared with individuals who develop diabetes later in life. These differences largely remain for several years after diagnosis and support the notion that early-onset type 2 diabetes may be a more pathogenic condition than late-onset disease.

[17] *Mooranian A, Negrulj R, Takechi R et al. The biological effects of the hypolipidaemic drug probucol microcapsules fed daily for 4 weeks, to an insulin-resistant mouse model: potential hypoglycaemic and anti-inflammatory effects. Drug delivery and translational research 2018.*

PM: <http://www.ncbi.nlm.nih.gov/pubmed/?term=29313296>

ABSTRACT

Probuco (PB) is an hypolipidaemic drug with potential antidiabetic effects. We showed recently using in vitro studies that when PB was incorporated with stabilising lipophilic bile acids and microencapsulated using the polymer sodium alginate, the microcapsules showed good stability but poor and irregular PB release. This suggests that PB microcapsules may exhibit better release profile and hence better absorption, if more hydrophilic bile acids were used, such as ursodeoxycholic acid (UDCA). Accordingly, this study aimed to produce PB-UDCA microcapsules and examine PB absorption and antidiabetic effects in our mouse-model of insulin-resistance and diabetes (fed high-fat diet; HFD). The study also aimed to examine the effects of the microcapsules on the bile acid profile. Healthy mice (fed low-fat diet; LFD) were used as control. Seventy mice were randomly allocated into seven equal groups: LFD, HFD given empty microcapsules, HFD given metformin (M), HFD given standard-dose probucol (PB-SD), HFD given high-dose probucol (PB-H), HFD given UDCA microcapsules and HFD given PB-UDCA microcapsules. Blood glucose (BG), inflammatory biomarkers (TNF-alpha, IFN-gamma, IL-1beta, IL-6, IL-10, IL-12 and IL-17), plasma cholesterol, non-esterified fatty acids and triglycerides were analysed together with plasma bile acid and probucol concentrations. PB-UDCA microcapsules reduced BG in HFD mice, but did not reduce inflammation or improve lipid profile, compared with positive control (HFD) group. Although PB-UDCA microcapsules did not exert hypolipidaemic or antiinflammatory effects, they resulted in significant hypoglycaemic effects in a mouse model of insulin resistance, which suggests potential applications in insulin-resistance and glucose haemostasis.

[18] *Drexel H. Cost-effectiveness with PCSK9 inhibitors: a matter of costs. European heart journal. Cardiovascular pharmacotherapy 2018; 4:23-24.*

PM: <http://www.ncbi.nlm.nih.gov/pubmed/?term=29315397>

ABSTRACT

[19] *Ruscica M, Macchi C, Pavanello C et al. Appropriateness of statin prescription in the elderly. European journal of internal medicine 2018.*

PM: <http://www.ncbi.nlm.nih.gov/pubmed/?term=29310996>

ABSTRACT

Statins, the most widely used drugs in the Western world, have become a pivotal component in the primary and secondary prevention of vascular diseases. Although benefits have been well documented in younger-than-75-year-old individuals, the value of statins in people aged >75years and over is controversial. The CTT meta-analysis calculated an absolute risk reduction of 0.6%/year per 38.7mg/dl reduction in LDL-C levels in patients aged >75years, that would translate into a number needed to treat of 167. However, the absolute effect of a 38.7mg/dl cholesterol lowering on the rate of annual ischemic heart disease mortality is 10-fold larger in older vs younger patients. In order to advise physician prescription, three major Guidelines have been published over the last few years, i.e. the AHA/ACC and the NLA in the US, and the ESC/EAS in Europe. Moreover, statin prescription in the elderly should also consider the cardiovascular outcomes of elderly patients reported in classical statin preventive trials which give important clues on adherence and persistence of use, as well as on drug safety. The present review discusses benefits of intensive vs moderate statin therapy, justifications for the use of aggressive lipid management in the very old and the use of statins in frail elderlies. The final decision on the therapeutic strategy with statins in elderlies at higher risk to develop cardiovascular events should be always based on a careful analysis of the patient's general health and on the presence of metabolic abnormalities or drug interactions potentially leading to risk.

[20] *Chen CH, Cheng CY, Chen YC et al. Corrigendum to ' Rosuvastatin inhibits pressure-induced fibrotic responses via the expression regulation of prostacyclin and prostaglandin E 2 in rat renal tubular cells.': [European Journal of Pharmacology 700 (2013) 65-73]. European journal of pharmacology 2018; 819:290.*

PM: <http://www.ncbi.nlm.nih.gov/pubmed/?term=29325908>

ABSTRACT

[21] *Carru C, Da Boit M, Paliogiannis P et al. Associations between markers of oxidative stress, skeletal muscle mass and function and to the influence of resistance exercise training, in older adults. Experimental gerontology 2018.*

PM: <http://www.ncbi.nlm.nih.gov/pubmed/?term=29326089>

ABSTRACT

BACKGROUND: Oxidative stress (OS) negatively affects skeletal muscle homeostasis in experimental models of ageing. However, little is known about the associations between circulating OS markers and parameters of muscle mass and function, and their responses to exercise training, in humans. METHODS: Maximal voluntary contraction (MVC, primary outcome) and isokinetic torque of the knee extensors at 30 degrees s(-1) (MIT), muscle cross-sectional area (MCSA) and quality (MQ, secondary outcomes), and plasma concentrations of malondialdehyde (MDA, pro-OS), homocysteine (HCY, pro-OS), taurine (TAU, anti-OS), and

Literature update week 02 (2018)

protein sulphhydryl groups (PSH, anti-OS) were measured in 27 healthy older males and 23 females at baseline and after an 18-week resistance exercise program, with or without a nutritional intervention (fish oil vs. placebo). RESULTS: After adjusting for age, glomerular filtration rate, and nutritional intervention, there were no significant correlations between baseline OS markers and muscle parameters, barring a positive association between TAU and MIT in females ($r=0.53$, $P=.035$) and between MDA and MCSA in males ($r=0.69$, $P=.001$). Training did not significantly change OS markers, except for a reduction in MDA in females ($-0.27\text{ }\mu\text{mol/L}$, 95% CI -0.51 to -0.02 , $P=.034$). In females, there were significant correlations between baseline MDA and exercise-induced changes in MVC ($P=.018$), baseline TAU and changes in MCSA ($P=.026$), and baseline HCY and changes in MCSA ($P=.046$) and MQ ($P=.022$). In males, baseline MDA was significantly associated with exercise-induced changes in MVC ($P=.040$). CONCLUSIONS: Plasma MDA, HCY, and TAU were significantly associated with baseline and/or exercise-induced changes in muscle mass and function in healthy older adults, primarily in females. Pending further confirmation in other populations, specific OS markers, particularly MDA, might predict muscle responses to resistance exercise programs in old age.

[22] *Badimon L, Suades R, Arderiu G et al. Microvesicles in Atherosclerosis and Angiogenesis: From Bench to Bedside and Reverse. Frontiers in cardiovascular medicine 2017; 4:77.*

PM: <http://www.ncbi.nlm.nih.gov/pubmed/?term=29326946>

ABSTRACT

Atherosclerosis (AT) is a progressive chronic disease involving lipid accumulation, fibrosis, and inflammation in medium and large-sized arteries, and it is the main cause of cardiovascular disease (CVD). AT is caused by dyslipidemia and mediated by both innate and adaptive immune responses. Despite lipid-lowering drugs have shown to decrease the risk of cardiovascular events (CVEs), there is a significant burden of AT-related morbidity and mortality. Identification of subjects at increased risk for CVE as well as discovery of novel therapeutic targets for improved treatment strategies are still unmet clinical needs in CVD. Microvesicles (MVs), small extracellular plasma membrane particles shed by activated and apoptotic cells have been widely linked to the development of CVD. MVs from vascular and resident cells by facilitating exchange of biological information between neighboring cells serve as cellular effectors in the bloodstream and play a key role in all stages of disease progression. This article reviews the current knowledge on the role of MVs in AT and CVD. Attention is focused on novel aspects of MV-mediated regulatory mechanisms from endothelial dysfunction, vascular wall inflammation, oxidative stress, and apoptosis to coagulation and thrombosis in the progression and development of atherothrombosis. MV contribution to vascular remodeling is also discussed, with a particular emphasis on the effect of MVs on the crosstalk between endothelial cells and smooth muscle cells, and their role regulating the active process of AT-driven angiogenesis and neovascularization. This review also highlights the latest findings and main challenges on the potential prognostic, diagnostic, and therapeutic value of cell-derived MVs in CVD. In summary, MVs have emerged as new regulators of biological functions in atherothrombosis and might be instrumental in cardiovascular precision medicine; however, significant efforts are still needed to translate into clinics the latest findings on MV regulation and function.

Literature update week 02 (2018)

[23] *Katsuki S, Matoba T, Koga JI et al. Anti-inflammatory Nanomedicine for Cardiovascular Disease. Frontiers in cardiovascular medicine 2017; 4:87.*

PM: <http://www.ncbi.nlm.nih.gov/pubmed/?term=29312961>

ABSTRACT

Coronary artery disease, in the development of which inflammation mediated by innate immune cells plays a critical role, is one of the leading causes of death worldwide. The 3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitors (statins) are a widely used lipid-lowering drug that has lipid-independent vasculoprotective effects, such as improvement of endothelial dysfunction, antioxidant properties, and inhibitory effects on inflammation. Despite recent advances in lipid-lowering therapy, clinical trials of statins suggest that anti-inflammatory therapy beyond lipid-lowering therapy is indispensable to further reduce cardiovascular events. One possible therapeutic option to the residual risk is to directly intervene in the inflammatory process by utilizing a nanotechnology-based drug delivery system (nano-DDS). Various nano-sized materials are currently developed as DDS, including micelles, liposomes, polymeric nanoparticles, dendrimers, carbon nanotubes, and metallic nanoparticles. The application of nano-DDS to coronary artery disease is a feasible strategy since the inflammatory milieu enhances incorporation of nano-sized materials into mononuclear phagocytic system and permeability of target lesions, which confers nano-DDS on "passive-targeting" property. Recently, we have developed a polymeric nanoparticle-incorporating statin to maximize its anti-inflammatory property. This statin nanoparticle has been tested in various disease models, including plaque destabilization and rupture, myocardial ischemia-reperfusion injury, and ventricular remodeling after acute myocardial infarction, and its clinical application is in progress. In this review, we present current development of DDS and future perspective on the application of anti-inflammatory nanomedicine to treat life-threatening cardiovascular diseases.

[24] *Head T, Daunert S, Goldschmidt-Clermont PJ. The Aging Risk and Atherosclerosis: A Fresh Look at Arterial Homeostasis. Frontiers in genetics 2017; 8:216.*

PM: <http://www.ncbi.nlm.nih.gov/pubmed/?term=29312440>

ABSTRACT

A considerable volume of research over the last decade has focused on understanding the fundamental mechanisms for the progression of atherosclerosis-the underlying cause for the vast majority of all cardiovascular (CVD)-related complications. Aging is the dominant risk factor for clinically significant atherosclerotic lesion formation, yet the heightened impact of aging on the disease is not accounted for by changes in traditional risk factors, such as lack of physical activity, smoking, hypertension, hyperlipidemia, or diabetes mellitus. This review will examine the pathological and biochemical processes of atherosclerotic plaque formation and growth, with particular focus on the aging risk vis-a-vis arterial homeostasis. Particular focus will be placed on the impact of a number of important contributors to arterial homeostasis including bone marrow (BM)-derived vascular progenitor cells, differential monocyte subpopulations, and the role of cellular senescence. Finally, this review will explore many critical observations in the way the disease process has been reassessed both by clinicians and researchers, and will highlight recent advances in this field that have provided a greater understanding of this aging-driven disease.

[25] *Teng O, Ang CKE, Guan XL. Macrophage-Bacteria Interactions-A Lipid-Centric Relationship. Frontiers in immunology* 2017; 8:1836.

PM: <http://www.ncbi.nlm.nih.gov/pubmed/?term=29326713>

ABSTRACT

Macrophages are professional phagocytes at the front line of immune defenses against foreign bodies and microbial pathogens. Various bacteria, which are responsible for deadly diseases including tuberculosis and salmonellosis, are capable of hijacking this important immune cell type and thrive intracellularly, either in the cytoplasm or in specialized vacuoles. Tight regulation of cellular metabolism is critical in shaping the macrophage polarization states and immune functions. Lipids, besides being the bulk component of biological membranes, serve as energy sources as well as signaling molecules during infection and inflammation. With the advent of systems-scale analyses of genes, transcripts, proteins, and metabolites, in combination with classical biology, it is increasingly evident that macrophages undergo extensive lipid remodeling during activation and infection. Each bacterium species has evolved its own tactics to manipulate host metabolism toward its own advantage. Furthermore, modulation of host lipid metabolism affects disease susceptibility and outcome of infections, highlighting the critical roles of lipids in infectious diseases. Here, we will review the emerging roles of lipids in the complex host-pathogen relationship and discuss recent methodologies employed to probe these versatile metabolites during the infection process. An improved understanding of the lipid-centric nature of infections can lead to the identification of the Achilles' heel of the pathogens and host-directed targets for therapeutic interventions. Currently, lipid-moderating drugs are clinically available for a range of non-communicable diseases, which we anticipate can potentially be tapped into for various infections.

[26] *Zhou X, Zong Y, Zhang R et al. Differential Modulation of GABAA and NMDA Receptors by an alpha7-nicotinic Acetylcholine Receptor Agonist in Chronic Glaucoma. Frontiers in molecular neuroscience* 2017; 10:422.

PM: <http://www.ncbi.nlm.nih.gov/pubmed/?term=29326549>

ABSTRACT

Presynaptic modulation of gamma-aminobutyric acid (GABA) release by an alpha7 nicotinic acetylcholine receptor (alpha7-nAChR) agonist promotes retinal ganglion cell (RGC) survival and function, as suggested by a previous study on a chronic glaucomatous model from our laboratory. However, the role of excitatory and inhibitory amino acid receptors and their interaction with alpha7-nAChR in physiological and glaucomatous events remains unknown. In this study, we investigated GABAA and N-methyl-D-aspartate (NMDA) receptor activity in control and glaucomatous retinal slices and the regulation of amino acid receptor expression and function by alpha7-nAChR. Whole-cell patch-clamp recordings from RGCs revealed that the alpha7-nAChR specific agonist PNU-282987 enhanced the amplitude of currents elicited by GABA and reduced the amplitude of currents elicited by NMDA. The positive modulation of GABAA receptor and the negative modulation of NMDA receptor (NMDAR) by PNU-282987-evoked were prevented by pre-administration of the alpha7-nAChR antagonist methyllycaconitine (MLA). The frequency and the amplitude of glutamate receptor-mediated miniature glutamatergic excitatory postsynaptic currents (mEPSCs) were not significantly

Literature update week 02 (2018)

different between the control and glaucomatous RGCs. Additionally, PNU-282987-treated slices showed no alteration in the frequency or amplitude of mEPSCs relative to control RGCs. Moreover, we showed that expression of the alpha1 subunit of the GABAA receptor was downregulated and the expression of the NMDAR NR2B subunit was upregulated by intraocular pressure (IOP) elevation, and the changes of high IOP were blocked by PNU-282987. In conclusion, retina GABAA and NMDARs are modulated positively and negatively, respectively, by activation of alpha7-nAChR in in vivo chronic glaucomatous models.

[27] *Liu W, Lu S, Feng Y et al. Truth of Floating Carotid Plaques. Frontiers in neurology 2017; 8:673.*

PM: <http://www.ncbi.nlm.nih.gov/pubmed/?term=29312114>

ABSTRACT

The floating plaque in carotid artery is an uncommon condition that can be detected by a duplex ultrasonography scan and is a high-risk factor for embolic cerebrovascular disease. The histopathological features of floating plaque in carotid artery vary. To the best of our knowledge, there is still considerable controversy about the treatment of floating carotid plaque. In this case, the floating carotid plaque was located in the edge of atherosclerotic plaque in common carotid artery, pathological finding following carotid endarterectomy confirmed that the mobile substances were formed by the contents of the plaque protruding into the carotid lumen after the rupture of the fibrous cap, without mural thrombus. This pathological change was different from those of the mobile substances, which were commonly considered as mural thrombotic substances of ulcer plaque caused by the ruptures of fibrous cap of vulnerable plaque. According to pathological differences, we investigated pathogenesis of ischemic cerebrovascular disease caused by floating carotid plaque and possible treatments.

[28] *Qin M, Luo Y, Lu S et al. Ginsenoside F1 Ameliorates Endothelial Cell Inflammatory Injury and Prevents Atherosclerosis in Mice through A20-Mediated Suppression of NF-kB Signaling. Frontiers in pharmacology 2017; 8:953.*

PM: <http://www.ncbi.nlm.nih.gov/pubmed/?term=29311947>

ABSTRACT

Atherosclerosis (AS) is a chronic inflammatory disease and endothelial cell injury is the initial event. In this study, we investigated the protective effects of ginsenoside F1 (GF1) on AS and the potential molecular mechanisms of ox-LDL induced endothelial injury. ApoE^{-/-} mice were fed a high fat diet and orally treated with GF1 (50 mg/kg/day) for 8 weeks. Atherosclerotic plaque and LOX-1, TLR4, NF-kappaB expression levels in the aortic root and inflammatory factor MPO in whole body were measured. The treatment with GF1 induced a remarkable reduction in the atherosclerotic lesion area, LOX-1, TLR4 expression and decreased the MPO distribution. Meanwhile, in vitro study, we confirmed that GF1 treatment greatly increased ox-LDL-injured endothelial cell viability, ameliorated LOX-1, TLR4 expression levels and reduced monocytes adhesion. Protein microarray demonstrated that GF1 significantly inhibited G-CSF, ICAM-1, MIP-1delta, IL-1alpha, IL-15, IL-16 levels. Mechanistically, the GF1 treatment suppressed the NF-kappaB nuclear translocation. Furthermore, our data indicated that GF1 significantly increased A20 expression level and A20 siRNA markedly abolished the attenuation of GF1 on NF-kappaB

Literature update week 02 (2018)

nuclear translocation and inflammatory factors expression. Our results suggest that the GF1 may be a potential drug for anti-atherosclerosis.

[29] *Rebalka IA, Cao AW, Raleigh MJ et al. Statin Therapy Negatively Impacts Skeletal Muscle Regeneration and Cutaneous Wound Repair in Type 1 Diabetic Mice. Front Physiol* 2017; 8:1088.

PM: <http://www.ncbi.nlm.nih.gov/pubmed/?term=29311999>

ABSTRACT

Those with diabetes invariably develop complications including cardiovascular disease (CVD). To reduce their CVD risk, diabetics are generally prescribed cholesterol-lowering 3-hydroxy-methylglutaryl coenzyme A reductase inhibitors (i.e., statins). Statins inhibit cholesterol biosynthesis, but also reduce the synthesis of a number of mevalonate pathway intermediates, leading to several cholesterol-independent effects. One of the pleiotropic effects of statins is the reduction of the anti-fibrinolytic hormone plasminogen activator inhibitor-1 (PAI-1). We have previously demonstrated that a PAI-1 specific inhibitor alleviated diabetes-induced delays in skin and muscle repair. Here we tested if statin administration, through its pleiotropic effects on PAI-1, could improve skin and muscle repair in a diabetic rodent model. Six weeks after diabetes onset, adult male streptozotocin-induced diabetic (STZ), and WT mice were assigned to receive control chow or a diet enriched with 600 mg/kg Fluvastatin. Tibialis anterior muscles were injured via Cardiotoxin injection to induce skeletal muscle injury. Punch biopsies were administered on the dorsal scapular region to induce injury of skin. Twenty-four days after the onset of statin therapy (10 days post-injury), tissues were harvested and analyzed. PAI-1 levels were attenuated in statin-treated diabetic tissue when compared to control-treated tissue, however no differences were observed in non-diabetic tissue as a result of treatment. Muscle and skin repair were significantly attenuated in Fluvastatin-treated STZ-diabetic mice as demonstrated by larger wound areas, less mature granulation tissue, and an increased presence of smaller regenerating muscle fibers. Despite attenuating PAI-1 levels in diabetic tissue, Fluvastatin treatment impaired cutaneous healing and skeletal muscle repair in STZ-diabetic mice.

[30] *Sai C, Li J, Yingbin X, Ruiyan M. Atorvastatin Prevents Postoperative Atrial Fibrillation for Patients undergoing Cardiac Surgery. Hellenic journal of cardiology : HJC = Hellenike kardiologike epitheorese* 2018.

PM: <http://www.ncbi.nlm.nih.gov/pubmed/?term=29307691>

ABSTRACT

BACKGROUND: Observational studies suggested that statins might reduce postoperative atrial fibrillation for patients undergoing cardiac surgery (AF). However, a number of retrospective studies showed equivocal results. We aimed to evaluate whether different statins can reduce risk of AF in different doses. **METHODS:** We searched PubMed, EMBASE and the Cochrane Database for all published randomized controlled trials (RCTs) that examined effects of statin therapy on AF up to June 2016. A random effects model was used when there was substantial heterogeneity. **RESULTS:** Eighteen published studies including 4003 (2009 receiving statins, 1994 receiving regime) statin-naive patients with sinus rhythm before cardiac surgeries were identified for inclusion in the analysis. Thirteen studies investigated prevention of AF by

Literature update week 02 (2018)

atorvastatin, two studies investigated prevention of AF by rosuvastatin, two studies investigated prevention of AF by simvastatin, and one study investigated prevention of AF by pravastatin. The rest two studies compared effects of different doses of atorvastatin on prevention of AF for patients undergoing coronary artery bypass grafting (CABG). Overall, statin therapy was associated with a significant decreased risk of AF (relative risk (RR) 0.57, 95% confidence interval (CI) 0.45-0.73, $P = 0.000$). However, subgroup analyses showed that only atorvastatin reduced the risk of new-onset AF in patients after cardiac surgery (RR 0.53, 95% CI 0.41-0.69, $P = 0.000$). Patients undergoing CABG possibly received more benefits from statin therapy (RR 0.52, 95% CI 0.39-0.68). Statin therapy in a moderate dose may be optimal (RR 0.42, 95% CI 0.28-0.64). **CONCLUSIONS:** This meta-analysis suggests that statin therapy has an overall protective effect against postoperative AF, among which, atorvastatin in a moderate dose was significantly associated with a decreased risk of new-onset AF in patients after coronary surgery. Moreover, simvastatin may also exert significant protective effect against the AF recurrences in patients undergoing cardiac surgeries, thus further prospective studies are warranted.

[31] *Borghi C, Rodriguez-Artalejo F, De Backer G et al. Serum uric acid levels are associated with cardiovascular risk score: A post hoc analysis of the EURIKA study. International journal of cardiology* 2018; 253:167-173.

PM: <http://www.ncbi.nlm.nih.gov/pubmed/?term=29306459>

ABSTRACT

BACKGROUND: Reports are conflicting on whether serum uric acid (sUA) levels are independently associated with increased cardiovascular (CV) death risk. **METHODS:** This post hoc analysis assessed the relationship between sUA levels and CV death risk score in 7531 patients from the cross-sectional, multinational EURIKA study (NCT00882336). Patients had at least one CV risk factor but no clinical CV disease. Ten-year risk of CV death was estimated using SCORE-HDL and SCORE algorithms, categorized as low (<1%), intermediate (1% to <5%), high (>=5% to <10%) or very high (>=10%). **RESULTS:** Mean serum sUA levels increased significantly with increasing CV death risk category in the overall population and in subgroups stratified by diuretics use or renal function (all $P < 0.0001$). Multivariate ordinal logistic regression analyses, adjusted for factors significantly associated with CV death risk in univariate analyses (study country, body mass index, number of CV risk factors and comorbidities, use of lipid lowering therapies, antihypertensives and antidiabetics), showed a significant association between sUA levels and SCORE-HDL category in the overall population (OR: 1.39 [95% CI: 1.34-1.44]) and all subgroups (using diuretics: 1.32 [1.24-1.40]; not using diuretics: 1.46 [1.39-1.53]; estimated glomerular filtration rate [eGFR] < 60 ml/min/1.73 m²: 1.30 [1.22-1.38]; eGFR >= 60 ml/min/1.73 m²: 1.44 [1.38-1.51]; all $P < 0.0001$). Similar results were obtained when using SCORE. **CONCLUSIONS:** Higher sUA levels are associated with progressively higher 10-year CV death risk score in patients with at least one CV risk factor but no CV disease.

[32] *Carbone F, Rigamonti F, Burger F et al. Serum levels of osteopontin predict major adverse cardiovascular events in patients with severe carotid artery stenosis. International journal of cardiology* 2018.

PM: <http://www.ncbi.nlm.nih.gov/pubmed/?term=29317141>

ABSTRACT

BACKGROUND: Inflammatory mediators in the blood stream and within plaques are key determinants in atherogenesis. Here, we investigated serum osteopontin (OPN) as a potential predictor of poor outcome in patients with severe carotid atherosclerosis. **METHODS:** Carotid plaques and serum were collected from patients asymptomatic (n=185) or symptomatic (n=40) for ischemic stroke. Plaques were stained for lipids, smooth muscle cells, neutrophils, M1 and M2 macrophage subsets and matrix metalloproteinase-9 (MMP-9). Serum levels of OPN and interleukin-6 (IL-6) were determined by colorimetric enzyme-linked immunosorbent assays. **RESULTS:** Symptomatic patients showed a two-fold increase in serum OPN levels. In both symptomatic and asymptomatic patients, OPN levels positively correlated with intraplaque count of neutrophils, total macrophages, and MMP-9 content. In asymptomatic patients, OPN levels also positively correlated with lipids and M1 macrophage subsets. Receiver operating characteristic curve analysis identified serum OPN concentration of 70ng/ml as the best cut-off value to predict major adverse cardiovascular events (MACEs). Patients with high OPN levels had more vulnerable plaque phenotype and reduced levels of HDL-cholesterol and IL-6 as compared to low OPN levels. Kaplan-Meier curve confirmed that patients with OPN levels >70ng/ml had more MACEs at a 24-month follow-up. In the multivariate survival analysis, OPN levels >70ng/ml predicted MACEs, independently of age, gender, and symptomatic status. **CONCLUSION:** High circulating OPN levels were strongly correlated with vulnerability parameters within plaques and predict MACEs in patients with severe carotid artery stenosis. Although confirmation is needed from larger trials, OPN could be a promising clinical tool to assess atherosclerotic outcomes.

[33] *Stam-Slob MC, van der Graaf Y, de Boer A et al. Cost-effectiveness of PCSK9 inhibition in addition to standard lipid-lowering therapy in patients at high risk for vascular disease.*

International journal of cardiology 2018; 253:148-154.

PM: <http://www.ncbi.nlm.nih.gov/pubmed/?term=29306457>

ABSTRACT

BACKGROUND: As proprotein convertase subtilisin-kexin type 9 (PCSK9) monoclonal antibodies are entering the market, we assessed the cost-effectiveness of PCSK9 inhibition added to standard lipid-lowering therapy in patient groups at high risk for major adverse cardiovascular events (MACE). **METHODS:** A lifetime Markov Model was designed to estimate healthcare costs, quality-adjusted life years (QALYs) and incremental cost-effectiveness ratios (ICERs) for PCSK9 inhibition added to standard therapy in patients with Familial Hypercholesterolemia (FH), patients with vascular disease at high MACE recurrence risk, and patients with vascular disease with diabetes mellitus. The balance between costs and health outcomes was established for a broad range of potential relative risk reductions and drug costs. **RESULTS:** The expected QALY gain per patient and ICER in the main scenario were 1.4 QALYs for euro78,485/QALY gained in patients with FH, 0.22 QALYs for euro176,735/QALY gained in those with vascular disease and a predicted risk of MACE \geq 30% in 10years, and 0.22 QALYs for euro295,543/QALY gained in those with vascular disease and diabetes. Results were sensitive to assumptions on PCSK9 inhibitor treatment efficacy, and vascular event risks. **CONCLUSION:** The costs and effects of PCSK9 inhibition added to standard lipid-lowering treatment in patient groups at high risk for MACE can be estimated and adapted to a specific clinical setting. PCSK9 inhibition could be

Literature update week 02 (2018)

cost-effective in patients with FH. In patients with vascular disease PCSK9 inhibition is less cost-effective, however, a price development may change clinical practice. This model may aid treatment and reimbursement decisions regarding PCSK9 inhibitors.

[34] *Buoite Stella A, Gortan Cappellari G, Barazzoni R, Zanetti M. Update on the Impact of Omega 3 Fatty Acids on Inflammation, Insulin Resistance and Sarcopenia: A Review.*

International journal of molecular sciences 2018; 19.

PM: <http://www.ncbi.nlm.nih.gov/pubmed/?term=29324650>

ABSTRACT

Elderly and patients affected by chronic diseases face a high risk of muscle loss and impaired physical function. Omega 3 fatty acids (FA) attenuate inflammation and age-associated muscle loss, prevent systemic insulin resistance and improve plasma lipids, potentially impacting on sarcopenia. This paper aims to review recent randomized clinical studies assessing the effects a chronic omega 3 FA supplementation on inflammatory and metabolic profile during conditions characterized by sarcopenia (aging, insulin resistance, type 2 diabetes, chronic renal failure). A comprehensive search of three online databases was performed to identify eligible trials published between 2012 and 2017. A total of 36 studies met inclusion criteria. Omega 3 FA yielded mixed results on plasma triglycerides in the elderly and no effects in renal patients. No changes in systemic insulin resistance were observed. Inflammation markers did not benefit from omega 3 FA in insulin resistant and in renal subjects while decreasing in obese and elderly. Muscle related parameters improved in elderly and in renal patients. In conclusion, in aging- and in chronic disease-associated sarcopenia omega 3 FA are promising independently of associated anabolic stimuli or of anti-inflammatory effects. The evidence for improved glucose metabolism in insulin resistant and in chronic inflammatory states is less solid.

[35] *Schmocker C, Zhang IW, Kiesler S et al. Effect of Omega-3 Fatty Acid Supplementation on Oxylipins in a Routine Clinical Setting.* *International journal of molecular sciences* 2018; 19.

PM: <http://www.ncbi.nlm.nih.gov/pubmed/?term=29316682>

ABSTRACT

Omega-6 polyunsaturated fatty acid (n-6 PUFA) is the predominant polyunsaturated fatty acid (PUFA), especially in Western diet. A high omega-6/omega-3 ratio in Western diets is implicated in the development of cardiovascular diseases and inflammatory processes. Studies in animal models and in humans have demonstrated beneficial effects of omega-3 PUFA (n-3 PUFA) in a variety of diseases, including cardiac arrhythmias and inflammatory diseases, as well as breast and colon cancer. The molecular mechanisms underlying the effects of n-3 PUFA are still not well understood. Possible mechanisms include competition between n-3 and n-6 PUFAs at the cyclooxygenase (COX) and lipoxygenase (LOX) and cytochrome P450 levels, and subsequent formation of oxylipins with specific anti-inflammatory or anti-arrhythmic effects. In this study, we report the impact of routine long-term treatment with prescription-grade n-3 PUFA (either 840 mg or 1680 mg per day) on blood cell membrane fatty acid composition, as well as plasma oxylipin patterns, in a patient population with severe hyperlipidemia and cardiovascular disease who are on standard lipid-lowering and cardioprotective medications. Lipidomics analyses were performed by LC/ESI-MS/MS. Supplementation led to a dose-dependent increase in n-3 PUFA eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) in the blood cell fraction. We also

Literature update week 02 (2018)

observed a dose-dependent increase in EPA- and DHA-derived epoxy metabolites, whereas the effect of n-3 PUFA supplementation on LOX-dependent EPA- and DHA-derived hydroxy metabolites was less pronounced, with a tendency towards lower metabolites in subjects with higher n-3 PUFA levels. These data thus generally confirm effects of n-3 PUFA supplementation observed previously in healthy individuals. Additionally, they indicate a suppressive effect of high n-3 PUFA supplementation on the formation of LOX metabolites in the context of concomitant aspirin medication.

[36] *Pluess TT, Hayoz D, Berger MM et al. Erratum to: Intravenous fish oil blunts the physiological response to endotoxin in healthy subjects. Intensive care medicine* 2007; 33:1310.

PM: <http://www.ncbi.nlm.nih.gov/pubmed/?term=29330566>

ABSTRACT

[37] *Heidari MM, Derakhshani M, Sedighi F, Foruzan-Nia SK. Mutation Analysis of the Mitochondrial tRNA Genes in Iranian Coronary Atherosclerosis Patients. Iranian journal of public health* 2017; 46:1379-1385.

PM: <http://www.ncbi.nlm.nih.gov/pubmed/?term=29308382>

ABSTRACT

Background: Atherosclerosis is a disease that affects large and medium size arteries in the body that underlies coronary heart disease. Several nucleotide changes in mitochondrial tRNA genes have been reported in various diseases. The purpose of the study was to identify hotspot mitochondrial tRNA mutations in atherosclerotic patients. Methods: In this case-control study, the variations of ten mitochondrial tRNA genes (about 50%) were investigated in 70 patients from October 2013 and June 2015 suffered from atherosclerosis. The related mitochondrial area was amplified using PCR method. The mutation analysis was performed by Single Strand Conformational Polymorphism (SSCP) and Restriction Fragment Length Polymorphism (RFLP). All the positive samples were sequenced. Results: We found one novel heteroplasmic mutation (m.5725T>G) and three reported single nucleotide polymorphisms (SNPs) previously in other diseases including m.5568A>G, m.5711A>G and m.12308A>G. Conclusion: These tRNA mutations can alter their steady state level and affect the structure of tRNA. The role of mitochondrial tRNA mutations in the pathogenesis of atherosclerosis could potentially be important for the understanding of mitochondrial dysfunction in coronary atherosclerotic plaque formation.

[38] *Fujiyoshi N, Arima H, Satoh A et al. Associations between Socioeconomic Status and the Prevalence and Treatment of Hypercholesterolemia in a General Japanese Population: NIPPON DATA2010. Journal of atherosclerosis and thrombosis* 2018.

PM: <http://www.ncbi.nlm.nih.gov/pubmed/?term=29321397>

ABSTRACT

AIM: To investigate associations between socioeconomic status (SES) and the prevalence and treatment status of hypercholesterolemia in a general Japanese population. METHODS: In 2010, we established a cohort study of 2417 adults (age 20-91 yr) from 300 randomly selected areas across Japan who participated in the National Health and Nutrition Survey of Japan. We

Literature update week 02 (2018)

cross-sectionally examined an association between SES and (1) prevalence of hypercholesterolemia in 2417 participants (999 men and 1418 women) and (2) not receiving medication for hypercholesterolemia in 654 participants (215 men and 439 women). SES included employment status, marital status, length of education, and household expenditures. Hypercholesterolemia was defined as a total serum cholesterol level of ≥ 6.21 mmol/L (240 mg/dL) or the use of lipid-lowering medications. RESULTS: The overall prevalence of hypercholesterolemia was 21.5% in men and 31.0% in women. In men, the lowest quintile of household expenditures was associated with a higher prevalence of hypercholesterolemia (28.3%) compared with the upper 4 quintiles (19.9%) (multivariable-adjusted odds ratio 1.66; 95% confidence interval [CI] 1.16-2.38). Among participants with hypercholesterolemia, 55.4% of men and 55.1% of women were not receiving medication. Unmarried men were more likely to be untreated (75.0%) than married men (50.9%) (multivariable-adjusted odds ratio 2.53; 95%CI 1.05-6.08). SES had no significant effects in women. CONCLUSION: In a general population of Japanese men, low household expenditures were associated with a higher prevalence of hypercholesterolemia, and unmarried men with hypercholesterolemia were less likely to receive medication.

[39] *Hosny H, Ibrahim M, El-Siory W, Abdel-Monem A. Comparative Study Between Conventional Fasting Versus Overnight Infusion of Lipid or Carbohydrate on Insulin and Free Fatty Acids in Obese Patients Undergoing Elective On-pump Coronary Artery Bypass Grafting. A Prospective Randomized Trial. Journal of cardiothoracic and vascular anesthesia* 2017.

PM: <http://www.ncbi.nlm.nih.gov/pubmed/?term=29306619>

ABSTRACT

OBJECTIVES: Postoperative insulin resistance represents a major component of postoperative metabolic disorder. The authors compared the effects of preoperative infusion of lipid emulsion or carbohydrate to conventional preoperative fasting on postoperative insulin and free fatty acid (FFA) levels. DESIGN: A prospective randomized double-blinded study. SETTINGS: Tertiary university hospital. PARTICIPANTS: Sixty-three patients undergoing coronary artery bypass grafting. INTERVENTION: Participants were randomized into 3 equal groups. Group G received 500 mL of glucose 10% (50 g glucose). Group L received 100 mL of 2% lipid emulsion (soybean 30%, medium chain triglycerides (TG) 30%, olive oil 25%, fish oil 15%, and 20 mg vitamin E). Group C fasted overnight except for clear fluids allowed until 4 hours preoperatively. Serum insulin at the start of infusion (T1), 1-hour preinduction (T2), on admission to the intensive care unit (T3), after 24 hours of admission (T4), and after 48 hours of admission (T5), and FFA at T1 and T2 were measured. Serum very-low-density lipoprotein (VLDL), serum TG, and blood sugar were all measured (T1-T4). Bypass time, ischemic time, need for inotropic support, and length of intensive care unit stay also were measured. MEASUREMENTS AND MAIN RESULTS: At the end of infusion FFAs were significantly lower in the L group (1.1 +/- 0.76 mg/dL) compared with G (1.64 +/- 0.85 mg/dL) and C groups (1.48 +/- 0.76 mg/dL). Insulin levels were significantly lower in the L group compared with levels in the G and C groups at T2, T3, and T4. Also, TG, VLDL, and random blood sugar levels decreased significantly at T2, T3, and T4 in the L group compared with the other 2 groups and compared with baseline value within the same group. CONCLUSION: Preoperative lipid infusion lowered postoperative FFA, insulin, TG, VLDL, and random blood sugar in obese patients undergoing coronary artery bypass grafting surgeries.

Literature update week 02 (2018)

[40] *Bogsrud MP, Langslet G, Wium C et al. Treatment goal attainment in children with familial hypercholesterolemia: A cohort study of 302 children in Norway. Journal of clinical lipidology* 2017.

PM: <http://www.ncbi.nlm.nih.gov/pubmed/?term=29310990>

ABSTRACT

BACKGROUND: Consensus statements recommend that statin treatment in children with heterozygous familial hypercholesterolemia (FH) should be considered from 8 to 10 years of age. Although these recommendations are well known, less is known about actual treatment and treatment goal attainment in children with FH. **OBJECTIVE:** The objective of the study was to investigate if children with FH were treated according to current recommendations. **METHODS:** Retrospective collection of data from medical records of 302 children below 18 years visiting the Lipid Clinic, Oslo University hospital, during 2014 to 2016. **RESULTS:** Ninety-nine percent had a genetically verified FH diagnosis. Mean age (standard deviation) at diagnosis, age at first visit, and time followed at the clinic was 8.5 (3.2), 9.5 (2.9), and 4.4 (2.7) years, respectively. Mean pretreatment low-density lipoprotein cholesterol (LDL-C) was 5.4 (1.4) mmol/L. Mean age at start of lipid-lowering therapy (LLT) was 12.5 (2.0) years, with no significant difference between girls and boys. LLT, mainly statins, was used by 177 (59%) children at their last visit. LDL-C in children treated with LLT was 3.6 (1.2) mmol/L (38% reduction from pretreatment, $P < .001$). A treatment goal of LDL-C ≤ 3.5 mmol/L was achieved by 43% of all children, by 58% of the children on LLT, and by 22% of children not on LLT. **CONCLUSION:** Mean age at initiation of LLT is above the recommended 10 years of age and many children did not achieve the LDL-C treatment goal, even with follow-up at a dedicated lipid clinic. Earlier diagnosis and more frequent follow-ups are warranted.

[41] *Premstaller M, Perren M, Kocack K et al. Dyslipidemia and lipid-lowering treatment in a hematopoietic stem cell transplant cohort: 25 years of follow-up data. Journal of clinical lipidology* 2017.

PM: <http://www.ncbi.nlm.nih.gov/pubmed/?term=29310991>

ABSTRACT

BACKGROUND: Dyslipidemia is common after hematopoietic stem cell transplantation (HSCT). Few data regarding the time course of lipid profiles after HSCT, the effect of multiple transplantations, and efficacy and safety of lipid-lowering treatments are available. **OBJECTIVE:** The objective of the study was to determine the prevalence and treatment of dyslipidemia over a 25-year period in a large, single-center cohort. **METHODS:** One thousand one hundred ninety-six adult patients (≥ 16 years) who underwent HSCT during 1973 to 2013 and who survived ≥ 100 days were studied retrospectively. **RESULTS:** The prevalence of dyslipidemia before transplantation was 36% and 28% in the autologous and allogeneic groups, respectively ($P < .001$). Three months after HSCT, the prevalence rose to 62% and 74% ($P < .001$), and at 25 years, it was 67% and 89%. Lipid profiles were similar after first and subsequent transplants. Baseline dyslipidemia (odds ratio [OR] = 2.72), allogeneic transplant (OR = 2.44), and age ≥ 35 years (OR = 2.33) were independent risk factors for dyslipidemia at 1 year. Lipid-lowering treatment was given to 223 (19%) patients, primarily in the form of statins (86%) and was associated with a decrease in total cholesterol from 246 to 192 mg/dL ($P < .01$) and from 244 to

Literature update week 02 (2018)

195 mg/dL ($P < .001$) in the autologous and allogeneic groups, respectively. There were 10 cases (4%) of muscle symptoms prompting cessation of lipid-lowering therapy, including 1 case of rhabdomyolysis. The OR for dyslipidemia among patients who suffered a cardiovascular event (conditional logistic regression) was 3.5 (95% confidence interval = 1.6-7.7, $P = .002$).

CONCLUSION: This study confirms that dyslipidemia is a common and long-lasting phenomenon among both allogeneic and autologous HSCT patients. Statins are effective, generally well-tolerated and should be highly recommended for the management of post-HSCT dyslipidemia.

[42] Nuutinen S, Ailanen L, Savontaus E, Rinne P. **Melanocortin overexpression limits diet-induced inflammation and atherosclerosis in LDLR^{-/-} mice.** *The Journal of endocrinology* 2018.

PM: <http://www.ncbi.nlm.nih.gov/pubmed/?term=29317531>

ABSTRACT

Atherosclerosis is a chronic inflammatory disease of the arteries. The disease is initiated by endothelial dysfunction that allows the transport of leukocytes and low-density lipoprotein into the vessel wall forming atherosclerotic plaques. The melanocortin system is an endogenous peptide system that regulates, for example, energy homeostasis and cardiovascular function. Melanocortin treatment with endogenous or synthetic melanocortin peptides reduces body weight, protects the endothelium and alleviates vascular inflammation, but the long-term effects of melanocortin system activation on atheroprotection remain largely unknown. In this study, we evaluated the effects of transgenic melanocortin overexpression in a mouse model of atherosclerosis. Low-density lipoprotein receptor-deficient mice overexpressing alpha- and gamma3-MSH (MSH-OE) and their wild-type littermates were fed either a regular chow or Western-style diet for 16 weeks. During this time, their metabolic parameters were monitored. The aortae were collected for functional analysis and the plaques in the aortic root and arch were characterised by histological and immunohistochemical stainings. The aortic expression of inflammatory mediators was determined by quantitative PCR. We found that transgenic MSH-OE improved glucose tolerance and limited atherosclerotic plaque formation particularly in Western diet-fed mice. In terms of aortic vasoreactivity, MSH-OE blunted alpha1-adrenoceptor-mediated vasoconstriction and enhanced relaxation response to acetylcholine, indicating improved endothelial function. In addition, MSH-OE markedly attenuated Western-diet-induced upregulation of proinflammatory cytokines (Ccl2, Ccl5 and Il6) that contribute to the pathogenesis of atherosclerosis. These results show that the activation of the melanocortin system improves glucose homeostasis and limits diet-induced vascular inflammation and atherosclerotic plaque formation.

[43] Malone M, Tsai G. **The evidence for herbal and botanical remedies, Part 1.** *The Journal of family practice* 2018; 67:10-16.

PM: <http://www.ncbi.nlm.nih.gov/pubmed/?term=29309469>

ABSTRACT

There is evidence to support the use of capsaicin to relieve osteoarthritis and postherpetic neuralgia and support for green tea to serve as a lipid-lowering agent and help treat diabetes. Similarly, researchers have found that peppermint may be of value in the management of irritable bowel syndrome. We also review the literature on butterbur for migraine headaches, but serious safety issues exist.

Literature update week 02 (2018)

[44] Luo H, Zhang X, Shuai P et al. **Genetic variants influencing lipid levels and risk of dyslipidemia in Chinese population.** *Journal of genetics* 2017; 96:985-992.

PM: <http://www.ncbi.nlm.nih.gov/pubmed/?term=29321358>

ABSTRACT

Recently, several human genetic and genomewide association studies (GWAS) have discovered many genetic loci that are associated with the concentration of the blood lipids. To confirm the reported loci in Chinese population, we conducted a crosssection study to analyse the association of 25 reported SNPs, genotyped by the ABI SNaPshot method, with the blood levels of total cholesterol (TC), low-density lipoprotein cholesterol (LDL-C), high-density lipoprotein cholesterol (HDL-C) and triglycerides (TG) in 1900 individuals by multivariate analysis. Logistic regression was applied to assess the association of the genetic loci with the risk of different types of dyslipidemia. Our study has convincingly identified that 12 of 25 studied SNPs were strongly associated with one or more blood lipid parameters (TC, LDL, HDL and TG). Among the 12 associated SNPs, 10 significantly influence the risk of one or more types of dyslipidemia. We firstly found four SNPs (rs12654264 in HMGCR; rs2479409 in PCSK9; rs16996148 in CILP2, PBX4; rs4420638 in APOE-C1-C4-C2) robustly and independently associate with four types of dyslipidemia (MHL, mixed hyperlipidemia; IHTC, isolated hypercholesterolemia; ILH, isolated low HDL-C; IHTG, isolated hypertriglyceridemia). Our results suggest that genetic susceptibility is different on the same candidate locus for the different populations. Meanwhile, most of the reported genetic variants strongly influence one or more plasma lipid levels and the risk of dyslipidemia in Chinese population.

[45] Liu Y, Hwang HJ, Kim HS, Park H. **Time and Intervention Effects of Daily Almond Intake on the Changes of Lipid Profile and Body Composition Among Free-Living Healthy Adults.** *Journal of medicinal food* 2018.

PM: <http://www.ncbi.nlm.nih.gov/pubmed/?term=29315019>

ABSTRACT

Favorable health benefits of almond have been shown in several previous studies. However, repeated measures, randomized, controlled trials to investigate the changes due to almond intake based on the time effects have not yet been reported. The current study was conducted to evaluate the effects of daily almond intake on changes in body composition and lipid profiles for 20 weeks with four measurements among healthy adults. Participants in the almond group showed favorable changes on blood lipid profiles, including levels of triglycerides (TG), total cholesterol (TC), low-density lipoprotein cholesterol (LDL-C), and non-high-density lipoprotein (non-HDL-C) after consuming 56 g of almond per day for 20 weeks compared with those at baseline. At week 20, subjects in the almond group showed significantly decreased TC, LDL-C, non-HDL-C, TG, body fat mass, and waist-hip ratio compared with those of the control group who consumed isocaloric control food. The mixed model also confirmed that there were significant time effects in several bioimpedance indicators (i.e., total body protein, fat-free mass, etc.) and all of the lipid profile parameters in the almond group. These results confirm the effects of lipid-lowering and modifying body composition of almond consumption. In addition, our results suggest that the measuring time points would be critical to capture the effects of dietary intervention.

Literature update week 02 (2018)

[46] *Liu M, Lin X, Wang X. Decrease in serum chemerin through aerobic exercise plus dieting and its association with mitigation of cardio-metabolic risk in obese female adolescents. J Pediatr Endocrinol Metab* 2018.

PM: <http://www.ncbi.nlm.nih.gov/pubmed/?term=29306931>

ABSTRACT

BACKGROUND: The objective of this study was to determine the effects of a 4-week aerobic exercise plus dieting intervention on serum chemerin in obese female adolescents and its possible role in mitigating cardio-metabolic risk including glucose and lipid metabolism, central fat and inflammation. **METHODS:** Fifty obese female adolescents were randomly divided into two groups: exercise plus dieting group (n=30) and dieting group (n=20). The participants in the exercise plus dieting group completed 4 weeks of moderate aerobic exercise combined with dieting, while the subjects in the dieting group undertook only dieting. Before and after the experiments, anthropometric index, parameters of glucose and lipid metabolism, serum chemerin and classic inflammatory indicators (C-reactive protein [CRP], tumor necrosis factor-alpha [TNF-alpha], interleukin-1beta [IL-1beta], IL-6, leptin and adiponectin) were measured. **RESULTS:** Compared with the dieting group, a decrease in serum chemerin was found in the exercise plus dieting group, accompanied by significant improvements in anthropometric index, glucose and lipid metabolism and inflammatory factors. In addition, a higher serum chemerin level was found in obese adolescents with metabolic syndrome (MetS), and the disappearance of MetS induced by exercise plus dieting might be related to the decrease in chemerin. Correlation analysis showed the correlations of the decrease in chemerin with the changes in body fat, glucose and lipid metabolic index, leptin and adiponectin/leptin ratio. **CONCLUSIONS:** This is the first report that as short a duration as 4-week aerobic exercise plus dieting decreased serum chemerin in obese female adolescents, which might be associated with the improvement in glucose and lipid metabolism, mitigation of inflammation and decrease in MetS incidence, thus lowering cardio-metabolic risk, while no health benefit resulted from slight dieting.

[47] *Villard EF, Thedrez A, Blankenstein J et al. PCSK9 Modulates the Secretion But Not the Cellular Uptake of Lipoprotein(a) Ex Vivo: An Effect Blunted by Alirocumab. JACC. Basic to translational science* 2016; 1:419-427.

PM: <http://www.ncbi.nlm.nih.gov/pubmed/?term=29308438>

ABSTRACT

To elucidate how the proprotein convertase subtilisin kexin type 9 (PCSK9) inhibitor alirocumab modulates lipoprotein(a) [Lp(a)] plasma levels, the authors performed a series of Lp(a) uptake studies in primary human hepatocytes and dermal fibroblasts and measured Lp(a) secretion from human hepatocytes. They found that Lp(a) cellular uptake occurred in a low-density lipoprotein receptor-independent manner. Neither PCSK9 nor alirocumab altered Lp(a) internalization. By contrast, the secretion of apolipoprotein (a) from human hepatocytes was sharply increased by PCSK9, an effect that was reversed by alirocumab. They propose that PCSK9 does not significantly modulate Lp(a) catabolism, but rather enhances the secretion of Lp(a) from liver cells.

Literature update week 02 (2018)

[48] *Ferencik M, Mayrhofer T, Bittner DO et al. Use of High-Risk Coronary Atherosclerotic Plaque Detection for Risk Stratification of Patients With Stable Chest Pain: A Secondary Analysis of the PROMISE Randomized Clinical Trial. JAMA cardiology* 2018.

PM: <http://www.ncbi.nlm.nih.gov/pubmed/?term=29322167>

ABSTRACT

Importance: Coronary computed tomographic angiography (coronary CTA) can characterize coronary artery disease, including high-risk plaque. A noninvasive method of identifying high-risk plaque before major adverse cardiovascular events (MACE) could provide practice-changing optimizations in coronary artery disease care. Objective: To determine whether high-risk plaque detected by coronary CTA was associated with incident MACE independently of significant stenosis (SS) and cardiovascular risk factors. Design, Setting, and Participants: This prespecified nested observational cohort study was part of the Prospective Multicenter Imaging Study for Evaluation of Chest Pain (PROMISE) trial. All stable, symptomatic outpatients in this trial who required noninvasive cardiovascular testing and received coronary CTA were included and followed up for a median of 25 months. Exposures: Core laboratory assessment of coronary CTA for SS and high-risk plaque (eg, positive remodeling, low computed tomographic attenuation, or napkin-ring sign). Main Outcomes and Measures: The primary end point was an adjudicated composite of MACE (defined as death, myocardial infarction, or unstable angina). Results: The study included 4415 patients, of whom 2296 (52%) were women, with a mean age of 60.5 years, a median atherosclerotic cardiovascular disease (ASCVD) risk score of 11, and a MACE rate of 3% (131 events). A total of 676 patients (15.3%) had high-risk plaques, and 276 (6.3%) had SS. The presence of high-risk plaque was associated with a higher MACE rate (6.4% vs 2.4%; hazard ratio, 2.73; 95% CI, 1.89-3.93). This association persisted after adjustment for ASCVD risk score and SS (adjusted hazard ratio [aHR], 1.72; 95% CI, 1.13-2.62). Adding high-risk plaque to the ASCVD risk score and SS assessment led to a significant continuous net reclassification improvement (0.34; 95% CI, 0.02-0.51). Presence of high-risk plaque increased MACE risk among patients with nonobstructive coronary artery disease relative to patients without high-risk plaque (aHR, 4.31 vs 2.64; 95% CI, 2.25-8.26 vs 1.49-4.69). There were no significant differences in MACE in patients with SS and high-risk plaque as opposed to those with SS but not high-risk plaque (aHR, 8.68 vs. 9.31; 95% CI, 4.25-17.73 vs 4.21-20.61). High-risk plaque was a stronger predictor of MACE in women (aHR, 2.41; 95% CI, 1.25-4.64) vs men (aHR, 1.40; 95% CI, 0.81-2.39) and younger patients (aHR, 2.33; 95% CI, 1.20-4.51) vs older ones (aHR, 1.36; 95% CI, 0.77-2.39). Conclusions and Relevance: High-risk plaque found by coronary CTA was associated with a future MACE in a large US population of outpatients with stable chest pain. High-risk plaque may be an additional risk stratification tool, especially in patients with nonobstructive coronary artery disease, younger patients, and women. The importance of findings is limited by low absolute MACE rates and low positive predictive value of high-risk plaque. Trial Registration: clinicaltrials.gov Identifier: NCT01174550.

[49] *Gibbons RJ. High-Risk Coronary Atherosclerotic Plaque Assessment by Coronary Computed Tomography Angiography-Should We Use It? JAMA cardiology* 2018.

PM: <http://www.ncbi.nlm.nih.gov/pubmed/?term=29322177>

ABSTRACT

Literature update week 02 (2018)

[50] *Szymanski FM, Platek AE, Rys A et al. Utilization of the lipid-lowering therapies in outpatient settings in Poland - epidemiological survey Economedica Dyslipidemia 2015. Kardiol Pol 2018.*

PM: <http://www.ncbi.nlm.nih.gov/pubmed/?term=29313565>

ABSTRACT

BACKGROUND: Dyslipidemia, especially elevated low-density lipoprotein (LDL) cholesterol is one of the most important cardiovascular risk factors. Treatment of dyslipidemia and prevention of cardiovascular disease with lipid-lowering drugs is one of the key issues in reducing cardiovascular mortality. Nevertheless, underutilization of statins and lipid-lowering drugs is still a problem globally. **AIM:** The present study aimed to describe the utilization of lipid-lowering drugs in groups of patients with indications for statin treatment and elevated LDL cholesterol. **METHODS:** The study included adult patients with an indication for the use of a lipid-lowering therapy currently using or not using such therapy because of contraindications or statin intolerance, in whom LDL cholesterol concentration was > 70 mg/dL treated in outpatient settings. All patients were screened for cardiovascular disease and had blood cholesterol concentration assessed. Patients were also divided in /1/ patients with vascular disease; /2/ diabetes mellitus; /3/ aged \geq 65 years; and /4/ patients without the mentioned risk factors. **RESULTS:** The study group consisted of 2812 (51.4% male) patients. Major cardiovascular risk factors including arterial hypertension, type 2 diabetes mellitus and smoking were highly prevalent in the general population of the study (86.2%, 44.1% and 23.3%, respectively). Out of the prespecified risk factors (vascular disease, diabetes mellitus, age \geq 65 years) the study population was divided into patients without any of the mentioned risk factors (n = 520), those with all the three risk factors (n = 368), two out of three risk factors (n = 934), and one (n = 990). The study showed that 89.6% of patients were treated with statins (47.8% with atorvastatin, 27.8% with rosuvastatin and 13.8% with simvastatin. Fenofibrate was used in 5.8% of population and ezetimibe in 2.7%. In the whole group, 7.1% of patients did not receive any type of lipid-lowering therapy. Atorvastatin was more often used in patients with all the 3 prespecified risk factors, while rosuvastatin in patients without any of the factors. **CONCLUSIONS:** The most often-used lipid-lowering drugs in Poland are statins, with atorvastatin and rosuvastatin being used the most often. The present study shows, that a part of patients with LDL cholesterol concentration > 70 mg/dL and indication for lipid-lowering is not treated accordingly.

[51] *Clemens KK, Shariff SZ, McArthur E, Hegele RA. Ezetimibe prescriptions in older Canadian adults after an acute myocardial infarction: a population-based cohort study. Lipids in health and disease 2018; 17:8.*

PM: <http://www.ncbi.nlm.nih.gov/pubmed/?term=29310674>

ABSTRACT

BACKGROUND: The utility of ezetimibe in preventing cardiovascular outcomes remains controversial. To guide future assessments of the effectiveness of ezetimibe in routine care, we evaluated how this medication has been prescribed to high-risk older adults in Ontario, Canada. **METHODS:** Using linked healthcare databases, we carried out a population-based cohort study of older adults who were discharged from hospital following an acute myocardial infarction from 2005 until 2014. We ascertained the rate of ezetimibe initiation within 6 months of their

Literature update week 02 (2018)

discharge. We also examined the characteristics of new ezetimibe prescriptions, as well as the predictors for receiving the therapy. RESULTS: Seventy one thousand one hundred twenty five older adults were hospitalized for an acute myocardial infarction between 2005 and 2014 (mean age 78.36 +/- 7.71 years, 45.8% women). Only 1230 (1.7%) patients were newly prescribed ezetimibe within 6 months of their hospital discharge. The median duration of continuous use of ezetimibe was 1.2 years (IQR 0.3-3.5 years). Ezetimibe was prescribed more often to patients living in rural areas, with a history of coronary artery disease, on high-potency statins, and, with evidence of healthcare follow-up after hospital discharge. Prescriptions were less common in men, older patients, those living in long-term care facilities, those with a history of congestive heart failure, and those who were hospitalized for a myocardial infarction in more recent years. CONCLUSIONS: Real-world drug effectiveness studies can help to complement the findings of randomized controlled trials. In our region however, only a small proportion of high-risk older adults received a prescription for ezetimibe following a myocardial infarction. Clinical and research implications are discussed.

[52] *Gao S, Wang X, Cheng D et al. Overexpression of Cholesteryl Ester Transfer Protein Increases Macrophage-Derived Foam Cell Accumulation in Atherosclerotic Lesions of Transgenic Rabbits. Mediators of inflammation* 2017; 2017:3824276.

PM: <http://www.ncbi.nlm.nih.gov/pubmed/?term=29317793>

ABSTRACT

High levels of plasma high-density lipoprotein-cholesterol (HDL-C) are inversely associated with the risk of atherosclerosis and other cardiovascular diseases; thus, pharmacological inhibition of cholesteryl ester transfer protein (CETP) is considered to be a therapeutic method of raising HDL-C levels. However, many CETP inhibitors have failed to achieve a clinical benefit despite raising HDL-C. In the study, we generated transgenic (Tg) rabbits that overexpressed the human CETP gene to examine the influence of CETP on the development of atherosclerosis. Both Tg rabbits and their non-Tg littermates were fed a high cholesterol diet for 16 weeks. Plasma lipids and body weight were measured every 4 weeks. Gross lesion areas of the aortic atherosclerosis along with lesional cellular components were quantitatively analyzed. Overexpression of human CETP did not significantly alter the gross atherosclerotic lesion area, but the number of macrophages in lesions was significantly increased. Overexpression of human CETP did not change the plasma levels of total cholesterol or low-density lipoprotein cholesterol but lowered plasma HDL-C and increased triglycerides. These data revealed that human CETP may play an important role in the development of atherosclerosis mainly by decreasing HDL-C levels and increasing the accumulation of macrophage-derived foam cells.

[53] *Qiu C, Zhou Q, Li X et al. High circulating proprotein convertase subtilisin/Kexin type 9 concentration associates with cardiovascular risk: A meta-analysis of cohort studies. Medicine (Baltimore)* 2017; 96:e8848.

PM: <http://www.ncbi.nlm.nih.gov/pubmed/?term=29310364>

ABSTRACT

Whether the baseline circulating proprotein convertase subtilisin/Kexin type 9 (PCSK9) concentration associates with cardiovascular risk remains uncertain. This study aimed to investigate the predictive value of circulating PCSK9 in cardiovascular risk prediction. Relevant

Literature update week 02 (2018)

studies were searched through the MEDLINE, EMBASE, and Cochrane Library databases. The relative risk (RR) and 95% confidence interval (CI) were pooled to evaluate the association between the circulating PCSK9 concentration and cardiovascular risk. Dose-response meta-analysis was also performed in this study. A total of 11 cohort studies with 13,761 participants were included. The RR for cardiovascular risk was 1.25 (95% CI: 1.14-1.38, $P < .001$, $I^2 = 25\%$) while compared highest to lowest PCSK9 concentration. Subgroup meta-analysis, which sorted by ethnicity, base risk characteristic, and follow-up time, presented consistent results that there was a pronounced association between highest PCSK9 concentration and cardiovascular risk, such relationship was not significant in the statin-taking subjects. Seven studies were included in dose-response meta-analysis, and a nonlinear association between PCSK9 concentration and cardiovascular risk was observed [(chi test for nonlinearity = 6.7, (df = 2), $P = .036$]. This study suggests that high circulating PCSK9 concentration associates with significantly increased cardiovascular risk, and demonstrates for the first time that it is a nonlinear dose-response association between circulating PCSK9 concentration and cardiovascular risk. These results provide the evidence that PCSK9 is an independent risk factor beyond the traditional cardiovascular risk factors and indicates a potential role of PCSK9 measurement for medical decisions. The clinical value of PCSK9 measurement and the identification of risk threshold should be confirmed in appropriately designed clinical trials.

[54] *Kuda O, Rossmeis M, Kopecky J. Omega-3 fatty acids and adipose tissue biology. Molecular aspects of medicine* 2018.

PM: <http://www.ncbi.nlm.nih.gov/pubmed/?term=29329795>

ABSTRACT

This review provides evidence for the importance of white and brown adipose tissue (i.e. WAT and BAT) function for the maintenance of healthy metabolic phenotype and its preservation in response to omega-3 polyunsaturated fatty acids (omega-3 PUFA), namely in the context of diseased states linked to aberrant accumulation of body fat, systemic low-grade inflammation, dyslipidemia and insulin resistance. More specifically, the review deals with (i) the concept of immunometabolism, i.e. how adipose-resident immune cells and adipocytes affect each other and define the immune-metabolic interface; and (ii) the characteristic features of "healthy adipocytes" in WAT, which are relatively small fat cells endowed with a high capacity for mitochondrial oxidative phosphorylation, triacylglycerol/fatty acid (TAG/FA) cycling and de novo lipogenesis (DNL). The intrinsic metabolic features of WAT and their flexible regulations, reflecting the presence of "healthy adipocytes", provide beneficial local and systemic effects, including (i) protection against in situ endoplasmic reticulum stress and related inflammatory response during activation of adipocyte lipolysis; (ii) prevention of ectopic fat accumulation and dyslipidemia caused by increased hepatic VLDL synthesis, as well as prevention of lipotoxic damage of insulin signaling in extra-adipose tissues; and also (iii) increased synthesis of anti-inflammatory and insulin-sensitizing lipid mediators with pro-resolving properties, including the branched fatty acid esters of hydroxy fatty acids (FAHFAs), also depending on the activity of DNL in WAT. The "healthy adipocytes" phenotype can be induced in WAT of obese mice in response to various stimuli including dietary omega-3 PUFA, especially when combined with moderate calorie restriction, and possibly also with other life style (e.g. physical activity) or pharmacological (e.g. thiazolidinediones) interventions. While omega-3 PUFA could exert

Literature update week 02 (2018)

beneficial systemic effects by improving immunometabolism of WAT without a concomitant induction of BAT, it is currently not clear whether the metabolic effects of the combined intervention using omega-3 PUFA and calorie restriction or thiazolidinediones depend also on the activation of BAT function and/or the induction of brite/beige adipocytes in WAT. It remains to be established why omega-3 PUFA intervention in type 2 diabetic subjects does not improve insulin sensitivity and glucose homeostasis despite inducing various anti-inflammatory mediators in WAT, including the recently discovered docosahexaenoic esters of hydroxy linoleic acid, the lipokines from the FAHFAs family, as well as several endocannabinoid-related anti-inflammatory lipids. To answer the question whether and to which extent omega-3 PUFA supplementation could promote the formation of "healthy adipocytes" in WAT of human subjects, namely in the obese insulin-resistant patients, represents a challenging task that is of great importance for the treatment of some serious non-communicable diseases.

[55] **Canakinumab for Atherosclerotic Disease.** The New England journal of medicine 2018; 378:196-200.

PM: <http://www.ncbi.nlm.nih.gov/pubmed/?term=29320648>

ABSTRACT

[56] *Derlin T, Bengel FM.* **Canakinumab for Atherosclerotic Disease.** The New England journal of medicine 2018; 378:196-197.

PM: <http://www.ncbi.nlm.nih.gov/pubmed/?term=29322754>

ABSTRACT

[57] *Hjuler KF, Egeberg A.* **Canakinumab for Atherosclerotic Disease.** The New England journal of medicine 2018; 378:197.

PM: <http://www.ncbi.nlm.nih.gov/pubmed/?term=29322755>

ABSTRACT

[58] *Nerlekar N, Harper RW.* **Canakinumab for Atherosclerotic Disease.** The New England journal of medicine 2018; 378:199.

PM: <http://www.ncbi.nlm.nih.gov/pubmed/?term=29322758>

ABSTRACT

[59] *O'Neill LA, Cooper MA.* **Canakinumab for Atherosclerotic Disease.** The New England journal of medicine 2018; 378:198-199.

PM: <http://www.ncbi.nlm.nih.gov/pubmed/?term=29322757>

ABSTRACT

[60] *Rothman AM, Morton AC, Crossman DC.* **Canakinumab for Atherosclerotic Disease.** The New England journal of medicine 2018; 378:197-198.

PM: <http://www.ncbi.nlm.nih.gov/pubmed/?term=29322756>

ABSTRACT

Literature update week 02 (2018)

[61] *Schreiber K, Sciascia S, de Groot PG et al. Antiphospholipid syndrome. Nature reviews. Disease primers* 2018; 4:17103.

PM: <http://www.ncbi.nlm.nih.gov/pubmed/?term=29321641>

ABSTRACT

Antiphospholipid syndrome (APS) is an autoimmune disease characterized by the presence of antiphospholipid antibodies, such as lupus anticoagulant, anticardiolipin antibodies and anti-beta2-glycoprotein 1 antibodies. APS can present with a variety of clinical phenotypes, including thrombosis in the veins, arteries and microvasculature as well as obstetrical complications. The pathophysiological hallmark is thrombosis, but other factors such as complement activation might be important. Prevention of thrombotic manifestations associated with APS includes lifestyle changes and, in individuals at high risk, low-dose aspirin. Prevention and treatment of thrombotic events are dependent mainly on the use of vitamin K antagonists.

Immunosuppression and anticomplement therapy have been used anecdotally but have not been adequately tested. Pregnancy morbidity includes unexplained recurrent early miscarriage, fetal death and late obstetrical manifestation such as pre-eclampsia, premature birth or fetal growth restriction associated with placental insufficiency. Current treatment to prevent obstetrical morbidity is based on low-dose aspirin and/or low-molecular-weight heparin and has improved pregnancy outcomes to achieve successful live birth in >70% of pregnancies. Although hydroxychloroquine and pravastatin might further improve pregnancy outcomes, prospective clinical trials are required to confirm these findings.

[62] *Gondim PN, Rosa PV, Okamura D et al. Benefits of Fish Oil Consumption over Other Sources of Lipids on Metabolic Parameters in Obese Rats. Nutrients* 2018; 10.

PM: <http://www.ncbi.nlm.nih.gov/pubmed/?term=29320433>

ABSTRACT

This study evaluated the effect of the consumption of different levels and sources of lipids on metabolic parameters of Wistar rats. Animals were fed with high-fat diet (HFD) containing 20% of lard for 12 weeks to cause metabolic obesity. Subsequently, the animals were divided into six groups and were fed diets with lipid concentrations of 5% or 20% of lard (LD), soybean oil (SO) or fish oil (FO), for 4 weeks. Data were submitted to analysis of variance (two-way) followed by Tukey post hoc test ($p < 0.05$). The groups that consumed FO showed less weight gain and lower serum levels of triacylglycerol (TAG), total cholesterol and fractions, aspartate aminotransferase (AST) activity, atherogenic index, less amount of fat in the carcass, decreased Lee index and lower total leukocyte counting ($p < 0.05$). These same parameters were higher in LD treatment ($p < 0.05$). In the concentration of 20%, carcass fat content, blood glucose levels, as well as alanine aminotransferase (ALT) and gamma glutamyl transferase (GGT) decreased in FO groups ($p < 0.05$). The SO group had intermediate results regarding the other two treatments (FO and LD). We concluded that fish oil intake was able to modulate positively the metabolic changes resulting from HFD.

[63] *Michalsky MP, Inge TH, Jenkins TM et al. Cardiovascular Risk Factors After Adolescent Bariatric Surgery. Pediatrics* 2018.

PM: <http://www.ncbi.nlm.nih.gov/pubmed/?term=29311357>

ABSTRACT

Literature update week 02 (2018)

BACKGROUND AND OBJECTIVES: Severely obese adolescents harbor numerous cardiovascular disease risk factors (CVD-RFs), which improve after metabolic and bariatric surgery (MBS). However, predictors of change in CVD-RFs among adolescents have not yet been reported. **METHODS:** The Teen-Longitudinal Assessment of Bariatric Surgery study (NCT00474318) prospectively collected anthropometric and health status data on 242 adolescents undergoing MBS at 5 centers. Predictors of change in CVD-RFs (blood pressure, lipids, glucose homeostasis, and inflammation) 3 years after Roux-en-Y gastric bypass and vertical sleeve gastrectomy were examined. **RESULTS:** The mean (\pm SD) age of participants at baseline was 17 \pm 1.6 years; 76% were girls, and 72% were white, with a median BMI of 51. Participants underwent Roux-en-Y gastric bypass (n = 161), vertical sleeve gastrectomy (n = 67), or adjustable gastric banding (n = 14). Increasing weight loss was an independent predictor of normalization in dyslipidemia, elevated blood pressure (EBP), hyperinsulinemia, diabetes, and elevated high-sensitivity C-reactive protein. Older participants at time of surgery were less likely to resolve dyslipidemia compared with younger participants, whereas girls were more likely than boys to demonstrate improvements in EBP. Even those participants without frank dyslipidemia or EBP at baseline showed significant improvements in lipid and blood pressure values over time. **CONCLUSIONS:** Numerous CVD-RFs improve among adolescents undergoing MBS. Increased weight loss, female sex, and younger age predict a higher probability of resolution of specific CVD-RFs. The elucidation of predictors of change in CVD-RFs may lead to refinements in patient selection and optimal timing of adolescent bariatric surgery designed to improve clinical outcomes.

[64] Sun S, Wang R, Fan J et al. **Effects of Danshen tablets on pharmacokinetics of atorvastatin calcium in rats and its potential mechanism.** *Pharmaceutical biology* 2018; 56:104-108.

PM: <http://www.ncbi.nlm.nih.gov/pubmed/?term=29322864>

ABSTRACT

CONTEXT: Danshen tablets (DST), an effective traditional Chinese multi-herbal formula, are often combined with atorvastatin calcium (AC) for treating coronary heart disease in the clinic. **OBJECTIVE:** This study investigated the effects of DST on the pharmacokinetics of AC and the potential mechanism. **MATERIALS AND METHODS:** The pharmacokinetics of AC (1 mg/kg) with or without pretreatment of DST (100 mg/kg) were investigated using LC-MS/MS. The effects of DST (50 μ g/mL) on the metabolic stability of AC were also investigated using rat liver microsome incubation systems. **RESULTS:** The results indicated that C_{max} (23.87 \pm 4.27 vs. 38.94 \pm 5.32 ng/mL), AUC(0-t) (41.01 \pm 11.32 vs. 77.28 \pm 12.92 ng h/mL), and $t_{1/2}$ (1.91 \pm 0.18 vs. 2.74 \pm 0.23 h) decreased significantly ($p < 0.05$) when DST and AC were co-administered, which suggested that DST might influence the pharmacokinetic behavior of AC when they are co-administered. The metabolic stability ($t_{1/2}$) of AC was also decreased (25.7 \pm 5.2 vs. 42.5 \pm 6.1) with the pretreatment of DST. **DISCUSSION AND CONCLUSIONS:** This study indicated that the main components in DST could accelerate the metabolism of AC in rat liver microsomes and change the pharmacokinetic behaviors of AC. So these results showed that the herb-drug interaction between DST and AC might occur when they were co-administered. Therefore, the clinical dose of AC should be adjusted when DST and AC are co-administered.

Literature update week 02 (2018)

[65] *Rafeeq MM, Habib HS, Murad HAS et al. Effect of genetic polymorphisms in SREBF-SCAP pathway on therapeutic response to rosuvastatin in Saudi metabolic syndrome patients. Pharmacogenomics* 2018.

PM: <http://www.ncbi.nlm.nih.gov/pubmed/?term=29318930>

ABSTRACT

AIM: Genetic variants contribute to statins' therapeutic variability. SREBF-SCAP pathway is a key player in lipid homeostasis. Hence, effect of SREBF-SCAP polymorphisms on therapeutic response was studied. PATIENTS & METHODS: Metabolic syndrome patients of either sex were prescribed rosuvastatin 10 mg for 24 weeks. Clinical, anthropometric and lipid measurements were done before and after treatment. Genotyping was done by pyrosequencing. RESULTS & CONCLUSION: No associations of SCAP and SREBF-1a genotypes with baseline lipids but significant associations with lipid reductions were observed. Significant effect of SCAP (GG; B = -8.16, p = 0.001); SREBF-1a (GG; B = -7.47, p = 0.001) and SREBF-1a (-delG; B = -7.42, p = 0.001) was observed on total cholesterol reduction. Additive trend was found between SCAP genotypes and lipid reductions. A total of 88% responders have SCAP 'G' allele (p = 0.001). Patients carrying SCAP (GG) and SREBF-1a (GG and -delG) have 9.5-, 8.6- and 14.6-times more likelihood of being responders (p < 0.05). 'G' allele in SCAP and SREBF-1a is significant predictor of rosuvastatin response.

[66] Haheim LL, Fretheim A, Brors O *et al.* NIPH Systematic Reviews: Executive Summaries. In: Primary Prevention of Cardiovascular Disease, with Emphasis on Pharmacological Interventions. Oslo, Norway: Knowledge Centre for the Health Services at The Norwegian Institute of Public Health (NIPH)

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[67] *Zeybek B, Costantine M, Kilic GS, Borahay MA. Therapeutic Roles of Statins in Gynecology and Obstetrics: The Current Evidence. Reproductive sciences (Thousand Oaks, Calif.)* 2018:1933719117750751.

PM: <http://www.ncbi.nlm.nih.gov/pubmed/?term=29320955>

ABSTRACT

INTRODUCTION: Statins are a class of drugs, which act by inhibiting the rate-limiting enzyme of cholesterol biosynthesis (3-hydroxy-3-methyl-glutaryl-CoA reductase). The inhibition of mevalonate synthesis leads to subsequent inhibition of downstream products of this pathway, which explains the pleiotropic effects of these agents in addition to their well-known lipid-lowering effects. Accumulating evidence suggests that statins might be beneficial in various obstetric and gynecologic conditions. METHODS: Literature searches were performed in PubMed and EMBASE for articles with content related to statins in obstetrics and gynecology. The findings are hereby reviewed and discussed. RESULTS: Inhibition of mevalonate pathway leads to subsequent inhibition of downstream products such as geranyl pyrophosphate, farnesyl pyrophosphate, and geranylgeranyl pyrophosphate. These products are required for proper intracellular localization of several proteins, which play important roles in signaling pathways by regulating membrane trafficking, motility, proliferation, differentiation, and cytoskeletal organization. The pleiotropic effects of statins can be summarized in 4 categories: antiproliferative, anti-invasive, anti-inflammatory, and antiangiogenic. The growing body of evidence is promising for these agents to be beneficial in endometriosis, polycystic ovary

Literature update week 02 (2018)

syndrome, adhesion prevention, ovarian cancer, preeclampsia, and antiphospholipid syndrome. Although in vivo studies showed varying degrees of benefit on fibroids and preterm birth, appropriately designed clinical trials are needed to make definitive conclusions. **CONCLUSION:** Statins might play a role in the treatment of endometriosis, polycystic ovary syndrome, adhesion prevention, ovarian cancer, preeclampsia, and antiphospholipid syndrome.

[68] Khan TJ, Ahmed YM, Zamzami MA et al. **Effect of atorvastatin on the gut microbiota of high fat diet-induced hypercholesterolemic rats.** *Scientific reports* 2018; 8:662.

PM: <http://www.ncbi.nlm.nih.gov/pubmed/?term=29330433>

ABSTRACT

The aim of the present study was to investigate alterations in gut microbiota associated with hypercholesterolemia and treatment with atorvastatin, a commonly prescribed cholesterol-lowering drug. In this study, seven experimental groups of rats were developed based on diets [high-fat diet (HFD) and normal chow diet (NCD)] and various doses of atorvastatin in HFD and NCD groups. 16S rRNA amplicon sequencing was used to analyze the gut microbiota. Atorvastatin significantly reduced the cholesterol level in treated rats. Bacterial diversity was decreased in the drug-treated NCD group compared to the NCD control, but atorvastatin-treated HFD groups showed a relative increase in biodiversity compared to HFD control group. Atorvastatin promoted the relative abundance of Proteobacteria and reduced the abundance of Firmicutes in drug-treated HFD groups. Among the dominant taxa in the drug-treated HFD groups, Oscillospira, Parabacteroides, Ruminococcus, unclassified CF231, YRC22 (Paraprevotellaceae), and SMB53 (Clostridiaceae) showed reversion in population distribution toward NCD group relative to HFD group. Drug-treated HFD and NCD groups both showed an increased relative abundance of Helicobacter. Overall, bacterial community composition was altered, and diversity of gut microbiota increased with atorvastatin treatment in HFD group. Reversion in relative abundance of specific dominant taxa was observed with drug treatment to HFD rats.

[69] Acar D, Gulpembe M, Yildiz CG et al. **The reno-protective effects of atorvastatin in crush syndrome and rhabdomyolysis:is there a dilemma?** *Turk J Med Sci* 2017; 47:1920-1924.

PM: <http://www.ncbi.nlm.nih.gov/pubmed/?term=29306258>

ABSTRACT

Background/aim: We aim to determine the effects of low-dose atorvastatin treatment together with crush fluid resuscitation on renal functions and muscle enzyme levels in a rat model of crush syndrome. **Materials and methods:** The study involved female Wistar Albino rats weighing 250-300 g that were housed with free access to food and water. The crush model was obtained by compression. Rats were randomly divided into four groups: control (C) group, atorvastatin + crush fluid (ACF) group, crush fluid (CF) group, and hypertonic saline (3%) + mannitol + sodium bicarbonate (SM) group. Blood was obtained at 24, 48, and 72 h, and serum creatinine kinase, myoglobin, urea, creatinine, and lactate dehydrogenase levels were studied. **Results:** All parameters were statistically significantly higher in the control group than in the treatment groups at all hours. However, there was no statistically significant difference among treatment groups regarding any of the parameters. **Conclusion:** This is the first study determining the role of atorvastatin in the treatment of renal ischemia/reperfusion injury in a crush syndrome and

Literature update week 02 (2018)

rhabdomyolysis model setting. Larger studies with different atorvastatin doses are required to define the role of this drug in the treatment of renal ischemia/reperfusion injury during crush syndrome.

[70] Sun R, Wang L, Guan C et al. **Carotid atherosclerotic plaque features in patients with acute ischemic stroke.** *World neurosurgery* 2018.

PM: <http://www.ncbi.nlm.nih.gov/pubmed/?term=29325936>

ABSTRACT

OBJECTIVE: To investigate the carotid atherosclerotic plaque features in patients with acute ischemic stroke (AIS). **METHODS:** A total of 288 patients meeting the included criteria were enrolled and divided into ulcer plaque group (n = 139) and none ulcer plaque group (n = 149). Patients in ulcer plaque group were further subdivided into < and \geq 50% stenosis group. Carotid plaque components characteristics including luminal stenosis, carotid plaque volume, hypoechoic plaque volume and hyperechoic plaque volume were analyzed by color Doppler ultrasound measurement. Associations between ulcer plaque and carotid plaque features were also evaluated. Relationship between level of MMP-9, hs-CRP and carotid stenosis rate was detected by ELISA. **RESULTS:** The plaque volume, hypoechoic plaque volume and luminal stenosis in the ulcer plaque group were higher than that of none ulcer plaque group ($P < 0.05$). Ulcer plaque was positively associated with luminal stenosis, plaque volume and hypoechoic plaque volume after adjusting for sex and age. The result remained similar after adjusting for age, sex and carotid luminal stenosis. The level of MMP-9 and hs-CRP of ulcer plaque group was significantly higher than that of none ulcer plaque group ($P < 0.01$). For ulcer plaque group, the higher the carotid stenosis rate, the higher the level of MMP-9 and hs-CRP. **CONCLUSIONS:** Higher carotid atherosclerosis plaque volume, hypoechoic plaque volume and luminal carotid stenosis may be a symptom of ulcer plaque. Carotid stenosis may be pre-controlled through the regulation of MMP-9 and hs-CRP levels.