Literature update week 16 (2020)

[1] *Alhusseiny SM, El-Beshbishi SN*. **Omega polyunsaturated fatty acids and parasitic infections: An overview**. Acta tropica 2020; 207:105466.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=32302690
ABSTRACT
Omega-3 and omega-6 polyunsaturated fatty acids are synthesized from the essential fatty acids alpha-linolenic acid and linoleic acid, respectively. They are pivotal components of all mammalian cells and were found to be useful in prevention and treatment of a variety of health problems owing to their anti-inflammatory and anti-microbial properties. Omega-3 and omega-6 polyunsaturated fatty acids are further metabolized to anti-inflammatory mediators, such as lipoxins, resolvins, and protectins. Moreover, these polyunsaturated fatty acids were found to have in vivo and in vitro protective efficacies against some parasitic infections. Therefore, dietary intake of polyunsaturated fatty acids should be encouraged because of their considerable beneficial effects.

[2] *Das UN*. **Bioactive Lipids in Age-Related Disorders**. Advances in experimental medicine and biology 2020; 1260:33-83.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=32304030
ABSTRACT
Our own studies and those of others have shown that defects in essential fatty acid (EFA) metabolism occurs in age-related disorders such as obesity, type 2 diabetes mellitus, hypertension, atherosclerosis, coronary heart disease, immune dysfunction and cancer. It has been noted that in all these disorders there could occur a defect in the activities of desaturases, cyclo-oxygenase (COX), and lipoxygenase (LOX) enzymes leading to a decrease in the formation of their long-chain products gamma-linolenic acid (GLA), arachidonic acid, eicosapentaenoic acid (EPA), docosapentaenoic acid (DPA) and docosahexaenoic acid (DHA). This leads to an increase in the production of pro-inflammatory prostaglandin E2 (PGE2), thromboxanes (TXs), and leukotrienes (LTs) and a decrease in anti-inflammatory lipoxin A4, resolvins, protectins and maresins. All these bioactive molecules are termed as bioactive lipids (BALs). This imbalance in the metabolites of EFAs leads to low-grade systemic inflammation and at times acute inflammatory events at specific local sites that trigger the development of various age-related disorders such as obesity, type 2 diabetes mellitus, hypertension, coronary heart disease, atherosclerosis, and immune dysfunction as seen in rheumatoid arthritis, lupus, nephritis and other localized inflammatory conditions. This evidence implies that methods designed to restore BALs to normal can prevent age-related disorders and enhance longevity and health.

[3] *Chasman DI, Giulianini F, Demler OV, Udler MS*. **Pleiotropy-Based Decomposition of Genetic Risk Scores: Association and Interaction Analysis for Type 2 Diabetes and CAD**. Am J Hum Genet 2020; 106:646-658.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=32302534
ABSTRACT
Genetic risk for a disease in the population may be represented as a genetic risk score (GRS) constructed as the sum of inherited risk alleles, weighted by allelic effects established in an independent population. While this formulation captures overall genetic risk, it typically does not address risk due to specific biological mechanisms or pathways that may nevertheless be important for interpretation or treatment response. Here, a GRS for disease is resolved into independent or nearly

independent components pertaining to biological mechanisms inferred from pleiotropic relationships. The component GRSs' weights are derived from the singular value decomposition (SVD) of the matrix of appropriately scaled genetic effects, i.e., beta coefficients, of the disease variants across a panel of the disease-related phenotypes. The SVD-based formalism also associates combinations of disease-related phenotypes with inferred disease pathways. Applied to incident type 2 diabetes (T2D) in the Women's Genome Health Study (N = 23,294), component GRSs discriminate glycemic control and lipid-based genetic risk, while revealing significant interactions between specific components and BMI or physical activity, the latter not observed with a GRS for overall T2D genetic liability. Applied to coronary artery disease (CAD) in both the WGHS and in JUPITER (N = 8,749), a randomized trial of rosuvastatin for primary prevention of CVD, component GRSs discriminate genetic risk associated with LDL-C from risk associated with reciprocal genetic effects on triglycerides and HDL-C. They also inform the pharmacogenetics of statin treatment by demonstrating that benefit from rosuvastatin is as strongly related to genetic risk from triglycerides and HDL-C as from LDL-C.

[4] *Banihani SA*. **Effect of statin on semen quality characteristics**. Andrologia 2020:e13592.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=32293050
ABSTRACT
Statins are lipid-lowering medications widely used to reduce the risk of cardiovascular diseases. Biochemically, they act by decreasing synthesis of cholesterol via inhibiting 3-hydroxy-3-methyl-glutaryl-coenzyme A reductase. Since 1992, various research studies have investigated the effect of statins on semen quality characteristics; however, to date, there is no collective summary to such effect. Here, we have systematically discussed and abridged all research studies published in Scopus, PubMed and Web of Science databases that are directly linking statin to semen fertility characteristics using the keywords "statin" versus "sperm" and "semen". In summary, considering the animal studies, statins, in general, were found to ameliorate semen quality characteristics in reproductive detrimental conditions, while, in human males or in in vivo systems with normal reproductive conditions, in general, statins showed negative to blunt effects against semen quality characteristics, mainly sperm motility. However, further research studies, in particular human studies, in this specific research setting is still needed to approve these effects.

[5] *Yeo SH, Toh MPH, Lee SH et al.* **Temporal Trends and Patient Characteristics Associated With Drug Utilisation After First-Ever Stroke: Insights From Chronic Disease Registry Data in Singapore**. Ann Acad Med Singapore 2020; 49:137-154.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=32301477
ABSTRACT
INTRODUCTION: Data on drug utilisation among stroke patients of Asian ethnicities are lacking. The objectives of the study were to examine the temporal trends and patient characteristics associated with prescription of thrombolytic, antithrombotic and statin medications among patients with first-ever stroke. MATERIALS AND METHODS: First-ever ischaemic and haemorrhagic stroke patients admitted to 2 Singapore tertiary hospitals between 20102014 were included. Data were extracted from the National Healthcare Group Chronic Disease Management System. Association between drug utilisation and admission year, as well as characteristics associated with drug use, were explored using multivariable logistic regression. RESULTS: There was an increasing trend in the combined use of all 3 guideline medications in ischaemic stroke patients (P <0.001)-specifically thrombolytic agents (P

<0.001), oral antithrombotics (P = 0.002) and statins (P = 0.003) at discharge. Among antithrombotics, the use of clopidogrel (P <0.001) and aspirin-clopidogrel (P <0.001) had increased, whereas prescription of dipyridamole (P <0.001) and aspirin-dipyridamole (P <0.001) had declined. For statins, the increase in atorvastatin prescription (P <0.001) was accompanied by decreasing use of simvastatin (P <0.001). Age, ethnicity and certain comorbidities (hyperlipidaemia, atrial fibrillation and chronic kidney disease) were associated with the combined use of all 3 guideline medications (P <0.05). In haemorrhagic stroke, prescription of statins at discharge were comparatively lower. CONCLUSION: This study reveals changes in prescription behaviour over time in a multiethnic Asian population with first-ever stroke. Patient characteristics including younger age, Malay ethnicity and certain comorbidities (i.e. hyperlipidaemia, atrial fibrillation) were associated with the combined use of all 3 guideline medications among ischaemic stroke patients.

[6] *Pinilla-Monsalve GD, Lores J, Pachajoa H et al.* **A Novel APOC2 Mutation in a Colombian Patient with Recurrent Hypertriglyceridemic Pancreatitis**. The application of clinical genetics 2020; 13:63-69.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=32280258

ABSTRACT

Hypertriglyceridemia is a common disease with only 2% of cases exhibiting monogenic mutations. Familial chylomicronemia syndrome (FCS) is a rare genetic condition associated with recurrent and severe episodes of pancreatitis and is mainly caused by mutations in the LPL gene, with few cases related to abnormal function of apolipoprotein C-II. This is a 50-year-old female with a past medical history of arterial hypertension, miscarriage and recurrent pancreatitis. In the last four years, her triglycerides and lipase concentration reached >3000 mg/dL and >700 U/L, respectively. The patient was not responsive to statins, fibrates, or tetrahydrolipstatin. A novel homozygous frameshift mutation on exon 3 of the APOC2 gene was detected, c.133_134delTC. Subsequent Sanger sequencing confirmed that three first-degree relatives were carriers of the same mutation. To the best of our knowledge, we are reporting the first Colombian patient with FCS due to an APOC2 mutation. We propose that this mutation caused recurrent hypertriglyceridemic pancreatitis.

[7] *Penkauskas T, Zentelyte A, Ganpule S et al.* **Pleiotropic effects of statins via interaction with the lipid bilayer: A combined approach**. Biochim Biophys Acta Biomembr 2020; 1862:183306.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=32302615

ABSTRACT

Statins are effective inhibitors of cholesterol biosynthesis, largely used for prevention of cardiovascular diseases induced by hypercholesterolemia. However, their use in different clinical trials clearly indicate that the general benefits observed with statins are also related to effects beyond the cholesterol lowering. Increasing evidences suggest that some of these cholesterol-independent or "pleiotropic" effects of statins involve the interaction and modification of the membrane bilayers. In this manuscript, using a combined approach based on biophysical (electrochemical impedance spectroscopy on tethered bilayer lipid membranes) and biological methods (hemolysis on erythrocytes and immunocytochemistry on cancer cells), we demonstrate that lipophilic, but not hydrophilic statins are capable of reducing the damage caused by cholesterol-dependent cytolysins. This protection correlates with statins lipophilicity and capacity to interact with the lipid bilayer. Our data suggests lipophilic statins associate with membranes and interfere with the ability of cholesterol dependent cytolysins, to bind to membrane cholesterol. Evaluation of the capacity of statins to modulate cell membrane

properties is essential for developing a correct therapeutic approach for cardiovascular diseases as well as for understanding the potential of this class of drugs as adjuvants for drug delivery.

[8] *Meilhac O, Tanaka S, Couret D*. **High-Density Lipoproteins Are Bug Scavengers**. Biomolecules 2020; 10.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=32290632
ABSTRACT
Lipoproteins were initially defined according to their composition (lipids and proteins) and classified according to their density (from very low- to high-density lipoproteins-HDLs). Whereas their capacity to transport hydrophobic lipids in a hydrophilic environment (plasma) is not questionable, their primitive function of cholesterol transporter could be challenged. All lipoproteins are reported to bind and potentially neutralize bacterial lipopolysaccharides (LPS); this is particularly true for HDL particles. In addition, HDL levels are drastically decreased under infectious conditions such as sepsis, suggesting a potential role in the clearance of bacterial material and, particularly, LPS. Moreover, "omics" technologies have unveiled significant changes in HDL composition in different inflammatory states, ranging from acute inflammation occurring during septic shock to low-grade inflammation associated with moderate endotoxemia such as periodontal disease or obesity. In this review, we will discuss HDL modifications associated with exposure to pathogens including bacteria, viruses and parasites, with a special focus on sepsis and the potential of HDL therapy in this context. Low-grade inflammation associated with atherosclerosis, periodontitis or metabolic syndrome may also highlight the protective role of HDLs in theses pathologies by other mechanisms than the reverse transport of cholesterol.

[9] *Tahkola A, Korhonen P, Kautiainen H et al.* **Lifetime risk assessment in cholesterol management among hypertensive patients: observational cross-sectional study based on electronic health record data**. BMC family practice 2020; 21:62.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=32290820
ABSTRACT
BACKGROUND: In hypertensive patients, reducing plasma low-density lipoprotein cholesterol level (LDL-C) is one of the main interventions for preventing chronic cardiovascular diseases (CVD). However, LDL-C control remains generally insufficient, also in patients with hypertension. We analyzed Electronic Health Record (EHR) data of 7117 hypertensive patients to find the most potential age and sex subgroups in greatest need for improvement in real life dyslipidemia treatment. Taking into account the current discussion on lifetime CVD risk, we focused on the age dependence in LDL-C control. METHODS: In this observational cross-sectional study, based on routine electronic health record (EHR) data, we investigated LDL-C control of hypertensive, non-diabetic patients without renal dysfunction or CVD, aged 30 years or more in Finnish primary care setting. RESULTS: More than half (54% of women and 53% of men) of untreated patients did not meet the LDL-C target of < 3 mmol/l and one third (35% of women and 33% of men) of patients did not reach the target even with the lipid-lowering medication (LLM). Furthermore, higher age was strongly associated with better LDL-C control ($p < 0.001$) and lower LDL-C level ($p < 0.001$) in individuals with and without LLM. Higher age was also strongly associated with LLM prescription ($p < 0.001$). In total, about half of the patients were on LLM (53% of women and 51% of men). CONCLUSIONS: Our findings indicate that dyslipidemia treatment among Finnish primary care hypertensive patients is generally insufficient, particularly in younger age

groups who might benefit the most from CVD risk reduction over time. Clinicians should probably rely more on the lifetime risk of CVD, especially when treating working age hypertensive patients.

[10] *McKee M*. **A European roadmap out of the covid-19 pandemic**. Bmj 2020; 369:m1556.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=32303492
ABSTRACT

[11] *Schol-Gelok S, de Maat MPM, Biedermann JS et al.* **Rosuvastatin use increases plasma fibrinolytic potential: a randomised clinical trial**. British journal of haematology 2020.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=32301122
ABSTRACT
We conducted a study to assess the effect of rosuvastatin use on fibrinolysis in patients with previous venous thromboembolism (VTE). This was a post hoc analysis within the STAtins Reduce Thrombophilia (START) study (NCT01613794). Plasma fibrinolytic potential, fibrinogen, plasmin inhibitor, plasminogen activator inhibitor-1 (PAI-1) and thrombin-activatable fibrinolysis inhibitor (TAFI) were measured before and after four weeks of rosuvastatin or no treatment in participants with prior confirmed VTE, after ending anticoagulant therapy. In the non-rosuvastatin group (n = 121), plasma fibrinolytic potential and individual fibrinolysis parameters did not change at the end of the study versus the baseline, whereas in the rosuvastatin group (n = 126), plasma fibrinolytic potential increased: the mean clot lysis time decreased by 8.75 min (95% CI -13.8 to -3.72), and plasmin inhibitor levels and TAFI activity were lower at the end of the study (-0.05 U/ml; 95% CI -0.07 to -0.02 and -4.77%; 95% CI -6.81 to -2.73, respectively). PAI-1 levels did not change and fibrinogen levels were 0.17 g/l (95% CI 0.04-0.29) higher. In participants with prior VTE, rosuvastatin use led to an increased fibrinolytic potential compared with non-statin use. Our findings support the need for further studies on the possible role for statins in the secondary prevention of VTE.

[12] *Hsia DS, Zhang DJ, Beyl RS et al.* **Effect of Daily Consumption of Cranberry Beverage on Insulin Sensitivity and Modification of Cardiovascular Risk Factors in Obese Adults: A Pilot Randomized Placebo-Controlled Study**. The British journal of nutrition 2020:1-27.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=32301407
ABSTRACT
Cranberries are high in polyphenols and epidemiologic studies have shown a high polyphenol diet may reduce risk factors for diabetes and cardiovascular disease. This study aimed to determine if short term cranberry beverage consumption would improve insulin sensitivity and other cardiovascular risk factors. Thirty-five obese individuals with elevated fasting glucose or impaired glucose tolerance participated in a randomized, double blind, placebo controlled, parallel designed pilot trial. Participants consumed 450 mL of low-calorie cranberry beverage or placebo daily for 8 weeks. Changes in insulin sensitivity and cardiovascular risk factors including vascular reactivity, blood pressure, resting metabolic rate, glucose tolerance, lipid profiles, and oxidative stress biomarkers were evaluated. Change in insulin sensitivity via hyperinsulinemic euglycemic clamp was not different between the two groups. Levels of 8-isoprostane (biomarker of lipid peroxidation) decreased in the cranberry group but increased in the placebo group (-2.18 pg/mL vs +20.81 pg/mL, p=0.02). When stratified by baseline C-reactive protein (CRP) levels, participants with high CRP levels (> 4 mg/L) benefited more from cranberry consumption. In this group, significant differences in the mean change from baseline

between the cranberry (n=10) and the placebo groups (n=7) in levels of triglyceride (-13.75% vs +10.32%; p=0.04), nitrate (+3.26 microM/L vs -6.28 microM/L; p=0.02), and 8-isoprostane (+0.32 pg/mL vs +30.8 pg/mL; p=0.05) were observed. These findings indicate that 8 weeks of daily cranberry beverage consumption may not impact insulin sensitivity but may be helpful in lowering triglycerides and changing certain oxidative stress biomarkers in obese individuals with a proinflammatory state.

[13] *Chapman RW, Lynch KD*. **Obeticholic acid-a new therapy in PBC and NASH**. Br Med Bull 2020; 133:95-104.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=32282030
ABSTRACT
INTRODUCTION: Obeticholic acid (OCA) is a semi-synthetic hydrophobic bile acid (BA) analogue that is highly selective agonist of farnesoid X receptor (FXR), a key nuclear BA receptor, which induces expression of gut-derived hormones, in particular fibroblast growth factor 19. The resulting beneficial effects of OCA on glucose and lipid metabolism and particularly hepatic inflammation make it a candidate for the treatment of a variety of conditions including primary biliary cholangitis (PBC) and nonalcoholic steatohepatitis (NASH). SOURCES OF DATA: In PBC patients who have not initially responded to ursodeoxycholic acid, OCA has been shown in double-blind controlled clinical trials to significantly reduce serum alkaline phosphatase. To date, OCA is the only therapy licensed by the FDA, EMA and endorsed by NICE as second line therapy for PBC.No medications are currently approved in Europe or the USA for the treatment of NASH.In recent clinical trials, OCA has been shown encouraging results by improving liver blood tests and reducing liver fibrosis with no worsening of NASH. AREAS OF AGREEMENT: OCA is the established second line therapy for PBC in those patients who fail to adequately respond to ursodeoxycholic acid. AREAS OF CONTROVERSY: The main side effects of OCA treatment in both PBC and NASH is that of dose-dependent pruritis which can lead to treatment discontinuation in ~1-10% of patients. In addition, OCA-treated patients may also exhibit (reversible) alterations in serum lipid levels; most notably a small decrease in high density lipoprotein cholesterol. It is not yet known whether these changes carry a long-term cardiovascular risk in NASH.In addition, the relatively high cost of OCA may limit its use in cash-limited health systems. GROWING POINTS: Additional clinical trials are in progress to ascertain the long-term effects of OCA on survival in PBC and NASH. AREAS TIMELY FOR DEVELOPING RESEARCH: New FXR agonists with a lower rate of side effects are being developed and trialed. Combination therapy with other agents may offer increased efficacy.

[14] *Mohammad Y, Alhoqbani T, Alfaqih R et al.* **Cardiovascular MRI: A valuable tool to detect cardiac source of emboli in cryptogenic ischemic strokes**. Brain and behavior 2020:e01620.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=32304360
ABSTRACT
OBJECTIVES: Despite a thorough work-up including transesophageal echocardiography, 20%-30% of stroke etiology remains cryptogenic. Transesophageal echocardiogram is considered the gold standard procedure to detect cardiac or aortic sources of emboli. In the recent years, cardiovascular MRI has emerged as a noninvasive, sound, and reliable modality to image morphological and functional abnormalities. In this study, we compared none contrast cardiovascular MRI to transesophageal echocardiogram, in the ability to detect cardiovascular source of embolus in cryptogenic ischemic strokes. METHODS: A series of 24 patients who were labeled, after a thorough stroke work-up, as having cryptogenic stroke, were examined with both transesophageal echocardiogram and

noncontrast cardiovascular MRI to assess for cardiac or aortic source of emboli. The cardiologist who interpreted the transesophageal echocardiograms was blinded to the results of cardiovascular MRI. At the same time, the radiologist who interpreted the cardiovascular MRI was also blinded to the results of transesophageal echocardiogram. The cardiac lesions, with potential source of emboli that were assessed in our study included left ventricular thrombus, atrial septal aneurysm, and aortic atherosclerotic disease. The ability of cardiovascular MRI to identify potential source of cardiac embolus was then compared to that of transesophageal echocardiogram. RESULTS: Transesophageal echocardiogram detected ascending or arch aortic atherosclerotic plaque in 14 of the 24 patients. Other abnormalities detected include two atrial septal aneurysms and two left ventricular thrombus. Cardiovascular MRI was able to identify aortic atheroma in 13 patients; as well as three atrial septal aneurysms and two left ventricular thrombus. The accuracy of cardiovascular MRI to detect aortic atheroma, atrial septal aneurysm or left ventricular thrombus was great; 96%, 95.83%, and 100%, respectively. CONCLUSION: This small study suggests that, in patients with cryptogenic stroke, cardiovascular MRI is comparable to transesophageal echocardiogram in detecting cardiac and aortic source of emboli.

[15] *Imran T, Wong A, Schneeweiss S, Desai RJ*. **Statin Lipophilicity and the Risk of Incident Heart Failure**. Cardiology 2020:1-9.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=32289796
ABSTRACT
BACKGROUND: To compare the risk of incident heart failure (HF) between initiators of hydrophilic and lipophilic statins. METHODS: Using claims data for commercial health insurance program enrollees in the USA (2005-2014), we identified new initiators of hydrophilic or lipophilic statins. Follow-up for the primary outcome of incident HF began after a lag period of 1 year after statin initiation. The outcome was defined as 1 inpatient or 2 outpatient diagnosis codes for HF and the use of loop diuretics. Propensity scores (PS) were used to account for confounding. Hazard ratios (HR) for incident HF were computed separately for low and high-intensity statin users, and then pooled to provide dose-adjusted effect estimates. RESULTS: A total of 7,820,204 patients met all our inclusion criteria for statin initiation (hydrophilic and lipophilic statins). Mean age was 58 years, 40% had hypertension, and 23% had diabetes mellitus. After PS matching, there were 691,584 patients in the low-intensity statin group and 807,370 patients in the high-intensity statin group. After a median follow-up of 725 days (IQR 500-1,153),there were 8,389 cases of incident HF (incidence rate 4.5/1,000 person years, 95% confidence interval [CI] 4.4-4.6). The unadjusted HR for the risk of HF was 0.77 (95% CI 0.76-0.79) and the pooled adjusted HR for incident HF after PS matching was 0.94 (95% CI 0.90-0.98) for hydrophilic versus lipophilic statins. The HR for incident HF was 1.06 (95% CI 1.00-1.12) for hydrophilic versus lipophilic statins for the low-intensity statin group and 0.82 (95% CI 0.78-0.87) for the high-intensity statin group. In subgroup analyses, a similar trend persisted for those younger and older than 65 years and when comparing rosuvastatin with atorvastatin. CONCLUSION: In this observational cohort study, hydrophilic statins were associated with a modest risk reduction in incident HF as compared to lipophilic statins. Future research replicating these findings in different populations is recommended.

[16] *Ueda M, Wolska A, Burke FM et al.* **Experimental Therapeutics for Challenging Clinical Care of a Patient with an Extremely Rare Homozygous APOC2 Mutation**. Case reports in endocrinology 2020; 2020:1865489.

Literature update week 16 (2020)

PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=32292609

ABSTRACT

Background: Among many causes of hypertriglyceridemia (HTG), familial chylomicronemia syndrome (FCS) is a rare monogenic disorder that manifests as severe HTG and acute pancreatitis. Among the known causal genes for FCS, mutations in APOC2 only account for <2% of cases. Medical nutrition therapy is critical for FCS because usual triglyceride- (TG-) lowering medications are ineffective. Therapeutic plasma exchange (TPE) with fresh frozen plasma (FFP) is an option to urgently reduce TG and pancreatitis episodes. Several novel biologics are under development to treat HTG and may provide therapeutic options for FCS in the future. Objective: We present the challenging care of a 43-year-old man with FCS with apoC-II deficiency and the results of two types of TPE and of investigational TG-lowering biologic therapies. Results: The patient's lipid profile was consistent with FCS. A novel homozygous variant was identified in APOC2, and its pathogenicity was confirmed. Even on a fat-restricted diet, his care was tremendously complicated with unremitting bouts of pancreatitis. TPE with FFP replacement lowered TG >90% post-sessions and appeared to reduce pancreatitis episodes. Experimental ANGPTL3 and APOC3 inhibitors each lowered TG by >50%. Conclusions: Our case demonstrates the importance of delineating and defining the underlying etiology of a rare disorder to optimize therapy and to minimize unfavorable outcomes.

[17] *Mehta S, Dhawan V*. **Exposure of cigarette smoke condensate activates NLRP3 inflammasome in THP-1 cells in a stage-specific manner: An underlying role of innate immunity in atherosclerosis**. Cellular signalling 2020; 72:109645.

PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=32305666

ABSTRACT

BACKGROUND: Smoking is known to affect all the phases of atherosclerosis, thus is considered as an independent and major risk factor. The underlying mechanism responsible for the atherogenic effects of smoking is still uncertain and a major concern. Recent evidence implicates NLRP3 inflammasome, an innate immunity component in the pathogenesis of atherosclerosis. Therefore, we hypothesized that NLRP3 inflammasome may be an associated pathway between smoking and atherosclerosis. METHODS AND RESULTS: Differentiation in monocytes, macrophages and foam cells are the key stages in atherosclerotic plaque development, best mimicked by THP-1 cells. Therefore, to determine whether cigarette smoke condensate (CSC) could induce differentiation of THP-1 monocytes into macrophages, morphological changes and the expression levels of the inflammatory surface markers, i.e. CD11b, CD14 and CD36 were analyzed. The results showed that CD14 and CD36 levels were significantly increased in CSC-treated THP-1 monocytes. Further, we investigated the effect of CSC exposure on the status of NLRP3 inflammasome markers, i.e. NLRP3, pro-caspase-1, caspase-1, pro-IL-18, pro-IL-1beta, IL-1beta and IL-18 in a stage-specific manner. For this, THP-1 monocytes, PMA-differentiated macrophages and oxidized-low density lipoprotein (ox-LDL)-induced macrophage foam cells were exposed to 10 mug/ml of CSC for 6 h. CSC exposure significantly upregulated the expression of NLRP3 inflammasome in CSC-treated cells at both transcriptional and translational levels. Moreover, downstream pro-cytokines, i.e. IL-1beta and IL-18 levels were also significantly increased in culture supernatants of CSC-exposed cells. CONCLUSION: These observations suggest that CSC exposure may activate NLRP3 inflammasome in a stage-specific manner and may promote initiation and progression of atherosclerosis.

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[18] *Bellia C, Lombardo M, Della-Morte D*. **Use of Troponin as a predictor for cardiovascular diseases in patients with type 2 Diabetes Mellitus**. Clinica chimica acta; international journal of clinical chemistry 2020; 507:54-61.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=32302683
ABSTRACT
People with type 2 diabetes mellitus (T2DM) have two- to four-fold increased cardiovascular mortality in comparison to the general population. With the identification of new therapeutic targets and hypoglycemic drugs for T2DM, the need for a better stratification of CVD risk has emerged to select patients who may need intensive or specific treatment. At present, risk stratification is based on clinical, demographic, and biochemical factors. High sensitivity cardiac troponin (hs-cTn) increases after several ischemic and non-ischemic insults and it is considered a marker of myocardial injury. This review summarizes the main findings about hs-cTn utilization for risk stratification in people with T2DM and no clinical CVD. Several large observational studies have documented the association between hs-cTn and adverse cardiovascular outcomes in both the general population and in patients with T2DM. Lifestyle interventions, and particularly promotion of physical activity and adoption of healthy nutritional habits, have been associated to a significant benefit on hs-cTn release in the general population. Randomized controlled trials suggested that hypoglycemic, anti-hypertensive and lipid-lowering therapy may influence the degree of T2DM-induced cardiac injury. Besides these promising findings, the efficacy of an hs-cTn-based approach for CVD prevention in T2DM patients still requires more investigations.

[19] *Ruiz AJ, Vargas-Uricoechea H, Urina-Triana M et al.* **Dyslipidaemias and their treatment in high complexity centres in Colombia**. Clinica e investigacion en arteriosclerosis : publicacion oficial de la Sociedad Espanola de Arteriosclerosis 2020.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=32284160
ABSTRACT
BACKGROUND AND OBJECTIVE: Data is scarce on the distribution of different types of dyslipidaemia in Colombia. The primary objective was to describe the frequency of dyslipidaemias. The secondary objectives were: frequency of cardiovascular comorbidity, statins and other lipid-lowering drugs use, frequency of statins intolerance, percentage of patients achieving c-LDL goals, and distribution of cardiovascular risk (CVR). MATERIALS AND METHODS: Cross-sectional study with retrospective data collection from 461 patients diagnosed with dyslipidaemia and treated in 17 highly specialised centres distributed into six geographic and economic regions of Colombia. RESULTS: Mean (SD) age was 66.4 (+/-12.3) years and 53.4% (246) were women. Dyslipidaemias were distributed as follows in order of frequency: mixed dyslipidaemia (51.4%), hypercholesterolaemia (41.0%), hypertriglyceridaemia (5.4%), familial hypercholesterolaemia (3.3%), and low c-HDL (0.7%). The most prescribed drugs were atorvastatin (75.7%) followed by rosuvastatin (24.9%). As for lipid control, 55% of all patients, and 28.6% of those with coronary heart disease, did not achieve their personal c-LDL goal despite treatment. The frequency of statin intolerance was 2.6% in this study. CONCLUSIONS: Mixed dyslipidaemia and hypercholesterolaemia are the most frequent dyslipidaemias in Colombia. A notable percentage of patients under treatment with lipid-lowering drugs, including those with coronary heart disease, did not achieve specific c-LDL goals. This poor lipid control may worsen patient's CVR, so that therapeutic strategies need to be changed, either with statin intensification or addition of new drugs in patients with higher CVR.

[20] *Villain C, Liabeuf S, Metzger M et al.* **Impact of age on cardiovascular drug use in patients with chronic kidney disease**. Clinical kidney journal 2020; 13:199-207.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=32296525
ABSTRACT
Background: Elderly patients with chronic kidney disease (CKD) are often excluded from clinical trials; this may affect their use of essential drugs for cardiovascular complications. We sought to assess the impact of age on cardiovascular drug use in elderly patients with CKD. Methods: We used baseline data from the Chronic Kidney Disease-Renal Epidemiology and Information Network (CKD-REIN) cohort including 3033 adult patients with CKD Stages 3 and 4. We studied the use of recommended drugs for coronary artery disease (CAD), stroke and atrial fibrillation by age, after adjusting for socio-demographic and clinical conditions. Results: The patients' mean age was 66.8 years (mean estimated glomerular filtration rate 32.9 mL/min/1.73 m(2)). The prevalence of CAD was 24.5% [81.3% receiving antiplatelet agents, 75.6% renin-angiotensin system (RAS) blockers, 65.4% beta-blockers and 81.3% lipid-lowering therapy], that of stroke 10.0% (88.8% receiving antithrombotic drugs) and that of atrial fibrillation 11.1% (69.5% receiving oral anticoagulants). Compared with patients aged <65 years, older age (>/=65 years) was associated with greater use of antithrombotic drugs in stroke [adjusted odds ratio (aOR) (95% confidence interval) = 2.83 (1.04-7.73) for patients aged (75-84 years)] and less use of RAS blockers [aOR = 0.39 (0.16-0.89) for patients aged >/=85 years], beta-blockers [aOR = 0.31 (0.19-0.53) for patients aged 75-84 years] and lipid-lowering therapy [aOR = 0.39 (0.15-1.02) for patients aged >/=85 years, P for trend = 0.01] in CAD. Older age was not associated with less use of antiplatelet agents in CAD or oral anticoagulants in atrial fibrillation. Conclusions: In patients with CKD, older age per se was not associated with the underuse of antithrombotic drugs but was for other major drugs, with a potential impact on cardiovascular outcomes.

[21] *Courlet P, Decosterd LA, Alves Saldanha S et al.* **Influence of Drug-Drug Interactions on the Pharmacokinetics of Atorvastatin and Its Major Active Metabolite ortho-OH-Atorvastatin in Aging People Living with HIV**. Clinical pharmacokinetics 2020.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=32281059
ABSTRACT
BACKGROUND: People living with HIV (PLWH) are aging and experience age-related physiological changes and comorbidities. Atorvastatin is a widely prescribed lipid-lowering agent metabolized by cytochrome P450 (CYP) 3A4, whose hepatocyte uptake is facilitated by organic anion transporting polypeptide (OATP) 1B1/1B3. Inhibition or induction of this enzyme and hepatic transporter can increase or decrease atorvastatin exposure, respectively. OBJECTIVE: This study aimed to describe the pharmacokinetic profile of atorvastatin and its major metabolite, and to evaluate drug-drug interactions (DDIs) with antiretrovirals (ARVs). METHODS: The atorvastatin pharmacokinetic profile was best described by a two-compartment model with first-order absorption and elimination. Metabolite concentrations were described by considering both linear metabolism from atorvastatin and presystemic metabolism. The influence of demographic and clinical covariates on drug and metabolite pharmacokinetics was assessed using NONMEM((R)). Model-based simulations were performed to evaluate the magnitude of DDIs with ARVs. RESULTS: Full pharmacokinetic profiles (98 atorvastatin + 62 o-OH-atorvastatin concentrations) and sparse concentrations (78 and 53 for atorvastatin and o-OH-atorvastatin, respectively) were collected in 59 PLWH. Interindividual variability

was high. The coadministration of boosted ARVs decreased atorvastatin clearance by 58% and slowed down o-OH-atorvastatin formation by 88%. Atorvastatin clearance increased by 78% when coadministered with CYP3A4 inducers. Simulations revealed a 180% increase and 44% decrease in atorvastatin exposure (area under the curve) in the presence of ARVs with inhibiting and inducing properties, respectively. CONCLUSION: This study showed an important interindividual variability in atorvastatin pharmacokinetics that remains largely unexplained after the inclusion of covariates. Since boosted ARVs double atorvastatin exposure, the initial dosage might be reduced by half, and titrated based on individual clinical targets.

[22] *Mourouzis K, Oikonomou E, Siasos G et al.* **Proinflammatory Cytokines in Acute Coronary Syndromes**. Current pharmaceutical design 2020.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=32282296
ABSTRACT
BACKGROUND: Over the last decades the role of inflammation and immune system activation in the initiation and progression of coronary artery disease (CAD) has been established. OBJECTIVES: To present the interplay between cytokines and their actions preceding and shortly after ACS. METHODS: We search in a systemic manner for identification of the most relevant articles to the topic inflammation, cytokines, vulnerable plaque and myocardial infarction in MEDLINE, COCHRANE and EMBASE databases. RESULTS: Different classes of cytokines (intereleukin [IL]-1 family, Tumor necrosis factor alpha (TNF-alpha) family, chemokines, adipokines, interferons) are implicated in the entire process leading to destabilization of the atherosclerotic plaque and consequently to the incidence of myocardial infraction. Especially IL-1 and TNF-alpha family are involved in inflammatory cell accumulation, vulnerable plaque formation, platelet aggregation, cardiomyocyte apoptosis and adverse remodeling following myocardial infraction. Several cytokines such as IL-6, adiponectin, interferon-gamma, appear with significant prognostic value in ACS patients. Thus, research interest focuses on the modulation of inflammation in ACS to improve clinical outcomes. CONCLUSION: Understanding the unique characteristics that accompany each cytokine-cytokine receptor interaction could illuminate the signaling pathways involved in plaque destabilization and indicate future treatment strategies to improve cardiovascular prognosis in ACS patients.

[23] *Tejada S, Capo X, Mascaro CM et al.* **Hepatoprotective effects of resveratrol in non-alcoholic fatty live disease**. Current pharmaceutical design 2020.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=32303170
ABSTRACT
BACKGROUND: Non-alcoholic fatty liver disease (NAFLD) is one of the most common causes of chronic liver disease worldwide directly related to the progressive increase in overweight and obesity. The accumulation of lipids in patients with NAFLD contributes to the development of insulin resistance, inflammatory response and oxidative stress in hepatocytes and an alteration of the circulating lipid and glycaemic profile. However, to date there are no effective pharmacological treatments for patients with NAFLD. Lifestyle changes and dietary modifications aimed to weight loss are the best current alternatives, therefore, new approaches should be considered. Resveratrol, a natural polyphenol of the stilbene group, is a potential candidate to be aware of the management of NAFLD for its anti-inflammatory, antioxidant properties, and calorie restriction-like effects. METHODS: In this review, the available information on the potential therapeutic effects of resveratrol on NAFLD developed mainly in

animal models and in some clinical trials are summarize. RESULTS: In vitro and animal model studies have shown beneficial effects of resveratrol treatment on NAFLD. Resveratrol reduces hepatic accumulation of lipids and improves lipid and glycaemic metabolism. Some of the mechanisms of action are the signalling pathways of AMP-activated protein kinase, sirtuin 1 and nuclear factor kappaB. However, the results obtained in clinical trials are inconclusive. CONCLUSION: Although preclinical trials have shown promising results of resveratrol against NALFD, the lack of clear results in clinical trials makes necessary more studies with a larger number of patients and for a longer time.

[24] *Mantovani A, Lunardi G, Bonapace S et al.* **Association between increased plasma ceramides and chronic kidney disease in patients with and without ischemic heart disease**. Diabetes Metab 2020.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=32283179
ABSTRACT
AIM: Plasma levels of certain ceramides are increased in patients with ischemic heart disease (IHD). Many risk factors for IHD are also risk factors for chronic kidney disease (CKD), but it is currently uncertain whether plasma ceramide levels are increased in patients with CKD. METHODS: We measured six previously identified high-risk plasma ceramide concentrations [Cer(d18:1/16:0), Cer(d18:1/18:0), Cer(d18:1/20:0), Cer(d18:1/22:0), Cer(d18:1/24:0) and Cer(d18:1/24:1)] in 415 middle-aged individuals who attended our clinical Cardiology and Diabetes services over a period of 9 months. RESULTS: A total of 97 patients had CKD (defined as e-GFRCKD-EPI<60ml/min/1.73m(2) and/or urinary albumin-to-creatinine ratio>/=30mg/g), 117 had established IHD and 242 had type 2 diabetes. Patients with CKD had significantly (P=0.005 or less) higher levels of plasma Cer(d18:1/16:0), Cer(d18:1/18:0), Cer(d18:1/20:0), Cer(d18:1/22:0), Cer(d18:1/24:0), and Cer(d18:1/24:1) compared to those without CKD. The presence of CKD remained significantly associated with higher levels of plasma ceramides (standardized beta coefficients ranging from 0.124 to 0.227, P<0.001) even after adjustment for body mass index, smoking, hypertension, diabetes, prior IHD, plasma LDL-cholesterol, hs-C-reactive protein levels and use of any lipid-lowering medications. Notably, more advanced stages of CKD and abnormal albuminuria were both associated (independently of each other) with increased levels of plasma ceramides. These results were consistent in all subgroups considered, including patients with and without established IHD or those with and without diabetes. CONCLUSION: Increased levels of plasma ceramides are associated with CKD independently of pre-existing IHD, diabetes and other established cardiovascular risk factors.

[25] *Pariente A, Labat V, Mansiaux Y et al.* **DPP-4 Inhibitors in Combination with Lipid-Lowering Agents and Risk of Serious Muscular Injury: A Nested Case-Control Study in a Nationwide Cohort of Patients with Type 2 Diabetes Mellitus**. Drug Saf 2020.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=32306223
ABSTRACT
INTRODUCTION: After a safety warning was issued for a risk of muscular injury associated with dipeptidyl peptidase-4 (DPP-4) inhibitor use, especially when co-prescribed with statins, spontaneous reporting analyses provided conflicting results. OBJECTIVE: The aim of this study was to investigate the association between DPP-4 inhibitor use and the risk of muscular injury in individuals with type 2 diabetes mellitus using statins or fibrates. METHODS: We conducted a nested case-control study amongst a cohort of individuals with type 2 diabetes using statins or fibrates, identified from a nationwide French health insurance database (2009-2014). Cases of serious muscular injury were

defined as subjects hospitalized for rhabdomyolysis or myopathy, or for whom testing for myoglobin or creatine phosphokinase followed by a change in statin or fibrate prescription (dose decrease, treatment switch, or stop) was identified. Up to ten controls were matched to each case according to sex, age, and type of lipid-lowering agent. Associations between DPP-4 inhibitor use and serious muscular injury were estimated using a multivariate conditional logistic regression model, providing odds ratios (ORs) adjusted for alcoholism, chronic renal failure, hypothyroidism, and number of concomitant drugs. RESULTS: Within the 35,117 individuals with type 2 diabetes mellitus constituting the source cohort, 437 statin-user cases were identified who were matched to 4358 statin-user controls. Similarly, 54 fibrate-user cases were identified who were matched to 540 fibrate-user controls. The adjusted OR for DPP-4 inhibitor use and serious muscular injury was estimated at 1.0 (95% confidence interval [CI] 0.7-1.2) in statin users and 0.8 (95% CI 0.4-1.9) in fibrate users. CONCLUSION: In this study, DPP-4 inhibitor use was not associated with an increased risk of serious muscular injury among patients with type 2 diabetes mellitus using statins or fibrates.

[26] *Clemente GS, Rickmeier J, Antunes IF et al.* **[(18)F]Atorvastatin: synthesis of a potential molecular imaging tool for the assessment of statin-related mechanisms of action**. EJNMMI research 2020; 10:34.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=32296962
ABSTRACT
BACKGROUND: Statins are lipid-lowering agents that inhibit cholesterol synthesis and are clinically used in the primary and secondary prevention of cardiovascular diseases. However, a considerable group of patients does not respond to statin treatment, and the reason for this is still not completely understood. [(18)F]Atorvastatin, the (18)F-labeled version of one of the most widely prescribed statins, may be a useful tool for statin-related research. RESULTS: [(18)F]Atorvastatin was synthesized via an optimized ruthenium-mediated late-stage (18)F-deoxyfluorination. The defluoro-hydroxy precursor was produced via Paal-Knorr pyrrole synthesis and was followed by coordination of the phenol to a ruthenium complex, affording the labeling precursor in approximately 10% overall yield. Optimization and automation of the labeling procedure reliably yielded an injectable solution of [(18)F]atorvastatin in 19% +/- 6% (d.c.) with a molar activity of 65 +/- 32 GBq.mumol(-1). Incubation of [(18)F]atorvastatin in human serum did not lead to decomposition. Furthermore, we have shown the ability of [(18)F]atorvastatin to cross the hepatic cell membrane to the cytosolic and microsomal fractions where HMG-CoA reductase is known to be highly expressed. Blocking assays using rat liver sections confirmed the specific binding to HMG-CoA reductase. Autoradiography on rat aorta stimulated to develop atherosclerotic plaques revealed that [(18)F]atorvastatin significantly accumulates in this tissue when compared to the healthy model. CONCLUSIONS: The improved ruthenium-mediated (18)F-deoxyfluorination procedure overcomes previous hurdles such as the addition of salt additives, the drying steps, or the use of different solvent mixtures at different phases of the process, which increases its practical use, and may allow faster translation to clinical settings. Based on tissue uptake evaluations, [(18)F]atorvastatin showed the potential to be used as a tool for the understanding of the mechanism of action of statins. Further knowledge of the in vivo biodistribution of [(18)F]atorvastatin may help to better understand the origin of off-target effects and potentially allow to distinguish between statin-resistant and non-resistant patients.

Literature update week 16 (2020)

[27] *Acanfora D, Ciccone MM, Scicchitano P et al.* **Neprilysin inhibitor-angiotensin II receptor blocker combination (sacubitril/valsartan): rationale for adoption in SARS-CoV-2 patients**. European heart journal. Cardiovascular pharmacotherapy 2020; 6:135-136.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=32282032
ABSTRACT

[28] *Misaka S, Shimomura K*. **Atorvastatin-Green Tea Interaction: Possible Mechanisms are Complicated, But Clinical Relevance is Not?** European journal of drug metabolism and pharmacokinetics 2020; 45:423-425.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=32297048
ABSTRACT

[29] *Barrett HE, Meester EJ, van Gaalen K et al.* **Imaging of inflammatory cellular protagonists in human atherosclerosis: a dual-isotope SPECT approach**. European journal of nuclear medicine and molecular imaging 2020.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=32291511
ABSTRACT
PURPOSE: Atherosclerotic plaque development and progression signifies a complex inflammatory disease mediated by a multitude of proinflammatory leukocyte subsets. Using single photon emission computed tomography (SPECT) coupled with computed tomography (CT), this study tested a new dual-isotope acquisition protocol to assess each radiotracer's capability to identify plaque phenotype and inflammation levels pertaining to leukocytes expressing leukocyte function-associated antigen-1 (LFA-1) and the leukocyte subset of proinflammatory macrophages expressing somatostatin receptor subtype-2 (SST2). Individual radiotracer uptake was quantified and the presence of corresponding immunohistological cell markers was assessed. METHODS: Human symptomatic carotid plaque segments were obtained from endarterectomy. Segments were incubated in dual-isotope radiotracers [(111)In]In-DOTA-butylamino-NorBIRT ([(111)In]In-Danbirt) and [(99m)Tc]Tc-[N(0-1)4,Asp(0),Tyr(3)]-octreotate ([(99m)Tc]Tc-Demotate 2) before scanning with SPECT/CT. Plaque phenotype was classified as pathological intimal thickening, fibrous cap atheroma or fibrocalcific using histology sections based on distinct morphological characteristics. Plaque segments were subsequently immuno-stained with LFA-1 and SST2 and quantified in terms of positive area fraction and compared against the corresponding SPECT images. RESULTS: Focal uptake of co-localising dual-radiotracers identified the heterogeneous distribution of inflamed regions in the plaques which co-localised with positive immuno-stained regions of LFA-1 and SST2. [(111)In]In-Danbirt and [(99m)Tc]Tc-Demotate 2 uptake demonstrated a significant positive correlation ($r = 0.651$; $p = 0.001$). Fibrous cap atheroma plaque phenotype correlated with the highest [(111)In]In-Danbirt and [(99m)Tc]Tc-Demotate 2 uptake compared with fibrocalcific plaques and pathological intimal thickening phenotypes, in line with the immunohistological analyses. CONCLUSION: A dual-isotope acquisition protocol permits the imaging of multiple leukocyte subsets and the pro-inflammatory macrophages simultaneously in atherosclerotic plaque tissue. [(111)In]In-Danbirt may have added value for assessing the total inflammation levels in atherosclerotic plaques in addition to classifying plaque phenotype.

[30] *Gallego-Colon E, Daum A, Yosefy C*. **Statins and PCSK9 inhibitors: A new lipid-lowering therapy**. European journal of pharmacology 2020; 878:173114.

PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=32302598

ABSTRACT

The clinical benefit of lipid-lowering therapies is to reduce circulating levels of atherogenic particles and to ameliorate the risk of atherosclerotic cardiovascular disease (ASCVD). The completion of two major clinical trials on PCSK9 inhibitors (PCSK9i), the FOURIER and the ODYSSEY outcome trials, has marked the beginning of a new era of lipid-lowering drugs. PCSK9i, evolocumab and alirocumab, are monoclonal antibodies that inactivate the liver proprotein convertase subtilisin kexin 9 (PCSK9). Inhibition of PCSK9 increases the number of low-density lipoprotein (LDL) receptors available leading to a profound reduction in circulating LDL particles. By preventing LDL receptor destruction, PCSK9i as adjunct to statin therapy can reduce LDL-C by 50-60% above that achieved by statin therapy alone. In addition, PCSK9i in combination with high-dose statins may reduce cardiovascular events and all-cause mortality in patients with clinical ASCVD. Based on evidence from clinical trials, the 2019 European Society of Cardiology (ESC)/European Atherosclerosis Society (EAS) guidelines for the management of dyslipidemias now include the use of PCSK9i to very high-risk ASCVD patients who are not achieving treatment goals on a maximum tolerated dose of a statin and ezetimibe. However, the cost-effectiveness of PCSK9i therapy is limited to secondary prevention in high-risk patients. This review outlines the main clinical trials leading to a change in the guidelines, clinical practice as well as the future challenges of PCSK9i therapy.

[31] *Tomlinson B, Chan P, Lam CWK*. **Postprandial hyperlipidemia as a risk factor in patients with type 2 diabetes**. Expert review of endocrinology & metabolism 2020; 15:147-157.

PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=32292091

ABSTRACT

Introduction: Postprandial hyperlipidemia is a common feature of the atherogenic dyslipidemia in patients with type 2 diabetes. Quantification of this with oral fat tolerance tests is not used routinely in clinical practice and abnormal postprandial lipids are usually inferred from non-fasting plasma triglyceride levels. Identifying excessive postprandial hyperlipidemia may help to refine cardiovascular risk assessment but there are no treatments currently available which selectively target postprandial lipids and no large cardiovascular outcome trials using this as the entry criterion.Areas covered: In this review of relevant published material, we summarize the findings from the most important publications in this area.Expert opinion: Postprandial hyperlipidemia appears to contribute to the cardiovascular risk in patients with diabetes. Non-fasting triglyceride levels provide a surrogate marker of postprandial hyperlipidemia but more specific markers such as apoB48 levels may prove to be more reliable. Omega-3 fatty acids, fibrates and ezetimibe can reduce postprandial lipids but may not correct them completely. Several novel treatments have been developed to target hypertriglyceridemia and some of these may be particularly effective in improving postprandial levels. Further clinical trials are needed to establish the role of postprandial lipids in assessment of cardiovascular risk and to identify the most effective treatments.

[32] *Shakarneh JK, Hallak HO, Awadallah HB et al.* **Necessity and concerns about lipid-lowering medical treatments and risk factors for non-adherence: A cross-sectional study in Palestine**. Int J Clin Pract 2020:e13511.

PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=32279380

ABSTRACT

AIMS: Strong evidence indicates that drugs reduce blood lipids and improve cardiovascular end-points, leading to their wide usage. However, the success of these drugs can be affected by poor patient's adherence to prescribed medication. This study aimed to evaluate medication adherence in patients with dyslipidaemia in association with patient beliefs about medicines. METHODS: The study was conducted from January 2019 to July 2019 at the middle governmental primary healthcare clinics in Ramallah and Bethlehem cities, and used a cross-sectional design. Adherence was determined using the 4-item Morisky medication adherence scale, while beliefs were determined using the Beliefs about Medicines Questionnaire. RESULTS: Of 220 patients, 185 agreed to participate in the study, resulting in a response rate of 84.1%. Of the participants, 106 (57.3%) were men, and almost half (88, 46.5%) were >/=56 years. Medication non-adherence was high (47.6%), but a majority (65.5%) reported believing their treatment to be necessary for their continued good health. Accordingly, the mean necessity score (17.3, SD 3.7) significantly outweighed (P < .001) the mean concerns score (14.0, SD 3.5). Multivariate regression demonstrated four variables to be significantly correlated with non-adherence: illiterate (OR = 2.52; CI: 0.9-4.3; P = .03), polypharmacy (OR = 3.18; CI: 1.9-5.7; P = .007), having comorbidity (OR = 3.10; CI: 2.2-4.6; P = .005) and having concerns about side effects (OR = 2.89; CI: 1.1-4.6, P = .04). CONCLUSION: Non-adherence among patients taking lipid-lowering agents was high despite most holding positive beliefs regarding medication necessity. This may be due to concern also being high. Physicians should identify and target high-risk patients and individualise their treatment plans in order to achieve adequate control of dyslipidaemia.

[33] *Opazo-Rios L, Mas S, Marin-Royo G et al.* **Lipotoxicity and Diabetic Nephropathy: Novel Mechanistic Insights and Therapeutic Opportunities**. International journal of molecular sciences 2020; 21.

PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=32290082

ABSTRACT

Lipotoxicity is characterized by the ectopic accumulation of lipids in organs different from adipose tissue. Lipotoxicity is mainly associated with dysfunctional signaling and insulin resistance response in non-adipose tissue such as myocardium, pancreas, skeletal muscle, liver, and kidney. Serum lipid abnormalities and renal ectopic lipid accumulation have been associated with the development of kidney diseases, in particular diabetic nephropathy. Chronic hyperinsulinemia, often seen in type 2 diabetes, plays a crucial role in blood and liver lipid metabolism abnormalities, thus resulting in increased non-esterified fatty acids (NEFA). Excessive lipid accumulation alters cellular homeostasis and activates lipogenic and glycogenic cell-signaling pathways. Recent evidences indicate that both quantity and quality of lipids are involved in renal damage associated to lipotoxicity by activating inflammation, oxidative stress, mitochondrial dysfunction, and cell-death. The pathological effects of lipotoxicity have been observed in renal cells, thus promoting podocyte injury, tubular damage, mesangial proliferation, endothelial activation, and formation of macrophage-derived foam cells. Therefore, this review examines the recent preclinical and clinical research about the potentially harmful effects of lipids in the kidney, metabolic markers associated with these mechanisms, major signaling pathways affected, the causes of excessive lipid accumulation, and the types of lipids involved, as well as offers a comprehensive update of therapeutic strategies targeting lipotoxicity.

[34] *Orekhov AN, Sukhorukov VN, Nikiforov NG et al.* **Signaling Pathways Potentially Responsible for Foam Cell Formation: Cholesterol Accumulation or Inflammatory Response-What is First?** International journal of molecular sciences 2020; 21.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=32295185
ABSTRACT
Accumulation of lipid-laden (foam) cells in the arterial wall is known to be the earliest step in the pathogenesis of atherosclerosis. There is almost no doubt that atherogenic modified low-density lipoproteins (LDL) are the main sources of accumulating lipids in foam cells. Atherogenic modified LDL are taken up by arterial cells, such as macrophages, pericytes, and smooth muscle cells in an unregulated manner bypassing the LDL receptor. The present study was conducted to reveal possible common mechanisms in the interaction of macrophages with associates of modified LDL and non-lipid latex particles of a similar size. To determine regulatory pathways that are potentially responsible for cholesterol accumulation in human macrophages after the exposure to naturally occurring atherogenic or artificially modified LDL, we used transcriptome analysis. Previous studies of our group demonstrated that any type of LDL modification facilitates the self-association of lipoprotein particles. The size of such self-associates hinders their interaction with a specific LDL receptor. As a result, self-associates are taken up by nonspecific phagocytosis bypassing the LDL receptor. That is why we used latex beads as a stimulator of macrophage phagocytotic activity. We revealed at least 12 signaling pathways that were regulated by the interaction of macrophages with the multiple-modified atherogenic naturally occurring LDL and with latex beads in a similar manner. Therefore, modified LDL was shown to stimulate phagocytosis through the upregulation of certain genes. We have identified at least three genes (F2RL1, EIF2AK3, and IL15) encoding inflammatory molecules and associated with signaling pathways that were upregulated in response to the interaction of modified LDL with macrophages. Knockdown of two of these genes, EIF2AK3 and IL15, completely suppressed cholesterol accumulation in macrophages. Correspondingly, the upregulation of EIF2AK3 and IL15 promoted cholesterol accumulation. These data confirmed our hypothesis of the following chain of events in atherosclerosis: LDL particles undergo atherogenic modification; this is accompanied by the formation of self-associates; large LDL associates stimulate phagocytosis; as a result of phagocytosis stimulation, pro-inflammatory molecules are secreted; these molecules cause or at least contribute to the accumulation of intracellular cholesterol. This chain of events may explain the relationship between cholesterol accumulation and inflammation. The primary sequence of events in this chain is related to inflammatory response rather than cholesterol accumulation.

[35] *Yang G, Han D, Ma J, Zhang X*. **Efficacy of Ezetimibe/Simvastatin (10/10 mg) versus High Dose Statin in Dyslipidemia Patients: A Meta-Analysis of Randomized Controlled Trials**. Iranian journal of public health 2019; 48:1405-1417.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=32292723
ABSTRACT
Background: The monotherapies of statin and ezetimibe had not successfully achieved their objectives in the management of lipid levels of dyslipidemia patients. We aimed to compare the effects of combined low-dose simvastatin and ezetimibe versus high-dose statin on the lipid-lowering treatment of dyslipidemia patients. Methods: We searched five databases published before May 2018, namely PubMed, EMBASE, Cochrane, Web of Science, and Clinicaltrials.gov. Completely published randomized controlled trials (RCTs) comparing the effect of high-dose statin (S) with ezetimibe/simvastatin (10/10

mg; E/S) on the management of dyslipidemia patients were included. Results: A total of ten RCTs met the inclusion criteria, including 1,624 patients (E/S:691, S:933). Six outcomes underwent pooled analysis, including weighted mean difference (WMD) from baseline in total cholesterol (TC), low-density lipoprotein cholesterol (LDL-C), high-density lipoprotein cholesterol (HDL-C), high sensitivity C-reactive protein (hs-CRP), triglyceride (TG), and non-high-density lipoprotein cholesterol (non-HDL-C). No significant gap was found between high-dose statin and ezetimibe/simvastatin (10/10 mg) in LDL-C (-1.55; 95% confidence interval [CI]: -4.42 approximately 1.31, P=0 .29), HDL-C (1.05; 95%CI: -0.21 approximately 2.3, P=0 .1), TG (4.03; 95%CI: -4.53 approximately 12.58, P=0.36), and hs-CRP (0.14; 95%CI: -0.50 approximately 0.78, P=0.67). However, there was significant difference found between the two lipid-lowering treatments in TC (-0.45; 95%CI: -9.07 approximately -0.83, P=0.02) and non-HDL-C (-4.97; 95%CI -8.46 approximately -1.49, P=0.005). Conclusion: Ezetimibe co-administered with simvastatin (10 mg) and high-dose statin monotherapy may show similar effects in reducing LDL-C, TG, and hs-CRP levels and in increasing HDL-C levels. However, the results suggest that there was greater TC and non-HDL-C lowering through high-dose statin monotherapy as compared with ezetimibe/simvastatin co-administration.

[36] *Shin JM, Jung KE, Yim SH et al.* **Putative therapeutic mechanisms of simvastatin in the treatment of alopecia areata**. Journal of the American Academy of Dermatology 2020.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=32278796
ABSTRACT

[37] *Alfian SD, Annisa N, Fajriansyah F et al.* **Modifiable Factors Associated with Non-adherence to Antihypertensive or Antihyperlipidemic Drugs Are Dissimilar: a Multicenter Study Among Patients with Diabetes in Indonesia**. Journal of general internal medicine 2020.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=32301043
ABSTRACT
BACKGROUND: To develop targeted and tailored interventions for addressing medication non-adherence, it is important to identify underlying factors. OBJECTIVE: To identify factors associated with non-adherence as well as subtypes of non-adherence to antihypertensive or antihyperlipidemic drugs among patients with type 2 diabetes in Indonesia. DESIGN: An observational multicenter cross-sectional survey. PARTICIPANTS: Patients with type 2 diabetes using either antihypertensive or antihyperlipidemic drugs in four regions in Indonesia. MAIN MEASURES: Non-adherence and its subtypes of intentional and unintentional non-adherence were assessed using the Medication Adherence Report Scale. Necessity and concern beliefs were assessed with the Beliefs about Medicines Questionnaire. We applied binary and multinomial logistic regression to assess associations of medication beliefs, sociodemographic factors, and clinical-related factors to non-adherence and report odds ratios (OR) with 95% confidence intervals (CI). KEY RESULTS: Of 571 participating patients (response rate 97%), 45.5% and 52.7% were non-adherent to antihypertensive and antihyperlipidemic drugs, respectively. Older age was associated with non-adherence to antihypertensive drugs (60-69 years) (OR, 5.65; 95% CI, 2.68-11.92), while higher necessity beliefs (OR, 0.92; 95% CI, 0.88-0.95) were associated with less non-adherence. Factors associated with non-adherence to antihyperlipidemic drugs were female gender (OR, 1.84; 95% CI, 1.03-3.27) and higher concern beliefs (OR, 1.10; 95% CI, 1.03-1.18), while higher necessity beliefs (OR, 0.89; 95% CI, 0.83-0.96) were associated with less non-adherence. CONCLUSIONS: The main factors associated with non-adherence to antihypertensive and

antihyperlipidemic drugs are modifiable. In general, beliefs about the necessity of the drug are important but for antihyperlipidemic drugs concerns are important as well. Healthcare providers should pay attention to identify and address medication beliefs during patient counselling.

[38] *Shirani F, Teimoori A, McAinch AJ et al.* **Human adenovirus 36 improves insulin sensitivity and lipid profiles and increases inflammatory markers in Wistar rats**. Journal of investigative medicine : the official publication of the American Federation for Clinical Research 2020.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=32303633
ABSTRACT
Human adenovirus 36 (Ad-36) causes obesity with increased adiposity, in contrast, Ad-36 infection reduces glucose and lipid metabolism; the results, however, are not consistent. In the current study, the effects of Ad-36 infection on glucose and lipid profile and inflammatory markers in Wistar rats were investigated. Sixty male Wistar rats were randomly divided into infected and control groups. Ad-36 virus suspension was injected in the experimental group rats. Blood samples were collected in the beginning and after 12 weeks in both groups. After 12 weeks, a significant improvement was observed in fasting blood glucose, fasting serum insulin, insulin sensitivity, serum triglycerides and total cholesterol in the infected group compared with the non-infected groups. There were no significant differences in inflammatory biomarkers including tumor necrosis factor-alpha, interleukin 6 and monocyte chemoattractant protein-1 levels between infected and control groups. This study showed that Ad-36 had favorable effects on glycemic and lipid control in infected rats, but inflammatory biomarker levels were similar for 2 groups. Ad-36 infections could potentially be a new way to develop novel antidiabetic and antihyperlipidemic therapeutic agents.

[39] *Chapman MJ, Orsoni A, Tan R et al.* **LDL subclass lipidomics in atherogenic dyslipidemia:Effect of statin therapy on bioactive lipids and dense LDL**. Journal of lipid research 2020.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=32295829
ABSTRACT
Atherogenic LDL particles are physicochemically and metabolically heterogeneous. Can bioactive lipid cargo differentiate LDL subclasses, and thus potential atherogenicity? What is the effect of statin treatment? Obese, hypertriglyceridemic, hypercholesterolemic males (n=12; Lp(a) <10 mg/dL) received pitavastatin calcium (4mg/day) for 180 days in a single-phase, unblinded study. The lipidomic profiles (23 lipid classes) of five LDL subclasses fractionated from baseline and post-statin plasmas were determined by LC-MS. At baseline and on statin treatment, very small dense LDL (LDL5) was preferentially enriched (up to 3-fold) in specific lysophospholipids (lysophosphatidylcholine (LPC); lysophosphatidylinositol (LPI); lyso-platelet activating factor (LPC(O)); 9,0.2 and 0.14 mol/mol apoB respectively; all p<0.001 versus LDL1-4), suggesting elevated inflammatory potential per particle. In contrast, lysophosphatidylethanolamine was uniformly distributed among LDL subclasses. Statin treatment markedly reduced absolute plasma concentrations of all LDL subclasses (up to 33.5%), including LPC, LPI and LPC(O) contents (up to -52%), consistent with reduction in cardiovascular risk. Despite such reductions, lipotoxic ceramide load per particle in LDL1-5 (1.5 - 3 mol/mol apoB; 3 - 7 mmol/mol phosphatidylcholine) was either conserved or elevated. Bioactive lipids may constitute biomarkers for the cardiometabolic risk associated with specific LDL subclasses in atherogenic dyslipidemia at baseline, and with residual risk on statin therapy.

Literature update week 16 (2020)

[40] *Magro Dos Reis I, Houben T, Oligschlager Y et al.* **Dietary plant stanol ester supplementation reduces peripheral symptoms in a mouse model of Niemann-Pick type C1 disease**. Journal of lipid research 2020.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=32291331
ABSTRACT
Niemann-Pick type C1 (NPC1) disease is a rare genetic condition in which the function of the lysosomal cholesterol transporter NPC1 protein is impaired. Consequently, sphingolipids and cholesterol accumulate in lysosomes of all tissues, triggering a cascade of pathological events that culminate in severe systemic and neurological symptoms. Lysosomal cholesterol accumulation is also a key-factor in the development of atherosclerosis and non-alcoholic steatohepatitis (NASH). In these two metabolic diseases, the administration of plant stanol esters has been shown to ameliorate cellular cholesterol accumulation and inflammation. Given the overlap of pathological mechanisms among atherosclerosis, NASH and NPC1 disease, we sought to investigate whether dietary supplementation with plant stanol esters improves the peripheral features of NPC1 disease. To this end, we used an NPC1 murine model featuring an Npc1 null allele (Npc1(nih)), creating a dysfunctional NPC1 protein. Npc1(nih) mice were fed a two or six percent plant stanol esters-enriched diet over the course of 5 weeks. During this period, hepatic and blood lipid and inflammatory profiles were assessed. Npc1(nih) mice fed the plant stanol-enriched diet exhibited lower hepatic cholesterol accumulation, damage and inflammation than regular chow-fed Npc1(nih) mice. Moreover, plant stanol consumption shifted circulating T-cells and monocytes in particular towards an anti-inflammatory profile. Overall, these effects were stronger following dietary supplementation with 6% stanols, suggesting a dose-dependent effect. The findings of our study highlight the potential use of plant stanols as an affordable complementary means to ameliorate disorders in hepatic and blood lipid metabolism and reduce inflammation in NPC1 disease.

[41] *Mosca L, Navar AM, Kass Wenger N*. **Reducing Cardiovascular Disease Risk in Women Beyond Statin Therapy: New Insights 2020**. Journal of women's health (2002) 2020.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=32297837
ABSTRACT
Management of residual and persistent cardiovascular disease (CVD) risk among statin-treated individuals has emerged as an important preventive strategy. The purpose of this article is to review the unique landscape of CVD in women and relevant prior prevention trials, and to discuss how the recent results of the Reduction of Cardiovascular Events with Icosapent Ethyl-Intervention Trial (REDUCE-IT) might apply to the contemporary management of CVD risk among statin-treated women. Women have unique risk factors that may impact CVD and its prevention. Historically, women have been underrepresented in CVD trials, posing a challenge to development of clinical recommendations for women. Low-density lipoprotein cholesterol-targeting treatments have demonstrated CVD risk reduction, with comparable effects in both sexes. In contrast, triglyceride-lowering treatments (niacin, fenofibrate, and omega-3 fatty acids) have reported mixed findings for CVD risk reduction. Recent clinical trials of combination omega-3 fatty acids (docosahexaenoic acid/eicosapentaenoic acid [EPA]) have not found significant CVD risk reduction. The recently published REDUCE-IT study found that icosapent ethyl, an EPA-only omega-3 fatty acid, in combination with statins, significantly reduced CVD events in high-risk patients. The icosapent ethyl group had a significantly lower occurrence of the primary composite CVD endpoint (17.2%) than the placebo group (22.0%; hazard ratio 0.75; 95% confidence interval 0.68-0.83; $p < 0.001$). CVD risk reduction with icosapent ethyl treatment was

comparable between women and men (p for interaction, 0.33). Data from REDUCE-IT suggest women benefit similarly to men with respect to icosapent ethyl, a novel therapy for prevention of CVD.

[42] *Arafa MH, Mohammad NS, Atteia HH*. **Rho-Kinase inhibitors ameliorated diclofenac-induced cardiotoxicity in chloroquine-treated adjuvant arthritic rats**. Life sciences 2020:117605.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=32278692
ABSTRACT
AIMS: Although chloroquine and diclofenac are not cardiovascular drugs, their chronic administration may trigger cardiotoxicity. We, therefore, evaluated the cardiotoxic impact of diclofenac in chloroquine-treated adjuvant arthritic rats. METHODS: 50 male rats were equally distributed into 5 groups including control. Arthritis was induced by S.C injection of Complete Freund's adjuvant in hind paw planter surface. Arthritic rats were subdivided into 4 groups, orally treated with: no drug, chloroquine (50mg/kg), diclofenac sodium (1mg/kg) and chloroquine+diclofenac. KEY FINDINGS: All treatments significantly elevated serum cardiac injury and dysfunction markers as well as left ventricular malondialdehyde but depleted antioxidants with the greatest effect in the combination group. Chloroquine and/or diclofenac; in particular, their combination shifted the balance between left ventricular pro- and anti-apoptotic proteins towards myocardial apoptosis. Surprisingly, treatment with diclofenac or chloroquine/diclofenac markedly up-regulated cardiac RhoA and Rho-kinase1. Such up-regulation was coupled with a greater increase in cardiac oxidative damage biomarkers in the combination group than in individually-treated ones. Owing to their anti-inflammatory properties, statins may be used in adjunct with antirheumatics. To study the role of Rho-kinase in chloroquine/diclofenac-triggered cardiotoxicity here, four additional arthritic groups were co-treated with Rho-kinase inhibitors (fasudil or atorvastatin) along with diclofenac and chloroquine+diclofenac. Rho-kinase inhibition protected against chloroquine/diclofenac-induced increases in myocardial oxidative damage markers. SIGNIFICANCE: Diclofenac greatly amplified cardiac oxidative damage in chloroquine-treated arthritic rats via up-regulation of Rho-kinase1. However, Rho-kinase inhibitors provided cardioprotection against diclofenac toxicity. Overall, they could be used as safer adjuvants to chloroquine and diclofenac during the treatment of rheumatoid arthritis.

[43] *Szczuko M, Kaczkan M, Malgorzewicz S et al.* **The C18:3n6/C22:4n6 ratio is a good lipid marker of chronic kidney disease (CKD) progression**. Lipids in health and disease 2020; 19:77.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=32303226
ABSTRACT
BACKGROUND: Chronic kidney disease (CKD) is a major challenge for public health due to increased risk of cardiovascular diseases (CVD) and premature death. The aim of this study was to determine the clinical picture of FA and the course of the pathophysiological mechanisms of CKD. METHODS: The study involved 149 patients with CKD and a control group including 43 people. Fatty acid profiles were investigated using gas chromatography. A total of 30 fatty acids and their derivatives were identified and quantified. The omega3, omega6, SFA, MUFA, and PUFA fatty acid contents were calculated. The correlation matrix was obtained for parameters relating to patients with CKD vs. FA, taking patients' sex into consideration. The index C18:3n6/C22:4n6 was calculated according to the length of the treatment. Statistica 12.0 software (Tulsa, Oklahoma, USA) was used for the statistical analyses. RESULTS: The results showed decreased levels of total PUFA and increased concentrations of MUFA, including the activation of the palmitic and oleic acid pathway. An increase in the levels of n-6 9C22:

4n6 family fatty acids in all the patients and a reduction in the n-3 family (EPA, DHA) were observed. C18:3n6 was negatively correlated and C22:4n6 was positively correlated with the duration of the treatment. The index C18:3n6/C22:4n6 was defined as a new marker in the progression of the disease. Moreover, the index C18:3n6/ C22:4n6 was drastically decreased in later period. Nervonic acid was higher in the CKD group. In the group of men with CKD, there was a negative correlation between the excretion of K+, anthropometric measurements, and the levels of EPA and DHA. CONCLUSIONS: The course of inflammation in CKD occurs through the decrease in PUFA and the synthesis of MUFA. The dominating cascade of changes is the elongation of GLA-C18:3n6 into DGLA-C20:3n6 and AA-C20:4n6. As CKD progresses, along with worsening anthropometrical parameters and increased secretion of potassium, the activity of 6-desaturase decreases, reducing the synthesis of EPA and DHA. The synthesis of AdA-C22:4n6 increases and the ratio C18:3n6/C22:4n6 drastically decreases after 5 years. This parameter can be used to diagnose disease progression.

[44] *Zhou Q, Zhang Z, Wang P et al.* **EPA+DHA, but not ALA, Improved Lipids and Inflammation Status in Hypercholesterolemic Adults: A Randomized, Double-Blind, Placebo-Controlled Trial**. Molecular nutrition & food research 2020; 64:e2070012.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=32285567
ABSTRACT

[45] *Aguilar EC, Navia-Pelaez JM, Fernandes-Braga W et al.* **Gluten exacerbates atherosclerotic plaque formation in ApoE(-/-) mice with diet-induced obesity**. Nutrition 2019; 75-76:110658.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=32305657
ABSTRACT
OBJECTIVES: Atherosclerosis is an underlying cause of cardiovascular disease, and obesity is one of the risk factors for atherogenesis. Although a gluten-free diet (GFD) has gained popularity as a strategy for weight loss, little is known about the effects of gluten on obesity. We have previously shown a negative effect of gluten on obesity in mice. However, its effects on atherogenesis are still unknown. Therefore, the aim of this study was to determine the effects of gluten on atherosclerosis progression during obesity. METHODS: Atherosclerosis-susceptible ApoE knockout mice were subjected to an obesogenic GFD or a diet with 4.5% gluten (GD) for 10 wk. RESULTS: Results from the study found that food intake and lipid profile were similar between the groups. However, GD promoted an increase in weight gain, adiposity, and plasma glucose. Pro-inflammatory factors such as tumor necrosis factor, interleukin-6, chemokine ligand-2, and matrix metalloproteinase-2 and -9 also were increased in the adipose tissue of gluten-fed mice. This inflammatory profile was associated with reduced phosphorylation of Akt, and consequently with the intensification of insulin resistance. The GD-enhanced vascular inflammation contributed to the worsening of atherosclerosis in the aorta and aortic root. Inflammatory cells, such as monocyte/macrophage and natural killer cells, and oxidative stress markers, such as superoxide and nitrotyrosine, were increased in atherosclerotic lesions of the GD group. Furthermore, the lesions presented higher necrotic core and lower collagen content, characterizing the less stable plaques. CONCLUSION: The gluten-containing high-fat diet was associated with a more severe proatherogenic profile than the gluten-free high-fat diet owing to increased inflammatory and oxidative status at atherosclerotic lesions in obese mice.