Literature update week 14 (2019)

[1] *Spannella F, Giulietti F, Di Pentima C, Sarzani R*. **Prevalence and Control of Dyslipidemia in Patients Referred for High Blood Pressure: The Disregarded "Double-Trouble" Lipid Profile in Overweight/Obese**. Adv Ther 2019.

PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=30953331

ABSTRACT

INTRODUCTION: We evaluated the prevalence and control of dyslipidemia in a wide sample of patients referred to our ESH "Hypertension Excellence Centre" for high blood pressure (BP). Furthermore, we evaluated the role of adiposity on the serum lipid profile. METHODS: Observational study on 1219 consecutive outpatients with valid ambulatory BP monitoring (ABPM) referred for high BP. Patients with body mass index (BMI) >/= 25 kg/m(2) were defined as overweight/obese (OW/OB). Dyslipidemia and the control rates of low-density lipoprotein cholesterol (LDLc) were defined according to the 2016 ESC/EAS Guidelines. RESULTS: Mean age: 56.5 +/- 13.7 years. Male prevalence: 55.6%. OW/OB patients were 70.2%. The prevalence of dyslipidemia was 91.1%. Lipid-lowering drugs were taken by 23.1% of patients. Patients with controlled LDLc comprised 28.5%, while BP was controlled in 41.6% of patients. Only 12.4% of patients had both 24-h BP and LDLc controlled at the same time. The higher the cardiovascular (CV) risk was, the lower was the rate of LDLc control ($p < 0.001$). Patients in secondary prevention had worse LDLc control than patients in primary prevention (OR 3.5 for uncontrolled LDLc, $p < 0.001$). OW/OB showed a more atherogenic lipid profile, characterized by lower high-density lipoprotein cholesterol (HDLc) ($p < 0.001$), higher non-HDLc ($p = 0.006$), higher triglycerides ($p < 0.001$), higher non-HDLc/HDLc ($p < 0.001$) and higher (non-HDLc + non-LDLc) ($p < 0.001$). CONCLUSION: Dyslipidemia is still too often neglected in hypertensives, especially in patients at higher CV risk. OW/OB hypertensives have a "double-trouble" atherogenic lipid pattern likely driven by adiposity. We encourage a comprehensive evaluation of the lipid profile in all hypertensives, especially if they are OW/OB, to correctly assess their CV risk and improve their management. FUNDING: Article processing charges funded by Servier SpA.

[2] *Lee JS, Rosoff DB, Luo A et al.* **PCSK9 Is Increased In Cerebrospinal Fluid Of Individuals With Alcohol Use Disorder**. Alcoholism, clinical and experimental research 2019.

PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=30933362

ABSTRACT

BACKGROUND: Recent studies have shown that alcohol use affects the regulation and expression of proprotein convertase subtilisin/kexin 9 (PCSK9). While a major role of PCSK9 in hepatic function and lipid regulation has been clearly established, other pleiotropic effects remain poorly understood. Existing research suggests a positive association between PCSK9 expression in the brain and psychopathology, with increased levels of PCSK9 in the cerebrospinal fluid (CSF) of individuals with dementia and epigenetic modifications of PCSK9 associated with Alcohol Use Disorder (AUD). In this study, we hypothesized that chronic alcohol use would increase PCSK9 expression in CSF. METHODS: PCSK9 levels in CSF were measured in individuals with AUD (n=42) admitted to an inpatient rehabilitation program and controls (n=25). CSF samples in AUD were assessed at two-time points, at day 5 and day 21 after admission. Furthermore, plasma samples were collected and measured from the individuals with AUD. RESULTS: PCSK9 in CSF was significantly increased in the AUD group at day 5 and day 21 compared to the controls ($p < 0.0001$). Plasma PCSK9 levels were correlated positively with CSF PCSK9 levels in AUD ($p= 0.0493$). CONCLUSIONS: Our data suggest that PCSK9 is elevated in the CSF of individuals with AUD, which may indicate a potential role of PCSK9 in AUD. Additional studies are

necessary to further elucidate the functions of PCSK9 in the brain.

[3] *Grinspoon SK, Fitch KV, Overton ET et al.* **Rationale and design of the Randomized Trial to Prevent Vascular Events in HIV (REPRIEVE)**. American heart journal 2019; 212:23-35.

PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=30928825

ABSTRACT

BACKGROUND: Cardiovascular disease (CVD) is more frequent among people with HIV (PWH) and may relate to traditional and nontraditional factors, including inflammation and immune activation. A critical need exists to develop effective strategies to prevent CVD in this population. METHODS: The Randomized Trial to Prevent Vascular Events in HIV (REPRIEVE) (A5332) is a prospective, randomized, placebo-controlled trial of a statin strategy for the primary prevention of major adverse cardiovascular events (MACE) in PWH with low to moderate traditional risk. At least 7,500 PWH, 40-75 years of age, on stable antiretroviral therapy, will be randomized to pitavastatin calcium (4 mg/d) or identical placebo and followed for up to 8 years. Participants are enrolled based on the 2013 American College of Cardiology (ACC)/American Heart Association (AHA) atherosclerotic cardiovascular disease (ASCVD) risk score and low-density lipoprotein cholesterol (LDL-C) level with a goal to identify a low- to moderate-risk population who might benefit from a pharmacologic CVD prevention strategy. Potential participants with a risk score </= 15% were eligible based on decreasing LDL-C thresholds for increasing risk score >7.5% (LDL-C <190 mg/dL for risk score <7.5%, LDL-C <160 mg/dL for risk score 7.6%-10%, and LDL-C<130 mg/dL for risk score 10.1%-15%). The primary objective is to determine effects on a composite end point of MACE. Formal and independent adjudication of clinical events will occur using standardized criteria. Key secondary end points include effects on MACE components, all-cause mortality, specified non-CVD events, AIDS and non-AIDS events, and safety. RESULTS: To date, REPRIEVE has enrolled >7,500 participants at approximately 120 sites across 11 countries, generating a diverse and representative population of PWH to investigate the primary objective of the trial. CONCLUSIONS: REPRIEVE is the first trial investigating a primary CVD prevention strategy in PWH. REPRIEVE will inform the field of the efficacy and safety of a statin strategy among HIV-infected participants on antiretroviral therapy and provide critical information on CVD mechanisms and non-CVD events in PWH.

[4] *Hoffmann U, Lu MT, Olalere D et al.* **Rationale and design of the Mechanistic Substudy of the Randomized Trial to Prevent Vascular Events in HIV (REPRIEVE): Effects of pitavastatin on coronary artery disease and inflammatory biomarkers**. American heart journal 2019; 212:1-12.

PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=30928823

ABSTRACT

BACKGROUND: People with HIV (PWH) have increased cardiovascular events, inflammation, and high-risk coronary atherosclerosis. Statin therapy has been shown to lower the risk of cardiovascular disease (CVD) in the general population, but whether this results from reductions in coronary atherosclerosis and is mediated by decreased inflammation remains unknown. METHODS: REPRIEVE is a randomized, placebo-controlled trial of pitavastatin calcium (4 mg/day) vs. placebo enrolling at least 7500 PWH between 40-75 years, on antiretroviral therapy (ART), with low to moderate traditional CVD risk. The Mechanistic Substudy of REPRIEVE (A5333s) is co-enrolling 800 participants from 31 US sites. These participants undergo serial contrast enhanced coronary computed tomography angiography (CCTA) and

measurements of biomarkers of inflammation and immune activation at baseline and after 2 years of follow-up. The primary objectives are to determine the effects of pitavastatin on noncalcified coronary atherosclerotic plaque (NCP) volume, low attenuation plaque, and positive remodeling and on changes in immune activation and inflammation and to assess relationships between the two. Changes in CAD will be assessed in a standardized fashion by a core lab with expert readers blinded to time points and participant information; immune activation and inflammation assessment is also performed centrally. RESULTS: To date the Mechanistic Substudy has completed planned enrollment, with 805 participants. CONCLUSION: This study represents the first large, randomized, CCTA-based assessment of the effects of a primary prevention strategy for CVD on high-risk CAD, immune activation and inflammation among PWH. The study will assess pitavastatin's effects on coronary plaque, and the interrelationship of these changes with biomarkers of immune activation and inflammation in PWH to determine mechanisms of CVD prevention and improved outcomes in this population.

[5] *Merlant M, Fite C, Kottler D et al.* **[Dermatomyositis-like syndrome revealing statin-induced necrotizing autoimmune myopathy with anti-HMGCR antibodies]**. Annales de dermatologie et de venereologie 2019.

PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=30929872

ABSTRACT

BACKGROUND: Statin-induced necrotizing autoimmune myopathy (NAM) has been recently characterized. Herein we report an accurate description of the clinical and histological characteristics of cutaneous rash associated with NAM. PATIENTS AND METHODS: A 61-year-old woman presented a skin rash involving the face, the chest and the back of the hands with heliotropic distribution coupled with proximal symmetrical muscle weakness. Rosuvastatin had been introduced 8 months earlier. Creatinine kinase levels were dramatically raised. Screening for lupus and dermatomyositis antibodies were negative. The cutaneous histology was consistent with neutrophilic lupus while a muscle biopsy revealed no inflammation but showed necrotic and regenerative myofibres. Finally, antibodies directed against 3-hydroxy-3-methylglutaryl-coenzyme A reductase (HMGCR) were found at high levels (1658UA/ml vs. normal<13.0UA/ml), resulting in diagnosis of necrotizing autoimmune myopathy (NAM). Intensive immunosuppressive therapy resulted in excellent improvement. DISCUSSION: NAM is a severe acquired autoimmune myopathy characterised by severe proximal weakness and specific positive antibodies (anti-HMGCR or anti-signal recognition particle). It is classically associated with statin use. Some extra-muscular symptoms have been described in previous studies. We report the third accurate description of cutaneous rash associated with statin-induced NAM involving HMGCR antibodies. The skin rash was evocative of connective tissue disease and our diagnosis was based on immunology and muscle histology. CONCLUSION: Dermatologists must be able to recognise this rare entity of "pseudo-dermatomyositis" and then discontinue statin intake if present and carry out further investigations consisting of muscle biopsy and serological tests.

[6] *Klein-Szanto AJP, Bassi D*. **Keep recycling going: new approaches to reduce LDL-C**. Biochem Pharmacol 2019.

PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=30953636

ABSTRACT

Literature update week 14 (2019)

Hypercholesterolemia represents a leading cause in the development of atherosclerotic plaques, increasing the risk for ACVS. It actually counts as a major cause of cardiovascular disease etiopathogenesis. The causes of hypercholesterolemia are multifactorial, spanning from genetic constitution, age, sex, to sedentary lifestyle and diets rich in sugars and lipids. Although dietary restriction in saturated fats, increased exercise, and other modification in lifestyle represent a first-line approach to treat very initial stages in hypercholesterolemia, most patients will require the addition of pharmacological agents. Pharmacological approaches include inhibition of cholesterol synthesis, decreased fat absorption from the GI tract, and increased degradation of FA. These strategies present a series of side effects, low therapeutic efficiency in some patients, and reduced tolerability. One of the major goals in treatment for hypercholesterolemia is to decrease the levels of low density lipoproteins (LDL), while maintaining those of high density lipoproteins (HDL). LDL particles contain about 80% of lipids, most of it cholesterol and cholesteryl esters, and 20% of the ApoB-100 protein. LDL carries cholesterol to the tissues, to be incorporated to biological membranes, or to be transformed to steroids. Excess of LDL translates into increased levels of circulating cholesterol particles and accumulation in certain tissues, especially vascular tissue, initiating a fatty streak, which may evolve to an atheroma, causing a series of cardiovascular problems, including impaired circulation, high blood pressure, increased cardiac workload, and coronary artery disease. It is essential to prevent LDL accumulation into the bloodstream to avoid the formation of these fatty streaks and the initiation of a cascade that will lead to the development of atherosclerosis. In healthy individuals. Under physiological conditions, LDL is effectively removed from circulation through receptor-mediated endocytosis. LDL clearance involves binding to its receptor, LDLR, which enables the internalization of the LDL particle and drives its degradation in lysosomes. Once the LDL particle is degraded, the free receptor recycles to the plasma membrane, and captures new LDL particles. Adequate levels of LDLR are essential to remove the excess of cholesterol-laden LDL. Proprotein convertase, subtilysin kexin type 9 (PCSK-9), expressed in liver and intestine, binds to LDLR, and internalized. Once inside the cell, PCSK-9 catalyzes the proteolysis of LDLR, preventing its recycling to the cell surface, and effectively decreasing the number of LDLR, notoriously decreasing the ability to clear LDL from circulation. Levels of PCSK-9 varies with age, gender, and levels of insulin, glucose, and triglycerides. Loss-of-function mutations in PCSK-9 gene invariably translates into lower levels of LDL, and decreased risk of developing coronary artery disease. Conversely, increased activity or expression of this enzyme leads to hypercholesterolemia. Inhibition of PCSK9 has proven to be successful in decreasing LDL levels and risk of the development of hypercholesterolemia with its associated higher risk for ASCVD. Patient with gain-of-function mutations in the PCSK9 undoubtedly benefit from therapies based on PCSK-9 inhibitors. However, millions of patients show statin intolerance, or cannot be efficiently controlled by statins alone- the most prevalent therapy for hypeprcholesterolemia. This commentary will evaluate the possibilities, caveats and future directions in the treatment of hypercholesterolemia, and therapies with combination of drugs.

[7] *Gianfrancesco MA, Dehairs J, L'Homme L et al.* **Saturated fatty acids induce NLRP3 activation in human macrophages through K(+) efflux resulting from phospholipid saturation and Na, K-ATPase disruption**. Biochimica et biophysica acta. Molecular and cell biology of lipids 2019.

PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=30953761

ABSTRACT

NLRP3 inflammasome plays a key role in Western diet-induced systemic inflammation and was recently shown to mediate long-lasting trained immunity in myeloid cells. Saturated fatty acids (SFAs) are sterile triggers able to induce the assembly of the NLRP3 inflammasome in macrophages, leading to IL-1beta

secretion while unsaturated ones (UFAs) prevent SFAs-mediated NLRP3 activation. Unlike previous studies using LPS-primed bone marrow derived macrophages, we do not see any ROS or IRE-1alpha involvement in SFAs-mediated NLRP3 activation in human monocytes-derived macrophages. Rather we show that SFAs need to enter the cells and to be activated into acyl-CoA to lead to NLRP3 activation in human macrophages. However, their beta-oxidation is dispensable. Instead, they are channeled towards phospholipids but redirected towards lipid droplets containing triacylglycerol in the presence of UFAs. Lipidomic analyses and Laurdan fluorescence experiments demonstrate that SFAs induce a dramatic saturation of phosphatidylcholine (PC) correlated with a loss of membrane fluidity, both events inhibited by UFAs. The silencing of CCTalpha, the key enzyme in PC synthesis, prevents SFA-mediated NLRP3 activation, demonstrating the essential role of the de novo PC synthesis. This SFA-induced membrane remodeling promotes a disruption of the plasma membrane Na, K-ATPase, instigating a K(+) efflux essential and sufficient for NLRP3 activation. This work opens novel therapeutic avenues to interfere with Western diet-associated diseases such as those targeting the glycerolipid pathway.

[8] *Ezhov M, Safarova M, Afanasieva O et al.* **Matrix Metalloproteinase 9 as a Predictor of Coronary Atherosclerotic Plaque Instability in Stable Coronary Heart Disease Patients with Elevated Lipoprotein(a) Levels**. Biomolecules 2019; 9.

PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=30934954

ABSTRACT

We sought to investigate whether levels of matrix metalloproteinases (MMPs) and their inhibitors predict coronary atherosclerotic plaque instability, as assessed by intravascular ultrasound (IVUS) virtual histology during coronary angiography. Blood samples were collected before angiography in 32 subjects (mean age 56 +/- 8 years) with stable coronary heart disease (CHD) and elevated lipoprotein(a) (Lp(a), 94 +/- 35 mg/dL). Levels of high-sensitivity C-reactive protein (hsCRP), apolipoprotein B100 (apoB100), MMP-7, MMP-9, tissue inhibitor of metalloproteinases (TIMP)-1, and TIMP-2 were determined using commercially available enzyme-linked immunosorbent assay kits. Results. The morphology of a total of sixty coronary lesions was assessed by virtual histology IVUS imaging. Eleven (18%) plaques in nine (28%) patients were classified as plaques with an unstable phenotype or a thin-cap fibroatheroma. Age, low-density lipoprotein cholesterol, apoB100, MMP-7, and MMP-9 levels were positively associated with necrotic core volume. Conversely, there was a negative relationship between MMP-7 and -9 levels and fibrous and fibro-fatty tissue volume. Multivariate regression analysis revealed that MMP-9 is a strong independent predictor of atherosclerotic plaque instability in stable CHD patients. In stable CHD patients with elevated Lp(a), MMP-9 levels are positively associated with the size of the necrotic core of coronary atherosclerotic plaques.

[9] *Paseban M, Mohebbati R, Niazmand S et al.* **Comparison of the Neuroprotective Effects of Aspirin, Atorvastatin, Captopril and Metformin in Diabetes Mellitus**. Biomolecules 2019; 9.

PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=30934759

ABSTRACT

OBJECTIVE: The aim of this study was to investigate the effect of combined intake of a high dose of aspirin, atorvastatin, captopril and metformin on oxidative stress in the brain cortex and hippocampus of streptozotocin (STZ)-induced diabetic rats. MATERIAL AND METHODS: Rats were randomly divided into the following 11 groups: control and diabetic (D), as well as 9 groups that were treated with

metformin (M, 300 mg/kg) or aspirin (ASA, 120 mg/kg) alone or in different combinations with captopril (C, 50 mg/kg) and/or atorvastatin (AT, 40 mg/kg) as follows: (D + M), (D + ASA), (D + M + ASA), (D + M + C), (D + M + AT), (D + M + C + ASA), (D + M + C + AT), (D + M + AT + ASA) and (D + M + C + AT + ASA). The rats in treatment groups received drugs by gavage daily for six weeks. Serum lipid profile and levels of oxidative markers in the brain cortex and hippocampus tissues were evaluated. RESULTS: The levels of malondialdehyde in the brain cortex and hippocampus in all the treated groups decreased significantly ($p < 0.05$). There was a significant increase in the total thiol concentration as well as catalase activity in treated rats in (M + AT), (M + C + ASA), (M + C + AT), (M + AT + ASA) and (M + C + AT + ASA) groups in cortex and hippocampus in comparison with the diabetic rats ($p < 0.05$). Also, the superoxide dismutase activity in all treated rats with medications was significantly increased compared to the diabetic rats ($p < 0.05(-)0.01$). CONCLUSION: Our findings showed that the combined use of high-dose aspirin, metformin, captopril and atorvastatin potentiated their antioxidant effects on the brain, and hence could potentially improve cognitive function with their neuroprotective effects on hippocampus.

[10] *Koopal C, Bemelmans R, Marais AD, Visseren FL*. **Severe hypertriglyceridaemia and pancreatitis in a patient with lipoprotein lipase deficiency based on mutations in lipoprotein lipase (LPL) and apolipoprotein A5 (APOA5) genes**. BMJ case reports 2019; 12.

PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=30948399

ABSTRACT

A 44-year-old woman was admitted with pancreatitis caused by hypertriglyceridaemia (fasting triglycerides 28 mmol/L). She used oral contraceptives and ezetimibe 10 mg. She was overweight (body mass index 29.7 kg/m(2)). Diabetes mellitus was ruled out, as were nephrotic syndrome, alcohol abuse, hypothyroidism and dysbetalipoproteinaemia. Genetic analysis revealed mutations in two genes involved in triglyceride metabolism (apolipoprotein A5 and lipoprotein lipase [LPL]). The LPL activity was 45% compared with pooled healthy controls. The post-heparin triglyceride reduction was 6%, compared with a normal reduction of >20%. The patient was initially treated with gemfibrozil, but this was discontinued due to side effects. Dietary triglyceride restriction and discontinuation of the oral contraceptives lowered the plasma triglycerides within 2 weeks to 3.4 mmol/L. Hypertriglyceridaemia is a risk factor for pancreatitis and cardiovascular disease, and has a broad differential diagnosis including genetic causes. Patients can achieve near-normal triglyceride values with a low-fat diet only.

[11] *Jensen JS, Weeke PE, Bang LE et al.* **Clinical characteristics and lipid lowering treatment of patients initiated on proprotein convertase subtilisin-kexin type 9 inhibitors: a nationwide cohort study**. BMJ open 2019; 9:e022702.

PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=30940751

ABSTRACT

OBJECTIVES: Given the novelty of proprotein convertase subtilisin-kexin type 9 inhibitors (PCSK9i), little is known regarding overall implementation or clinical characteristics among patients who initiate treatment. We aimed to assess the total number of patients initiated on PCSK9i along with a description of the clinical characteristics and lipid lowering treatment (LLT) of such patients. SETTING: A register-based descriptive cohort study of patients receiving a PCSK9i in the time period from 01 January 2016 to 31 March 2017 using a cross linkage between three nationwide Danish registers. Information regarding PCSK9i prescriptions, patient demographics, concurrent pharmacotherapy, comorbidities and previous

coronary procedures was identified. RESULTS: Overall, 137 patients initiated treatment with PCSK9i in the study period from 11 in the first quarter of 2016 to 40 in the first quarter of 2017. The majority had a history of ischaemic heart disease (IHD) (67.9%) with ischaemic stroke and diabetes mellitus being present in 7.3% and 16.8% of patients, respectively. All patients initiated on PCSK9i had been previously prescribed statin treatment with atorvastatin and simvastatin being most frequently prescribed in 53% and 36% of patients, respectively. The majority of patients had received both statins and ezetimibe (94.9%) and approximately half of these patients had also received bile acid sequestrant (45.3%). Clinical characteristics mainly differed in patients receiving triple LLT compared with patients not receiving triple LLT in the regards of heart failure. CONCLUSION: Patients treated with PCSK9i were rare, characterised by having IHD and had received various and intensive conventional LLT prior to PCSK9i initiation in agreement with current international guidelines.

[12] *Souza AFP, Souza LL, Oliveira LS et al.* **Fish oil supplementation during adolescence attenuates metabolic programming of perinatal maternal high-fat diet in adult offspring**. The British journal of nutrition 2019:1-30.

PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=30940241

ABSTRACT

Perinatal maternal high-fat diet (HFD) increases susceptibility to obesity and fatty liver diseases in adult offspring, which can be attenuated by potent hypolipidemic action of fish oil (FO), an n-3 polyunsaturated fatty acid source, during adult life. Previously, we described that adolescent HFD offspring showed resistance to FO hypolipidemic effects, although FO promoted hepatic molecular changes suggestive of reduced lipid accumulation. Here, we investigated whether this FO intervention only during adolescence period could impact the offspring metabolism in adulthood. Then, female Wistar rats received isoenergetic, standard (STD:9% fat) or high-fat (HFD:28.6% fat) diet before mating, and throughout pregnancy and lactation. After weaning, male offspring received standard diet; and from 25- to 45 days-old they received oral administration of soybean oil (SO) or FO. At 150 days-old, serum and hepatic metabolic parameters were evaluated. Maternal HFD adult offspring showed increased body weight, visceral adiposity, hyperleptinemia and decreased hepatic pSTAT3/ STAT3 ratio, suggestive of hepatic leptin resistance. FO intake only during adolescence period reduced visceral adiposity and serum leptin, regardless of maternal diet. Maternal HFD promoted dyslipidemia and hepatic triglyceride accumulation, which was correlated to reduced hepatic CPT-1a content, suggesting lipid oxidation impairment. FO intake did not change serum lipids; however, it restored hepatic triglyceride content and hepatic markers of lipid oxidation to STD offspring levels. Therefore, we concluded that FO intake exclusively during adolescence programmed STD offspring and reprogrammed HFD offspring male rats to a healthier metabolic phenotype at adult life, reducing visceral adiposity, serum leptin and hepatic triglycerides content in offspring adulthood.

[13] *Temple NJ, Guercio V, Tavani A*. **The Mediterranean Diet and Cardiovascular Disease: Gaps in the Evidence and Research Challenges**. Cardiology in review 2019; 27:127-130.

PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=30946700

ABSTRACT

In this article, we critically evaluate the evidence relating to the effects of the Mediterranean diet (MD) on the risk of cardiovascular disease (CVD). Strong evidence indicating that the MD prevents CVD has

come from prospective cohort studies. However, there is only weak supporting evidence from randomized controlled trials (RCTs) as none have compared subjects who follow an MD and those who do not. Instead, RCTs have tested the effect of 1 or 2 features of the MD. This was the case in the Prevenciomicronn con Dieta Mediterranea (PREDIMED) study: the major dietary change in the intervention groups was the addition of either extravirgin olive oil or nuts. Meta-analyses generally suggest that the MD causes small favorable changes in risk factors for CVD, including blood pressure, blood glucose, and waist circumference. However, the effect on blood lipids is generally weak. The MD may also decrease several biomarkers of inflammation, including C-reactive protein. The 7 key features of the MD can be divided into 2 groups. Some are clearly protective against CVD (olive oil as the main fat; high in legumes; high in fruits/vegetables/nuts; and low in meat/meat products and increased in fish). However, other features of the MD have a less clear relationship with CVD (low/moderate alcohol use, especially red wine; high in grains/cereals; and low/moderate in milk/dairy). In conclusion, the evidence indicates that the MD prevents CVD. There is a need for RCTs that test the effectiveness of the MD for preventing CVD. Key design features for such a study are proposed.

[14] *Zareh M, Katul R, Mohammadi H*. **Mechanics of Atherosclerotic Plaques: Effect of Heart Rate**. Cardiovascular engineering and technology 2019.

PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=30949919

ABSTRACT

PURPOSE: Atherosclerotic plaques are highly heterogeneous, nonlinear materials with uncharacteristic structural behaviors. It is well known that mechanics of atherosclerotic plaques significantly depend on plaque geometry, location, composition, and loading conditions. There is no question that atherosclerotic plaques are viscoelastic. Plaques are characterized as the buildup of low-density lipoprotein cholesterol, macrophages, monocytes, and foam cells at a place of inflammation inside arterial walls. Lipid core and fibrous cap are the two major ingredients that are frequently used for the identification of main constituting quantities of atherosclerotic plaques. The lipid core contains of debris from dead cells, esterified cholesterol and cholesterol crystals. The fibrous cap contains smooth muscle cells and collagen fibers. All these materials contribute to the viscoelastic properties of atherosclerotic plaques. Computational studies have shown great potential to characterize this mechanical behavior. Different types of plaque morphologies and mechanical properties have been used in a computational platform to estimate the stability of rupture-prone plaques and detect their locations. In this study for the first time to the best of authors' knowledge, we hypothesize that heart rate is also one of the major factors that should be taken into account while mechanics of plaques is studied. METHOD: We propose a tunable viscoelastic constitutive material model for the fibrous cap tissue in order to calculate the peak cap stress in normal physiological (dynamic) conditions while heart rate changes from 60 bpm to 150 bpm in 2D plane stress models. A critical discussion on stress distribution in the fibrous cap area is made with respect to heart rate for the first time. RESULTS: Results strongly suggest the viscoelastic properties of the fibrous cap tissue and heart rate together play a major role in the estimation of the pick cap stress values. CONCLUSIONS: The results of current study may provide a better understanding on the mechanics of vulnerable atherosclerotic plaques and that any experimental methods assessing the viscoelasticity of plaque composition during progression are highly desirable.

[15] *Patel C, Thompson C, Copley-Harris M, Hattab Y*. **Sitagliptin and Simvastatin Interaction Causing Rhabdomyolysis and AKI**. Case reports in medicine 2019; 2019:2601537.

PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=30936920

ABSTRACT

We report a case of rhabdomyolysis and severe acute kidney injury (AKI) requiring dialysis in a 69-year-old male who was recently started on sitagliptin while on chronic simvastatin therapy. This potential interaction is not included in the package insert for sitagliptin. A comprehensive literature review revealed six previous reports of rhabdomyolysis due to drug interaction between sitagliptin and statins including simvastatin, lovastatin, and atorvastatin. Of these six cases, only two had developed rhabdomyolysis-associated AKI, none of which were severe enough to require dialysis. As patients are commonly prescribed statins and sitagliptin for treatment of dyslipidemia and diabetes, health care professionals should be aware of this potential drug interaction and closely monitor their patients for signs and symptoms of rhabdomyolysis and AKI. This case highlights the importance of conducting further studies on the risk of muscular toxicity of sitagliptin especially when administered concurrently with statins.

[16] *Hirayama A, Yamashita S, Ruzza A et al.* **Long-Term Treatment With Evolocumab Among Japanese Patients- Final Report of the OSLER Open-Label Extension Studies**. Circulation journal : official journal of the Japanese Circulation Society 2019.

PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=30930429

ABSTRACT

BACKGROUND: Treatment with evolocumab reduces mean low-density lipoprotein cholesterol (LDL-C) up to 75% and cardiovascular events by 16% in the first year and 25% thereafter. Methods and Results: Japanese patients with hypercholesterolemia enrolled in the parent YUKAWA-1-2 studies could enroll, once eligible, in the OSLER studies (n=556). OSLER re-randomized patients 2:1 to evolocumab plus standard of care (SOC; evolocumab+SOC) or SOC alone for 1 year; after year 1, patients could enter the all-evolocumab+SOC open-label extension of OSLER. Patients received evolocumab+SOC from the 2nd year through up to 5 years. Long-term efficacy and safety, including antidrug antibodies, were evaluated. Of 556 patients, 532 continued to the all-evolocumab+SOC extension: mean (standard deviation [SD]) age 61 (10) years, 39% female. A total of 91% of 532 patients completed the studies. Mean (SD) LDL-C change from parent-study baseline with evolocumab from a mean (SD) baseline of 142.3 (21.3) and 105.0 (31.1) mg/dL in OSLER-1 and OSLER-2, respectively, was maintained through the end of the study: -58.0% (19.1%) at year 5 in OSLER-1, -62.7% (25.6%) at year 3 in OSLER-2. The overall safety profile of the evolocumab+SOC periods was similar to that of the year-1 controlled period. Antidrug antibodies were detected transiently in 3 patients. No neutralizing antibodies were detected. CONCLUSIONS: Japanese patients who continued evolocumab+SOC for up to 5 years experienced sustained high LDL-C level reduction. Long-term evolocumab+SOC exposure showed no new safety signals.

[17] **Correction to: High-Dose Versus Low-Dose Pitavastatin in Japanese Patients With Stable Coronary Artery Disease (REAL-CAD)**. Circulation 2019; 139:e836.

PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=30933616

ABSTRACT

Literature update week 14 (2019)

[18] *Cao J, Devaraj S*. **Recent AHA/ACC guidelines on cholesterol management expands the role of the clinical laboratory**. Clinica chimica acta; international journal of clinical chemistry 2019.

PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=30953613

ABSTRACT

The American Heart Association (AHA) and American College of Cardiology (ACC) recently published new guidelines on managing blood cholesterol. Five years from the publication of Pooled Cohort Equation to estimate 10-year risk of atherosclerotic cardiovascular disease (ASCVD), the newest guidelines put more focus on individualized risk assessment which necessitates increased participation of laboratory medicine in the prevention and management of ASCVD. This mini-review summarizes key ideas from the new guideline that influence laboratory practice, including the renewed low-density lipoprotein cholesterol (LDL-C) treatment targets in primary and secondary prevention, the use of non-fasting lipids, new calculations of LDL cholesterol, and recommendations on assessing risk-enhancing factors in certain populations to aid the decision on statin and non-statin therapy. The shift in strategies for monitoring and lowering LDL-C has created opportunities for clinical laboratorians to more actively contribute to better identification of individuals at risk for ASCVD and partner with physicians taking care of the patient.

[19] *Weingartner O, Lutjohann D, Meyer S et al.* **Low serum lathosterol levels associate with fatal cardiovascular disease and excess all-cause mortality: a prospective cohort study**. Clinical research in cardiology : official journal of the German Cardiac Society 2019.

PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=30949753

ABSTRACT

IMPORTANCE: A more precise identification of patients at "high cardiovascular risk" is preeminent in cardiovascular risk stratification. OBJECTIVE: To investigate the relationships between markers of cholesterol homeostasis, cardiovascular events and all-cause mortality. DESIGN, SETTING AND PARTICIPANTS: We quantified markers of cholesterol homeostasis by gas chromatography-mass spectrometry in 377 subjects with suspected coronary artery disease, who were not on lipid-lowering drugs at baseline. All patients were followed for occurrence of cardiovascular events and mortality over a period of 4.9 +/- 1.7 years. The standardized mortality ratio (SMR) was calculated as the ratio of the observed and the expected deaths based on the death rates of the Regional Databases Germany, and Poisson regression (rate ratio, RR) was used to compare subgroups. The SMR and RR were standardized for sex, age category and calendar period. In addition, Cox regression (Hazard ratio, HR) was used to determine the effect of co-variables on (cardiovascular) mortality within the cohort. MAIN OUTCOMES: Cardiovascular events, cardiovascular mortality and all-cause mortality. RESULTS: A total of 42 deaths were observed in 1818 person-years corresponding with an SMR of 0.99 (95% CI 0.71-1.33; p = 0.556). A fatal cardiovascular event occurred in 26 patients. Lower levels of lathosterol were associated with increased cardiovascular mortality (HR 1.59; 95% CI: 1.16-2.17; p = 0.004) and excess all-cause mortality (HR 1.41; 95% CI: 1.09-1.85; p = 0.011). Lower lathosterol tertile compared to the adjacent higher tertile was associated with 1.6 times higher all-cause mortality risk (RR 1.60; 95% CI 1.07-2.40; p for trend = 0.022). This corresponded with a 2.3 times higher mortality risk of a lathosterol-LDL ratio equal to or below the median (RR 2.29; 95% CI 1.19-4.43; p = 0.013). None of the other cholesterol homeostasis markers were associated with cardiovascular and all-cause mortality. CONCLUSIONS: In patients not on lipid-lowering agents, low serum lathosterol correlated with increased risk of cardiovascular events and excess all-cause mortality.

[20] *Zhu Y, Meng Y, Zhao Y et al.* **Toxicological exploration of peptide-based cationic liposomes in siRNA delivery**. Colloids and surfaces. B, Biointerfaces 2019; 179:66-76.

PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=30947085

ABSTRACT

The toxicology of cationic liposomes was explored to advance clinical trials of liposome-mediated gene therapy through the analysis of a peptide cationic liposome with DOTAP as a positive control. We first investigated the delivery of luciferase siRNA by several peptide liposomes in mice bearing lung cancer A549 cell xenografts. Of these, a cationic liposome (CDO14) was selected for further investigation. CDO14 efficiently mediated IGF-1R-siRNA delivery and inhibited the growth of the A549 cell xenografts. The in vivo toxicity and toxicological mechanisms of the selected liposome were evaluated to assess its potential utility for gene delivery. Specifically, the effects of CDO14 on mouse body weight, hematology, urine, serum biochemical indices, and histopathology were measured in acute toxicity and subchronic toxicity tests. CDO14 showed limited toxicological effects at low dosages although it induced pulmonary inflammation and liver injury at higher dosages. The toxicity of CDO14 was lower than that of DOTAP, and the toxicity of CDO14 did not change when complexed with siRNA. The pulmonary inflammation induced by CDO14 occurred via expressional up-regulation of the pro-inflammatory cytokines TNF-alpha and IL-6, and expressional down-regulation of the anti-inflammatory cytokine IL-10. Liver injury induced by CDO14 was mediated by the JAK2-STAT3 signaling pathway. Lastly, CDO14 did not affect the expression of apoptosis-related proteins in normal liver cells, suggesting that it did not induce apoptosis of normal cells. The toxicological results demonstrate that peptide-based headgroups in lipids are superior to those with quaternary ammonium headgroups that are used as gene vectors for cancer therapy.

[21] *Jia X, Al Rifai M, Birnbaum Y et al.* **The 2018 Cholesterol Management Guidelines: Topics in Secondary ASCVD Prevention Clinicians Need to Know**. Current atherosclerosis reports 2019; 21:20.

PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=30941517

ABSTRACT

PURPOSE OF REVIEW: The 2018 ACC/AHA Multisociety blood cholesterol guidelines provide updated recommendations based on contemporary evidence on the management of serum cholesterol for the prevention of atherosclerotic cardiovascular disease (ASCVD) events. This review discusses clinically important topics in the new guidelines related to secondary ASCVD prevention. RECENT FINDINGS: Since the 2013 ACC/AHA blood cholesterol guidelines, several large randomized control trials involving ezetimibe and proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitors (evolocumab and alirocumab) have been published. The trials provided evidence that these non-statin, LDL-cholesterol lowering agents are efficacious in reducing risk for ASCVD events in patients with clinical ASCVD. The 2018 guidelines incorporate these new findings into updated clinical recommendations on therapeutic strategies related to the use of ezetimibe and PCSK9 inhibitors. The guidelines also recommend risk stratification of secondary prevention patients to identify those at very high-risk of ASCVD events as these patients would derive the most absolute risk reduction from the addition of non-statin therapies. While high-intensity statins remain the first-line treatment to prevent recurrent ASCVD events in secondary prevention patients, ezetimibe and PCSK9 inhibitors are evidence-based non-statin agents that can be used when residual on top of maximally tolerated statin therapy in patients deemed to be at very-high risk of recurrent ASCVD events.

Literature update week 14 (2019)

[22] *Golbabapour S, Bagheri-Lankarani K, Ghavami S, Geramizadeh B*. **Autoimmune Hepatitis and Stellate Cells; an Insight into the Role of Autophagy**. Curr Med Chem 2019.

PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=30947648

ABSTRACT

Autoimmune hepatitis is a necroinflammatory process of liver, featuring interface hepatitis by T cells, macrophages and plasma cells that invade to periportal parenchyma. In this process a variety of cytokines is secreted and liver tissue undergoes fibrogenesis, that cause apoptosis of hepatocytes. Autophagy is a complementary mechanism for restraining intracellular pathogens to which the innate immune system does not provide an efficient endocytosis. Hepatocytes with their particular regenerative features are normally in a quiescent state, and, autophagy controls the accumulation of excess products, therefore the liver serves as a basic model for the study of autophagy. Impairment of autophagy in liver causes the accumulation of damaged organelles, misfolded proteins and exceeded lipids in hepatocytes as seen in metabolic diseases. In this review, we introduce autoimmune hepatitis in association with autophagy signaling. We also discuss some genes and proteins of autophagy, their regulatory roles in activation of hepatic stellate cells and the importance of lipophagy and tyrosine kinase in hepatic fibrogenesis. In order to provide a comprehensive overview on the regulatory role of autophagy in autoimmune hepatitis, a pathway analysis of autophagy in autoimmune hepatitis is also included in this article.

[23] *Tan YL, Ou HX, Zhang M et al.* **Tanshinone IIA promotes macrophage cholesterol efflux and attenuates atherosclerosis of apoE-/- mice by Omentin-1/ABCA1 pathway**. Current pharmaceutical biotechnology 2019.

PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=30947667

ABSTRACT

Background Tanshinone IIA (Tan IIA) and Omentin-1 have a protective role in the cardiovascular system. However, if and how Tan IIA and Omentin-1 regulate cholesterol metabolism in macrophages has not been fully elucidated. OBJECTIVE: To investigate the possible mechanisms of Tan IIA and Omentin-1 on preventing macrophage cholesterol accumulation and atherosclerosis development. METHODS: The effect of Tan IIA on the protein and mRNA levels of Omentin-1 and ATP-binding cassette transporter A1 (ABCA1) in macrophages was examined by Western blot and qRT-PCR assay, respectively. Cholesterol efflux was assessed by liquid scintillation counting (LSC). Cellular lipid droplet was measured by Oil Red O staining, and intracellular lipid content was detected by high performance liquid chromatography (HPLC). In addition, the serum lipid profile of apoE-/- mice was measured by an enzymatic method. The size of atherosclerotic lesion areas and content of lipids and collagen in the aortic of apoE-/- mice were examined by sudan IV, Oil-red O, and Masson staining, respectively. RESULTS: Tan IIA up-regulated expression of Omentin-1 and ABCA1 in THP-1 macrophages, promoting ABCA1-mediated cholesterol efflux and consequently decreasing cellular lipid content. Consistently, Tan IIA increased reverse cholesterol transport in apoE-/- mice. Plasma levels of high-density lipoprotein cholesterol (HDL-C), ABCA1 expression and atherosclerotic plaque collagen content were increased while plasma levels of low-density lipoprotein cholesterol (LDL-C) and atherosclerotic plaque sizes were reduced in Tan IIA-treated apoE-/- mice. These beneficial effects were, however, essentially blocked by knockdown of Omentin-1. CONCLUSIONS: Our results revealed that Tan IIA promotes cholesterol efflux and

ameliorates lipid accumulation in macrophages most likely via the Omentin-1/ABCA1pathway, reducing the development of aortic atherosclerosis.

[24] *Dabbous Z, Bashir M, Elzouki AN et al.* **Differential effects of gender and patient background diversity on the changes in metabolic and biophysical profiles in people with type-2 diabetes from different ethnicities who fast during Ramadan (H1439); a prospective study from Qatar**. Diabetes Res Clin Pract 2019.

PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=30930290

ABSTRACT

OBJECTIVE: The 'PROspective Study of dose adjustment of multiple anti-diabetic therapy for Type-2 diabetic patients FASTing the Month of Ramadan aimed to assess the biophysical and metabolic effects of fasting during Ramadan, including HbA1c, weight, blood pressure and lipid profile. STUDY DESIGN METHODS: We performed a prospective study of people with Type-2 diabetes who were on >/=3 drugs for lowering glucose before and after Ramadan of H1438 (May-June 2017) in Hamad Medical Corporation, Qatar. We enrolled 228 participants, of whom 181 completed the study and were included in the analysis. RESULTS: There were 115 (63.5%) men and 66 (36.5%) women, mean age 53.6+/-9.7years and mean diabetes duration of 10+/-6years. Both HBA1c [7.8% (62mmol/mol) vs. 7.6% (60mmol/mol); p=0.004]; and diastolic BP (75.7+/-8.55 vs. 68.8+/-23.1mmHg, P=0.001) improved significantly after Ramadan while there was an increase in total cholesterol (3.94+/-0.89mmol/l vs 4.11+/-1.02mmol/l; p=0.008) and triglycerides (1.55+/-0.72mmol/l vs 1.71+/-0.9mmol/l; p=0.012). Subgroup analysis showed that patients on sulphonylurea, South Asians and males had a significant reduction in both HBA1c and weight. CONCLUSION: Patients with Type 2 diabetes who fast during Ramadan show an improvement in glycaemic control and diastolic blood pressure, but a worsening of total cholesterol and triglycerides, particularly those of South Asian origin and men.

[25] *Rosenson RS, Daviglus ML, Handelsman Y et al.* **Efficacy and safety of evolocumab in individuals with type 2 diabetes mellitus: primary results of the randomised controlled BANTING study**. Diabetologia 2019.

PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=30953107

ABSTRACT

AIMS/HYPOTHESIS: The study aimed to examine the efficacy of 12 weeks of monthly evolocumab or placebo in lowering LDL-cholesterol (LDL-C) in individuals with type 2 diabetes and hypercholesterolaemia or mixed dyslipidaemia and on a maximum-tolerated statin of at least moderate intensity. METHODS: For this randomised, placebo-controlled outpatient study, eligible individuals were >/=18 years old with type 2 diabetes, HbA1c <10% (86 mmol/mol), had been on stable pharmacological therapy for diabetes for >/=6 months and were taking a maximum-tolerated statin dose of at least moderate intensity. Lipid eligibility criteria varied by history of clinical cardiovascular disease. Participants were randomised 2:1 to evolocumab 420 mg s.c. or placebo. Randomisation was performed centrally via an interactive web-based or voice recognition system. Allocation was concealed using the centralised randomisation process. Treatment assignment was blinded to the sponsor study team, investigators, site staff and patients throughout the study. Co-primary endpoints were mean percentage change in LDL-C from baseline to week 12 and to the mean of weeks 10 and 12. Additional endpoints included LDL-C <1.81 mmol/l, LDL-C reduction >/=50% and other lipids. Exploratory analyses included

percentage changes in fasting and post mixed-meal tolerance test (MMTT) lipoproteins and lipids, glucose metabolism variables and inflammatory biomarkers. RESULTS: In total, 421 individuals were randomised and analysed, having received evolocumab (280 participants) or placebo (141 participants) (mean [SD] age 62 [8] years; 44% women; 77% white). Evolocumab decreased LDL-C by 54.3% (1.4%) at week 12 (vs 1.1% [1.9%] decrease with placebo; p < 0.0001) and by 65.0% (1.3%) at the mean of weeks 10 and 12 (vs 0.8% [1.8%] decrease with placebo; p < 0.0001); it also decreased non-HDL-cholesterol (HDL-C) by 46.9% (1.3%) at week 12 (vs 0.6% [1.8%] decrease with placebo) and by 56.6% (1.2%) at the mean of weeks 10 and 12 (vs 0.1% [1.6%] decrease with placebo). Evolocumab significantly improved levels of other lipids and allowed more participants to reach LDL-C <1.81 mmol/l or a reduction in LDL-C levels >/=50%. After an MMTT (120 min), there were favourable changes (p < 0.05; nominal, post hoc, no multiplicity adjustment) in chylomicron triacylglycerol (triglycerides), chylomicron cholesterol, VLDL-C and LDL-C. Evolocumab had no effect on glycaemic variables and was well tolerated. CONCLUSIONS/INTERPRETATION: In statin-treated individuals with type 2 diabetes and hypercholesterolaemia or mixed dyslipidaemia, evolocumab significantly reduced LDL-C and non-HDL-C. Favourable changes (p < 0.05) were observed in postprandial levels of chylomicrons, VLDL-C and LDL-C. TRIAL REGISTRATION: ClinicalTrials.gov NCT02739984 FUNDING: This study was funded by Amgen Inc. DATA AVAILABILITY: Qualified researchers may request data from Amgen clinical studies. Complete details are available at www.amgen.com/datasharing .

[26] *Konishi H, Shirakawa J, Arai M, Terauchi Y*. **Drug-induced hyperglycemia in the Japanese Adverse Drug Event Report database: association of evelolimus use with diabetes**. Endocrine journal 2019.

PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=30944270

ABSTRACT

Some categories of drugs are known for causing hyperglycemia or diabetes such as steroids, antipsychotics, and immunosuppressant. However, there has been little evidence from studies about the proportion of each drug in the context of drug-induced diabetes. In this study, we used data from the Japanese Adverse Drug Event Report (JADER) database, a spontaneous reporting system database maintained at the Pharmaceuticals and Medical Devices Agency (PMDA) of Japan, reported between April 2004 and June 2017. Among 459,250 reports of adverse drug reactions in JADER database, reported instances of the adverse event of hyperglycemia or diabetes were extracted. After the exclusion of anti-diabetes drugs, the drugs frequently implicated in the development of hyperglycemia or diabetes, including prednisolone, tacrolimus, everolimus, ribavirin, quetiapine, aripiprazole, interferon alfa-2b, risperidone, atorvastatin, dexamethasone, ciclosporin, nilotinib, methylprednisolone, or nivolumab, were identified. Everolimus, a mammalian target of rapamycin (mTOR) inhibitor, was manifested as the third most frequently associated drug with hyperglycemia or diabetes (340 cases), following prednisolone (694 cases) and tacrolimus (393 cases), and the reporting odds ratio (ROR 8.56, 95% CI 7.65-9.57) of this drug was higher than that of the two aforementioned drugs (ROR 3.96, 95% CI 3.66-4.28 and ROR 3.51, 95% CI 3.17-3.89). These results suggest that there is a potent association of evelolimus with hyperglycemia in clinical practice in Japan.

[27] *Corsini A*. **Statin-associated muscle symptoms: is Proprotein convertase subtilisin/kexin type 9 inhibitors a therapeutic option?** European heart journal supplements : journal of the European Society of Cardiology 2019; 21:B48-b49.

PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=30948945

ABSTRACT

[28] *Prati F, Ruscica G, Marco V, Albertucci M*. **'Precision medicine' and ischaemic heart disease: the stage is set for the new antibody based therapies (lipid lowering and anti-inflammatory)**. European heart journal supplements : journal of the European Society of Cardiology 2019; 21:B73-b75.

PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=30948956

ABSTRACT

Improving cardiovascular risk assessment requires a 'personalized' approach. Appraisal of well-known cardiovascular risk factors should be integrated with markers of cardiovascular risk such as LDL cholesterol (C-LDL) and C-reactive protein (CRP). Results of the recent trials of PCSK9 inhibitor monoclonal antibodies open new interesting perspective. Data regarding the use of Evolocumab, in secondary prevention settings, in high-risk patients are very encouraging. In the same vein, the CANTOS study demonstrated, for the first time, that Canakinumbab, an antibody with anti-inflammatory action (with no effects on C-LDL levels), decreases significantly the risk of major cardiovascular events in a high-risk population with elevated CRP and optimal C-LDL. This trial, for the first time, suggested a strategy distinguishing the anti-inflammatory from the cholesterol lowering component, thus differentiating the treatment. In the ensuing years, we will probably witness the clinical application of this concept.

[29] *Olmos-Martinez JM, Molina H, Salas C et al.* **Acute Colchicine-induced Neuromyopathy in a Patient Treated with Atorvastatin and Clarithromycin**. European journal of case reports in internal medicine 2019; 6:001066.

PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=30931282

ABSTRACT

Neuromyopathy is a rare side effect of chronic colchicine therapy, especially without renal impairment. Drugs interacting with colchicine metabolism through CYP3A4 can accelerate accumulation and toxicity. We describe a case of an interaction between atorvastatin, clarithromycin and colchicine resulting in acute neuromyopathy. LEARNING POINTS: Colchicine has a narrow therapeutic window, and therefore, often produces side effects.Special caution should be adopted if patients with renal disease and concomitant medications are given colchicine.Before prescribing colchicine, the clinical history, including previous medications and conditions, should be carefully considered.

[30] *Khoury E, Brisson D, Roy N et al.* **Review of the long-term safety of lomitapide: a microsomal triglycerides transfer protein inhibitor for treating homozygous familial hypercholesterolemia**. Expert opinion on drug safety 2019.

PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=30945578

ABSTRACT

INTRODUCTION: Homozygous familial hypercholesterolemia (HoFH) is a rare and life-threatening lipid disorder characterized by extremely elevated low-density lipoprotein-cholesterol (LDL-C) concentrations and premature atherosclerotic cardiovascular disease (CVD). Conventional lipid-lowering agents remain insufficient in managing this disease, which emphasize the unmet medical need for potential therapies capable of lowering LDL-C and decreasing CVD risk in this patient population. Areas covered: Novel LDL

receptor (LDLR) independent drugs have been recently approved or are in development for the treatment of HoFH, including lomitapide (Juxtapid(R)). This oral microsomal triglyceride transfer protein (MTP) inhibitor was approved in 2012 in several countries as an adjunct to a low-fat diet and other lipid-lowering drugs with or without LDL apheresis to treat patients with HoFH. This review summarizes key safety and efficacy data of lomitapide from clinical trials and "real-life" experience. Expert opinion: While lomitapide is an interesting therapy for treating HoFH, long-term safety as well as cardiovascular outcome data are yet to be provided. Precision medicine has recently contributed to the development of several agents designed to address the unmet medical need of HoFH. However, combining safety, efficacy, accessibility and affordability in a single therapy constitutes very challenging individual and societal paradigms in HoFH treatment.

[31] *Polychronopoulos G, Tziomalos K*. **What special considerations must be made for the pharmacotherapeutic management of heterozygous familial hypercholesterolemia?** Expert opinion on pharmacotherapy 2019:1-6.

PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=30933542

ABSTRACT

[32] *Christie CF, Fang D, Hunt EG et al.* **Statin-dependent modulation of mitochondrial metabolism in cancer cells is independent of cholesterol content**. FASEB journal : official publication of the Federation of American Societies for Experimental Biology 2019:fj201802723R.

PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=30951369

ABSTRACT

Statins, widely used to treat hypercholesterolemia, inhibit the 3-hydroxy-3-methylglutaryl-coenzyme A reductase, the rate-limiting enzyme of de novo cholesterol (Chol) synthesis. Statins have been also reported to slow tumor progression. In cancer cells, ATP is generated both by glycolysis and oxidative phosphorylation. Mitochondrial membrane potential (DeltaPsi), a readout of mitochondrial metabolism, is sustained by the oxidation of respiratory substrates in the Krebs cycle to generate NADH and flavin adenine dinucleotide, which are further oxidized by the respiratory chain. Here, we studied the short-term effects of statins (3-24 h) on mitochondrial metabolism on cancer cells. Lovastatin (LOV) and simvastatin (SIM) increased DeltaPsi in HepG2 and Huh7 human hepatocarcinoma cells and HCC4006 human lung adenocarcinoma cells. Mitochondrial hyperpolarization after LOV and SIM was dose and time dependent. Maximal increase in DeltaPsi occurred at 10 microM and 24 h for both statins. The structurally unrelated atorvastatin also hyperpolarized mitochondria in HepG2 cells. Cellular and mitochondrial Chol remained unchanged after SIM. Both LOV and SIM decreased basal respiration, ATP-linked respiration, and ATP production. LOV and SIM did not change the rate of lactic acid production. In summary, statins modulate mitochondrial metabolism in cancer cells independently of the Chol content in cellular membranes without affecting glycolysis.-Christie, C. F., Fang, D., Hunt, E. G., Morris, M. E., Rovini, A., Heslop, K. A., Beeson, G. C., Beeson, C. C., Maldonado, E. N. Statin-dependent modulation of mitochondrial metabolism in cancer cells is independent of cholesterol content.

[33] *Zhong S, Li L, Shen X et al.* **An update on lipid oxidation and inflammation in cardiovascular diseases**. Free radical biology & medicine 2019.

Literature update week 14 (2019)

PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=30946962

ABSTRACT

Cardiovascular diseases (CVD), including ischemic heart diseases and cerebrovascular diseases, are the leading causes of morbidity and mortality worldwide. Atherosclerosis is the major underlying factor for most CVD. It is well-established that oxidative stress and inflammation are two major mechanisms leading to atherosclerosis. Under oxidative stress, polyunsaturated fatty acids (PUFA)-containing phospholipids and cholesterol esters in cellular membrane and lipoproteins can be readily oxidized through a free radical-induced lipid peroxidation (LPO) process to form a complex mixture of oxidation products. Overwhelming evidence demonstrates that these oxidized lipids are actively involved in the inflammatory responses in atherosclerosis by interacting with immune cells (such as macrophages) and endothelial cells. In addition to lipid lowering in the prevention and treatment of atherosclerotic CVD, targeting chronic inflammation has been entering the medical realm. Clinical trials are under way to lower the lipoprotein (a) (Lp(a)) and its associated oxidized phospholipids, which will provide clinical evidence that targeting inflammation caused by oxidized lipids is a viable approach for CVD. In this review, we aim to give an update on our understanding of the free radical oxidation of LPO, analytical technique to analyze the oxidation products, especially the oxidized phospholipids and cholesterol esters in low density lipoproteins (LDL), and focusing on the experimental and clinical evidence on the role of lipid oxidation in the inflammatory responses associated with CVD, including myocardial infarction and calcific aortic valve stenosis. The challenges and future directions in understanding the role of LPO in CVD will also be discussed.

[34] *Chen P, Chen X, Zhang S.* **Current Status of Familial Hypercholesterolemia in China: A Need for Patient FH Registry Systems**. Front Physiol 2019; 10:280.

PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=30949068

ABSTRACT

Background: Familial hypercholesterolemia (FH) greatly facilitates the development of cardiovascular disease (CVD). Without timely treatment, the incidence of coronary heart disease (CHD) in patients with FH is 3 to 4 times that in non-FH patients, and the onset of CVD would be advanced by approximately 10 years. There is ample evidence that the diagnosis and adequate treatment of FH are not properly considered for all ethnicities. The monogenic cause of FH includes apolipoprotein B (APOB), low-density lipoprotein receptor (LDLR), and proprotein convertase subtilisin/kexin 9 (PCSK9). There are approximately 2,765,420 to 6,913,550 cases of potential heterozygous FH (HeFH) and 2,205 to 4,609 cases of potential homozygous FH (HoFH) in China. Nevertheless, China lacks clinical diagnostic criteria specific to Chinese patients, such that most FH patients cannot be diagnosed until middle age or after their first cardiovascular event, thus precluding early treatment. Objective: This article explores the gene mutations, diagnosis and treatment of FH patients in China. Following the implementation of the two-child policy, there is a need to establish Chinese FH registry systems and genetic databases and to address the challenges in conducting cascade screening and long-term management. Conclusion: Advocating the establishment of FH registry systems and databases is an important rate-limiting step in improving long-term prognosis in FH patients, so that joint efforts of clinical experts and public communities are required. We recommend a process flow from case identification to entry into the registry system, and the widespread use of the system in clinical applications can provide the best treatment guidance for medical practice.

Literature update week 14 (2019)

[35] *Esteban-Fernandez A, Bover-Freire R, Guinea-Lopez R, Facila L*. **Impaired blood glucose levels in patients with dyslipidemia: what are the therapeutic implications? The PREVENDIAB study**. Future cardiology 2019.

PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=30950289

ABSTRACT

AIM: Dyslipidemia and diabetes are two of the main cardiovascular risk factors due to their impact and high prevalence. The aim of this study was to analyze the prevalence of impaired glucose metabolism in dyslipidemic patients attending the cardiology department. PATIENTS & METHODS: This was a multicenter, cross-sectional, observational epidemiological study that consecutively enrolled the first ten dyslipidemic patients who attended the cardiology outpatient clinic. To find associated factors between variables, a bivariate analysis was performed, using a Student's t-test and a Fisher's exact test. RESULTS: From the 490 analyzed patients, 67.4% of them presented impaired blood glucose levels, 39.2% with DM and 28.1% with prediabetes. CONCLUSION: More than half of the patients presented alterations of the glucose metabolism, very few reached a good metabolic control and a great number were found polymedicated.

[36] *Davila-Fajardo CL, Diaz-Villamarin X, Antunez-Rodriguez A et al.* **Pharmacogenetics in the Treatment of Cardiovascular Diseases and Its Current Progress Regarding Implementation in the Clinical Routine**. Genes 2019; 10.

PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=30939847

ABSTRACT

There is a special interest in the implementation of pharmacogenetics in clinical practice, although there are some barriers that are preventing this integration. A large part of these pharmacogenetic tests are focused on drugs used in oncology and psychiatry fields and for antiviral drugs. However, the scientific evidence is also high for other drugs used in other medical areas, for example, in cardiology. In this article, we discuss the evidence and guidelines currently available on pharmacogenetics for clopidogrel, warfarin, acenocoumarol, and simvastatin and its implementation in daily clinical practice.

[37] *Hong FF, Liang XY, Liu W et al.* **Roles of eNOS in atherosclerosis treatment**. Inflammation research : official journal of the European Histamine Research Society ... [et al.] 2019.

PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=30937466

ABSTRACT

BACKGROUND: Atherosclerosis (AS) is the main pathogeny of coronary heart disease, cerebral infarction and peripheral vascular disease. Endothelial dysfunction is one of the important pathogenesis of AS. As an important endothelium-derived relaxation factor, nitric oxide (NO) plays a role in cardiovascular protection and anti-AS function; but in the pathological state, endothelial nitric oxide synthase (eNOS) disorder causes an abnormal production of NO, which may damage endothelial function and trigger AS. This review summarized the research progresses in the treatment strategies for AS based on correcting the disordered eNOS/ NO signaling pathway. MAIN BODY: According to the topic, select the search terms 'atherosclerosis,' 'nitric oxide,' 'eNOS,' 'treatment,' 'management,' 'medication,' 'maintenance,' 'remission'. Using these terms, a structured literature search via multiple electronic databases was

performed for the most recent trial evidence in recent years. We read and analyze these literatures carefully, classified these literatures according to their content, and then summarized and outlined the common main points in these classified literatures. Finally, literature data were organized to discuss these main points logically. We found that both aberrant expression and dysfunction of eNOS are closely related to AS development, and some new treatment strategies aimed at eNOS have been proposed, including upregulation of eNOS expression and inhibition of eNOS uncoupling. The former one is mainly related to inflammatory inhibition and protection of the PKB-eNOS signaling pathway; whereas the latter one is associated with the addition of the L-arginine substrate of eNOS, arginase inhibition, and the supplement of tetrahydrobiopterin, which can elevate no level. CONCLUSIONS: eNOS can be an important target for prevention and treatment of AS, and eNOS drugs may be another potent class of effective therapeutic treatment for AS following traditional lipid-lowering, anti-platelet, vasodilator drugs. But applying these experimental results to clinic treatment still requires further studies and development of biotechnology.

[38] *Yin N, Zhang H, Ye R et al.* **Fluvastatin Sodium Ameliorates Obesity through Brown Fat Activation**. International journal of molecular sciences 2019; 20.

PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=30939798

ABSTRACT

Brown adipose tissue (BAT), an organ that burns energy through uncoupling thermogenesis, is a promising therapeutic target for obesity. However, there are still no safe anti-obesity drugs that target BAT in the market. In the current study, we performed large scale screening of 636 compounds which were approved by Food and Drug Administration (FDA) to find drugs that could significantly increase uncoupling protein 1 (UCP1) mRNA expression by real-time PCR. Among those UCP1 activators, most of them were antibiotics or carcinogenic compounds. We paid particular attention to fluvastatin sodium (FS), because as an inhibitor of the cellular hydroxymethyl glutaryl coenzyme A (HMG-CoA) reductase, FS has already been approved for treatment of hypercholesteremia. We found that in the cellular levels, FS treatment significantly increased UCP1 expression and BAT activity in human brown adipocytes. Consistently, the expression of oxidative phosphorylation-related genes was significantly increased upon FS treatment without differences in adipogenic gene expression. Furthermore, FS treatment resisted to high-fat diet (HFD)-induced body weight gain by activating BAT in the mice model. In addition, administration of FS significantly increased energy expenditure, improved glucose homeostasis and ameliorated hepatic steatosis. Furthermore, we reveal that FS induced browning in subcutaneous white adipose tissue (sWAT) known to have a beneficial effect on energy metabolism. Taken together, our results clearly demonstrate that as an effective BAT activator, FS may have great potential for treatment of obesity and related metabolic disorders.

[39] *Boulate G, Amazit L, Naman A et al.* **Potentiation of mitotane action by rosuvastatin: New insights for adrenocortical carcinoma management**. International journal of oncology 2019.

PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=30942448

ABSTRACT

Mitotane (also termed o,p'DDD) is the most effective therapy for advanced adrenocortical carcinoma (ACC). Mitotaneinduced dyslipidemia is treated with statins. Mitotane and statins are known to exert antiproliferative effects in vitro; however, the effects of statins have never been directly evaluated in

patients with ACC and ACC cells, at least to the best of our knowledge. Thus, in this study, we aimed to examine the effects of the rosuvastatin on ACC cells. It has been shown that the combined use of mitotane and statins significantly increases the tumor control rate in patients with ACC; however, it would be of interest to elucidate the molecular mechanisms involved in this potentiation. In this study, we examined the effects of mitotane, rosuvastatin and their combination in NCIH295R human ACC cells using proliferation assays, gene expression analyses and free intracellular cholesterol measurements. The results revealed that mitotane dosedependently reduced cell viability, induced apoptosis and increased intracellular free cholesterol levels, considered as one of the key features of mitotane action, while rosuvastatin alone reduced cell viability and increased apoptosis at high concentrations. We also demonstrated that rosuvastatin potentiated the effects of mitotane by reducing cell viability, inducing apoptosis, increasing intracellular free cholesterol levels, and by decreasing the expression of 3hydroxy3methylglutarylCoA reductase (HMGCR) and ATP binding cassette subfamily a member 1 (ABCA1), genes involved in cholesterol metabolism, and inhibiting steroidogenesis. Collectively, potentiating the effects of mitotane with the use of rosuvastatin may provide novel therapeutic strategies for ACC, given that the combination of these drugs, pending clinical validation, may lead to the better management of ACC.

[40] *Johnson K, Oparil S, Davis BR, Tereshchenko LG*. **Prevention of Heart Failure in Hypertension-Disentangling the Role of Evolving Left Ventricular Hypertrophy and Blood Pressure Lowering: The ALLHAT Study**. Journal of the American Heart Association 2019; 8:e011961.

PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=30943832

ABSTRACT

Background Hypertension is a known risk factor for heart failure (HF), possibly via the mechanism of cardiac remodeling and left ventricular hypertrophy (LVH). We studied the extent to which blood pressure (BP) change and evolving LVH contribute to the effect that lisinopril, doxazosin, and amlodipine have on HF compared with chlorthalidone. Methods and Results We conducted causal mediation analysis of ALLHAT (Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial) data (1994-2002; in-trial follow-up). ALLHAT participants with available serial ECG s and BP measurements were included (n=29 892; mean age 67+/-4 years; 32% black; 56% men): 11 008 were randomized to chlorthalidone, 5967 to doxazosin, 6593 to amlodipine, and 6324 to lisinopril. Evolving ECG LVH and BP lowering served as mediators. Incident symptomatic HF was the primary outcome. Linear regression (for mediator) and logistic regression (for outcome) models were adjusted for mediator-outcome confounders (demographic and clinical characteristics known to be associated both with both LVH /hypertension and HF). A large majority of participants (96%) had ECG LVH status unchanged, but 4% developed evolving ECG LVH . On average, BP decreased by 11/7 mm Hg. In adjusted Cox regression analyses, progressing ECG LVH (hazard ratio [HR] 1.78 [95% CI 1.43-2.22]), resolving ECG LVH (HR 1.33 [95% CI 1.03-1.70]), and baseline ECG LVH (1.17 [95% CI 1.04-1.31]) carried risk of incident HF . After full adjustment, evolving ECG LVH mediated 4% of the effect of doxazosin on HF . Systolic BP lowering mediated 12% of the effect of doxazosin, and diastolic BP lowering mediated 10% of the effect of doxazosin, 7% of the effect of amlodipine, and borderline 9% of the effect of lisinopril on HF . Conclusions Evolving ECG LVH and BP change account for 4% to 13% of the mechanism by which antihypertensive medications prevent HF . Clinical Trial Registration URL : http://www.clinicaltrials.gov . Unique identifier: NCT 00000542.

Literature update week 14 (2019)

[41] *Yamashita S, Masuda D, Matsuzawa Y*. **Clinical Applications of a Novel Selective PPARalpha Modulator, Pemafibrate, in Dyslipidemia and Metabolic Diseases**. Journal of atherosclerosis and thrombosis 2019.

PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=30930344

ABSTRACT

Fasting and postprandial hypertriglyceridemia is a risk factor for atherosclerotic cardiovascular diseases (ASCVD). Fibrates have been used to treat dyslipidemia, particularly hypertriglyceridemia, and low HDL-cholesterol (HDL-C). However, conventional fibrates have low selectivity for peroxisome proliferator-activated receptor (PPAR)alpha. Fibrates' clinical use causes side effects such as worsening liver function and elevating the creatinine level. Large-scale clinical trials of fibrates have shown negative results for prevention of ASCVD. To overcome these issues, the concept of the selective PPARalpha modulator (SPPARMalpha), with a superior balance of efficacy and safety, has been proposed. A SPPARMalpha, pemafibrate (K-877), was synthesized by Kowa Company, Ltd. for better efficacy and safety. Clinical trials conducted in Japan confirmed the superior effects of pemafibrate on triglyceride reduction and HDL-C elevation.Conventional fibrates showed elevated liver function test values and worsened kidney function test values, while pemafibrate demonstrated improved liver function test values and was less likely to increase serum creatinine or decrease the estimated glomerular filtration rate. There were extremely few drug interactions even when it was used concomitantly with various statins. Furthermore, unlike many of the conventional fibrates that are renal excretory-type drugs, pemafibrate is excreted into the bile, so it can be safely used even in patients with impaired renal function and there is no increase in its blood concentration.This novel SPPARMalpha, pemafibrate, has superior benefit-risk balance compared to conventional fibrates and can be used for patients for whom it was difficult to use existing fibrates, including those who are taking statins and those with renal dysfunction. A large-scale trial PROMINENT using pemafibrate for patients with type 2 diabetes is in progress. In the current review, the latest data on pemafibrate will be summarized.

[42] *Song J, Yang S, Yin R et al.* **MicroRNA-181a regulates the activation of the NLRP3 inflammatory pathway by targeting MEK1 in THP-1 macrophages stimulated by ox-LDL**. Journal of cellular biochemistry 2019.

PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=30938884

ABSTRACT

Atherosclerosis (AS) is a chronic inflammatory disease that is characterized by the deposition of lipids in the vascular wall and the formation of foam cells. Macrophages play a critical role in the development of this chronic inflammation. An increasing amount of research shows that microRNAs affect many steps of inflammation. The goal of our study was to investigate the regulatory effect of miR-181a on the NLRP3 inflammasome pathway and explore its possible mechanism. Compared with the control group, the expression of miR-181a was downregulated in the carotid tissue of AS group mice, while the expression of MEK1 and NLRP3-related proteins was upregulated significantly. In vitro, when THP-1 macrophages were stimulated with oxidized low-density lipoprotein (ox-LDL), the expression of miR-181a was decreased, the MEK/ERK/NF-kappaB inflammatory pathways were activated and the expression of NLRP3 inflammasome-related proteins was upregulated. Exogenous overexpression of miR-181a downregulated the activation of the MEK/ERK/NF-kappaB pathway and decreased the expression of NLRP3 inflammasome-related proteins (such as NLRP3, caspase-1, interleukin-18 [IL-18], IL-1beta, etc). Exogenous miR-181a knockdown showed the opposite results to those of overexpression group. A

luciferase reporter assay proved that miR-181a inhibited the expression of MEK1 by binding to its 3'-untranslated region. When we knocked down miR-181a and then treated cells with U0126 before ox-LDL stimulation, we found that U0126 reversed the increased activation of the MEK/ERK/NF-kappaB pathway and upregulation of NLRP3 inflammasome-related proteins (NLRP3, caspase-1, IL-18, IL-1beta) that resulted from miR-181a knockdown. Our study suggests that miR-181a regulates the activation of the NLRP3 inflammatory pathway by altering the activity of the MEK/ERK/NF-kappaB pathway via targeting of MEK1.

[43] *Liu X, Suo R, Chan CZY et al.* **The immune functions of PCSK9: Local and systemic perspectives**. Journal of cellular physiology 2019.

PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=30950043

ABSTRACT

Proprotein convertase subtilisin/kexin type 9 (PCSK9) binds to low-density lipoprotein receptor (LDLR) to trigger endocytosis and lysosome degradation in hepatocytes, regulating intracellular and plasma cholesterol levels. The discovery of PCSK9 has provided a new target for the management of hypercholesterolemia and cardiovascular risk reduction. There is emerging evidence that shows that PCSK9 may influence the activity of various cell types through either LDLR-dependent or LDLR-independent mechanisms. Changes in the circulating PCSK9 levels have been observed during infection and proinflammatory conditions. Furthermore, PCSK9 as a secreted protein has both local and systemic effects on cellular function. In this review, we summarize the roles of PCSK9 in inflammation.

[44] *Chacra APM, Ferrari MC, Rocha VZ, Santos RD*. **Case report: The efficiency and safety of lomitapide in a homozygous familial hypercholesterolemic child**. Journal of clinical lipidology 2019.

PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=30948303

ABSTRACT

We report for the first time the efficiency and safety of a 49-month compassionate use of the microsomal transfer protein inhibitor lomitapide in a child with homozygous familial hypercholesterolemia. On average, 20 mg of lomitapide caused a 37% reduction in low-density lipoprotein cholesterol levels on top of ezetimibe and atorvastatin. The drug was well tolerated with no changes in liver enzymes and occurrence of steatosis on hepatic ultrasound. The patient presented adequate growth and sexual maturation. Nonetheless, there was progression in either subclinical atherosclerotic carotid or aortic valve diseases. Further studies are necessary to test the impact and safety of lomitapide in children with homozygous familial hypercholesterolemia.

[45] *Morise AP, Hegele RA*. **Atypical familial dysbetalipoproteinemia associated with high polygenic cholesterol and triglyceride scores treated with ezetimibe and evolocumab**. Journal of clinical lipidology 2019.

PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=30930000

ABSTRACT

We present a 37-year-old man diagnosed with familial dysbetalipoproteinemia who presented with the severe hyperlipidemic phenotype. None of the usual metabolic triggers were found to explain his severe

lipid abnormalities. Genetic analysis revealed the expected APOE E2/E2 genotype, but no other mutations were found to explain any monogenic dyslipidemia or syndrome. Polygenic risk scores for quantitative lipid traits did reveal scores placing the patient in the >99th percentile for the general population concerning polygenic susceptibility for both high cholesterol and triglycerides. Owing to his gastrointestinal intolerance to two high-intensity statins, he was treated with both ezetimibe 10 mg a day and evolocumab 140 mg subcutaneously every 2 weeks. All measures of potentially atherogenic lipids were markedly improved and remained so for more than 10 months of follow-up. This case report shows an unusual trigger for severe hyperlipidemia with familial dysbetalipoproteinemia and a favorable therapeutic response to the combination of ezetimibe and evolocumab.

[46] *Warden BA, Duell PB*. **Management of dyslipidemia in adult solid organ transplant recipients**. Journal of clinical lipidology 2019.

PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=30928441

ABSTRACT

Solid organ transplantation (SOT) has revolutionized treatment of end-stage disease. Improvements in the SOT continuum of care have unmasked a significant burden of cardiovascular disease, manifesting as a leading cause of morbidity and mortality. Although several risk factors for development of post-transplant cardiovascular disease exist, dyslipidemia remains one of the most frequent and modifiable risks. An important contributor to dyslipidemia in SOT recipients is the off-target metabolic effects of immunosuppressive medications, which may alter lipoproteins and their metabolism. Dyslipidemia management is paramount as lipid-lowering therapy with statins has demonstrated reductions in graft vasculopathy, decreased rejection rates, and improved survival. Several nonstatin medication options are available, but data supporting their benefit in the SOT population are minimal, typically extrapolated from studies in the general population. Further compounding dyslipidemia management is the complex interplay of drug interactions between lipid-lowering and immunosuppressant medications, which can result in serious toxicity and/or therapeutic failure.

[47] *Pouwer MG, Heinonen SE, Behrendt M et al.* **The APOE(*)3-Leiden Heterozygous Glucokinase Knockout Mouse as Novel Translational Disease Model for Type 2 Diabetes, Dyslipidemia, and Diabetic Atherosclerosis**. Journal of diabetes research 2019; 2019:9727952.

PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=30949516

ABSTRACT

Background: There is a lack of predictive preclinical animal models combining atherosclerosis and type 2 diabetes. APOE *3-Leiden (E3L) mice are a well-established model for diet-induced hyperlipidemia and atherosclerosis, and glucokinase(+/-) (GK(+/-)) mice are a translatable disease model for glucose control in type 2 diabetes. The respective mice respond similarly to lipid-lowering and antidiabetic drugs as humans. The objective of this study was to evaluate/characterize the APOE(*)3-Leiden.glucokinase(+/-) (E3L.GK(+/-)) mouse as a novel disease model to study the metabolic syndrome and diabetic complications. Methods: Female E3L.GK(+/-), E3L, and GK(+/-) mice were fed fat- and cholesterol-containing diets for 37 weeks, and plasma parameters were measured throughout. Development of diabetic macro- and microvascular complications was evaluated. Results: Cholesterol and triglyceride levels were significantly elevated in E3L and E3L.GK(+/-) mice compared to GK(+/-) mice, whereas fasting glucose was significantly increased in E3L.GK(+/-) and GK(+/-) mice compared to E3L. Atherosclerotic

lesion size was increased 2.2-fold in E3L.GK(+/-) mice as compared to E3L (p = 0.037), which was predicted by glucose exposure (R (2) = 0.636, p = 0.001). E3L and E3L.GK(+/-) mice developed NASH with severe inflammation and fibrosis which, however, was not altered by introduction of the defective GK phenotype, whereas mild kidney pathology with tubular vacuolization was present in all three phenotypes. Conclusions: We conclude that the E3L.GK(+/-) mouse is a promising novel diet-inducible disease model for investigation of the etiology and evaluation of drug treatment on diabetic atherosclerosis.

[48] *Ramirez-Tortosa CL, Varela-Lopez A, Navarro-Hortal MD et al.* **Longevity and cause of death in male Wistar rats fed lifelong diets based on virgin olive oil, sunflower oil or fish oil**. J Gerontol A Biol Sci Med Sci 2019.

PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=30953048

ABSTRACT

Extending life by delaying the aging process have proven to be the most effective way to fight multiple chronic diseases in elderly adults. Evidence suggests that longevity is inversely related to unsaturation of membrane phospholipids. The present study investigated how different unsaturated dietary fats affect lifespan and cause death in male Wistar rats fed diets based on virgin olive oil (V), sunflower oil (S) or fish oil (F), which were supplemented or not with Coenzyme Q10 (CoQ10). Previous results suggest that individual longevity and survival probability at different ages may be modulated by an appropriate dietary fat treatment. Lifelong feeding with V or F diets would reduce death probability compared to feeding with S diet at certain ages, although the effects of V diet would be maintained for most of life. Furthermore, the addition of lower amounts of CoQ10 reduced mortality associated with S diet, but CoQ10 had no effect on survival when combined with virgin olive oil or fish oil. Supplementation with low doses of CoQ10 failed to increase the maximum lifespan potential of rats fed a V or F diet. No clear evidence showing that MUFA, n-3 PUFA or CoQ10 exerted the observed effects by modulating the rate of aging has been found.

[49] *Chiang SM, Yang YS, Yang SF et al.* **Variations of the proprotein convertase subtilisin/kexin type 9 gene in coronary artery disease**. J Int Med Res 2019:300060519839519.

PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=30947598

ABSTRACT

OBJECTIVE: Coronary artery disease (CAD) is the principal cause of mortality and morbidity worldwide. Studies have provided controversial results regarding whether variations in the proprotein convertase subtilisin/kexin type 9 gene (PCSK9) are risk factors for CAD. In this study, we evaluated the risk factors associated with PSCK9 genotypes and CAD in the Taiwanese population. METHODS: A total of 501 patients diagnosed with CAD by angiography and 334 CAD-free controls were recruited. Two single nucleotide polymorphisms of PSCK9 (rs505151 and rs529787) were genotyped. RESULTS: The prevalence of a positive family history for CAD was significantly higher in individuals carrying the AG + GG genotype of the PSCK9 rs505151 polymorphism. Among CAD patients with a positive family history, the prevalence of diabetes mellitus was significantly higher in those carrying the AG + GG genotype of the PSCK9 rs505151 polymorphism (73.3%) than in those carrying the AA genotype (39.2%). CONCLUSION: In CAD patients, the AG genotype of PSCK9 rs505151 is associated with diabetes and a positive family history of CAD.

Literature update week 14 (2019)

[50] *Blin MG, Bachelier R, Fallague K et al.* **CD146 deficiency promotes plaque formation in a mouse model of atherosclerosis by enhancing RANTES secretion and leukocyte recruitment**. Journal of molecular and cellular cardiology 2019; 130:76-87.

PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=30928429

ABSTRACT

AIMS: The progression of atherosclerosis is based on the continued recruitment of leukocytes in the vessel wall. The previously described role of CD146 in leukocyte infiltration suggests an involvement for this adhesion molecule in the inflammatory response. In this study, we investigated the role of CD146 in leukocyte recruitment by using an experimental model of atherogenesis. METHODS AND RESULTS: The role of CD146 was explored in atherosclerosis by crossing CD146-/- mice with ApoE-/- mice. CD146 -/-/ApoE -/- and ApoE -/- mice were fed a Western diet for 24weeks and were monitored for aortic wall thickness using high frequency ultrasound. The arterial wall was significantly thicker in CD146-deficient mice. After 24weeks of Western diet, a significant increase of atheroma in both total aortic lesion and aortic sinus of CD146-null mice was observed. In addition, atherosclerotic lesions were more inflammatory since plaques from CD146-deficient mice contained more neutrophils and macrophages. This was due to up-regulation of RANTES secretion by macrophages in CD146-deficient atherosclerotic arteries. This prompted us to further address the function of CD146 in leukocyte recruitment during acute inflammation by using a second experimental model of peritonitis induced by thioglycollate. Neutrophil recruitment was significantly increased in CD146-deficient mice 12h after peritonitis induction and associated with higher RANTES levels in the peritoneal cavity. In CD146-null macrophages, we also showed that increased RANTES production was dependent on constitutive inhibition of the p38-MAPK signaling pathway. Finally, Maraviroc, a RANTES receptor antagonist, was able to reduce atherosclerotic lesions and neutrophilia in CD146-deficient mice to the same level as that found in ApoE -/- mice. CONCLUSIONS: Our data indicate that CD146 deficiency is associated with the upregulation of RANTES production and increased inflammation of atheroma, which could influence the atherosclerotic plaque fate. Thus, these data identify CD146 agonists as potential new therapeutic candidates for atherosclerosis treatment.

[51] *Lutjohann D, Bjorkhem I, Friedrichs S et al.* **First international descriptive and interventional survey for cholesterol and non-cholesterol sterol determination by gas- and liquid-chromatography-Urgent need for harmonisation of analytical methods**. J Steroid Biochem Mol Biol 2019; 190:115-125.

PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=30940596

ABSTRACT

Serum concentrations of lathosterol, the plant sterols campesterol and sitosterol and the cholesterol metabolite 5alpha-cholestanol are widely used as surrogate markers of cholesterol synthesis and absorption, respectively. Increasing numbers of laboratories utilize a broad spectrum of well-established and recently developed methods for the determination of cholesterol and non-cholesterol sterols (NCS). In order to evaluate the quality of these measurements and to identify possible sources of analytical errors our group initiated the first international survey for cholesterol and NCS. The cholesterol and NCS survey was structured as a two-part survey which took place in the years 2013 and 2014. The first survey part was designed as descriptive, providing information about the variation of reported results from different laboratories. A set of two lyophilized pooled sera (A and B) was sent to twenty laboratories specialized in chromatographic lipid analysis. The different sterols were quantified either by gas

chromatography-flame ionization detection, gas chromatography- or liquid chromatography-mass selective detection. The participants were requested to determine cholesterol and NCS concentrations in the provided samples as part of their normal laboratory routine. The second part was designed as interventional survey. Twenty-two laboratories agreed to participate and received again two different lyophilized pooled sera (C and D). In contrast to the first international survey, each participant received standard stock solutions with defined concentrations of cholesterol and NCS. The participants were requested to use diluted calibration solutions from the provided standard stock solutions for quantification of cholesterol and NCS. In both surveys, each laboratory used its own internal standard (5alpha-cholestane, epicoprostanol or deuterium labelled sterols). Main outcome of the survey was, that unacceptably high interlaboratory variations for cholesterol and NCS concentrations are reported, even when the individual laboratories used the same calibration material. We discuss different sources of errors and recommend all laboratories analysing cholesterol and NCS to participate in regular quality control programs.

[52] *Schumacher-Petersen C, Christoffersen BO, Kirk RK et al.* **Experimental non-alcoholic steatohepatitis in Gottingen Minipigs: consequences of high fat-fructose-cholesterol diet and diabetes**. Journal of translational medicine 2019; 17:110.

PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=30943987

ABSTRACT

BACKGROUND: Non-alcoholic fatty liver disease (NAFLD) is the most common liver disease in humans, and ranges from steatosis to non-alcoholic steatohepatitis (NASH), the latter with risk of progression to cirrhosis. The Gottingen Minipig has been used in studies of obesity and diabetes, but liver changes have not been described. The aim of this study was to characterize hepatic changes in Gottingen Minipigs with or without diabetes, fed a diet high in fat, fructose, and cholesterol to see if liver alterations resemble features of human NAFLD/NASH. METHODS: Fifty-four male castrated minipigs (age 6 to 7 months) were distributed into four groups and diet-fed for 13 months. Groups were: lean controls fed standard diet (SD, n = 8), a group fed high fat/fructose/cholesterol diet (FFC, n = 16), a group fed high fat/fructose/cholesterol diet but changed to standard diet after 7 months (diet normalization, FFC/SD, n = 16), and a streptozotocin-induced diabetic group fed high fat/fructose/cholesterol diet (FFCDIA, n = 14). At termination, blood samples for analyses of circulating biomarkers and liver tissue for histopathological assessment and analyses of lipids and glycogen content were collected. RESULTS: In comparison with SD and FFC/SD, FFC and FFCDIA pigs developed hepatomegaly with increased content of cholesterol, whereas no difference in triglyceride content was found. FFC and FFCDIA groups had increased values of circulating total cholesterol and triglycerides and the hepatic circulating markers alkaline phosphatase and glutamate dehydrogenase. In the histopathological evaluation, fibrosis (mainly located periportally) and inflammation along with cytoplasmic alterations (characterized by hepatocytes with pale, granulated cytoplasm) were found in FFC and FFCDIA groups compared to SD and FFC/SD. Interestingly, FFC/SD also had fibrosis, a feature not seen in SD. Only two FFC and three FFCDIA pigs had > 5% steatosis, and no hepatocellular ballooning or Mallory-Denk bodies were found in any of the pigs. CONCLUSIONS: Fibrosis, inflammation and cytoplasmic alterations were characteristic features in the livers of FCC and FFCDIA pigs. Overall, diabetes did not exacerbate the hepatic changes compared to FFC. The limited presence of the key human-relevant pathological hepatic findings of steatosis and hepatocellular ballooning and the variation in the model, limits its use in preclinical research without further optimisation.

Literature update week 14 (2019)

[53] *Garcia-Berumen CI, Ortiz-Avila O, Vargas-Vargas MA et al.* **The severity of rat liver injury by fructose and high fat depends on the degree of respiratory dysfunction and oxidative stress induced in mitochondria**. Lipids in health and disease 2019; 18:78.

PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=30927921

ABSTRACT

BACKGROUND: High fat or fructose induces non-alcoholic fatty liver disease (NAFLD) accompanied of mitochondrial dysfunction and oxidative stress. Controversy remains about whether fructose or fat is more deleterious for NAFLD development. To get more insights about this issue and to determine if the severity of liver disease induced by fructose or fat is related to degree of mitochondrial dysfunction, we compared the effects of diets containing high fat (HF), fructose (Fr) or high fat plus fructose (HF + Fr) on NAFLD development, mitochondrial function, ROS production and lipid peroxidation. METHODS: Wistar rats were assigned to four groups: Control, fed with standard rodent chow; High fat (HF), supplemented with lard and hydrogenated vegetable oil; Fructose (Fr), supplemented with 25% fructose in the drinking water; High fat plus fructose group (HF + Fr), fed with both HF and Fr diets. Rats were sacrificed after 6 weeks of diets consumption and the liver was excised for histopathological analysis by hematoxylin and eosin staining and for mitochondria isolation. Mitochondrial function was evaluated by measuring both mitochondrial respiration and complex I activity. Lipid peroxidation and ROS production were evaluated in mitochondria by the thiobarbituric acid method and with the fluorescent ROS probe 2,4-H2DCFDA, respectively. RESULTS: Fr group underwent the lower degree of both liver damage and mitochondrial dysfunction that manifested like less than 20% of hepatocytes with microvesicular steatosis and partial decrease in state 3 respiration, respectively. HF group displayed an intermediate degree of damage as it showed 40% of hepatocytes with microvesicular steatosis and diminution of both state 3 respiration and complex I activity. HF + Fr group displayed more severe damage as showed microvesicular steatosis in 60% of hepatocytes and inflammation, while mitochondria exhibited fully inhibited state 3 respiration, impaired complex I activity and increased ROS generation. Exacerbation of mitochondrial lipid peroxidation was observed in both the Fr and HF + Fr groups. CONCLUSION: Severity of liver injury induced by fructose or fat was related to the degree of dysfunction and oxidative damage in mitochondria. Attention should be paid on the serious effects observed in the HF + Fr group as the typical Western diet is rich in both fat and carbohydrates.

[54] *Huang WW, Hong BH, Sun JP et al.* **Comparing the simultaneous determination of cis- and trans-palmitoleic acid in fish oil using HPLC and GC**. Lipids in health and disease 2019; 18:86.

PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=30947713

ABSTRACT

BACKGROUND: Cis- and trans-palmitoleic acids (Cis-POA and trans-POA) are isomers of palmitoleic acid, a monounsaturated fatty acid which affects glucose and lipid metabolism, and reduces insulin resistance. Trans-POA is used as a biomarker for indicating the risk of type II diabetes and coronary heart disease, but no methods of analysis or distinguishing between cis-POA and trans-POA have yet been reported. METHOD: An accurate and precise HPLC method was developed to determine cis- and trans-POA simultaneously, and compared with results from a GC method. Cis- and trans-POA were analyzed by HPLC on a reverse-phase BDS-C18 column, equilibrated and eluted with acetonitrile (A) and water (B). In the established and validated GC method used for comparison, potassium hydroxide ester exchange was chosen to derivatize the cis- and trans-POA, before being determined. RESULTS: The calibration curves for cis- and trans-POA were linear over the range 0.05 to 500 mug/mL. The HPLC method

exhibited good sensitivity, precision and accuracy. The limits of detection (LOD) for cis- and trans-POA were 0.2 and 0.05 mug/mL, respectively. The method successfully determined cis- and trans-POA in fish oil. For the GC method, the contents of cis-POA quantified were similar to those from the HPLC method, but the contents of trans-POA revealed significant variation between the two methods. CONCLUSIONS: After a comprehensive consideration of the characteristics of the saponification and methyl esterification methods which have been tested and verified, the HPLC method was found to be suitable for determining cis- and trans-POA contents in fish oil. It was also suggested that in natural fish oil, cis-POA may be in the glyceride state, and trans-POA almost completely in the free acid form. In comparison with the GC method, the HPLC method provided a simpler process and faster analyses for identifying and determining cis- and trans-POA. The study has also provided technical support for studying the pharmacological differences and relationship between structure and activity of cis- and trans-POA. This could help physicians to analyze patients' samples more quickly in 10 min and therefore provide a more rapid diagnosis of problems relating to the risk of type II diabetes and coronary heart disease.

[55] *Liu Y, Wang X, Han J et al.* **PCSK9 positively correlates with plasma sdLDL in community-dwelling population but not in diabetic participants after confounder adjustment**. Medicine (Baltimore) 2019; 98:e15062.

PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=30946354

ABSTRACT

This study aimed to investigate the relationship between plasma proprotein convertase subtilisin kexin 9 (PCSK9) and small dense low-density lipoprptein (sdLDL) in diabetic and non-diabetic participants in a community-dwelling cohort.The plasma levels of PCSK9 and sdLDL were detected in 1766 participants (median age: 61.40 years; 733 males vs 1033 females; 383 diabetic vs 1383 non-diabetic patients) from the Pingguoyuan community of Beijing, China.Results showed that Pearson correlation analysis revealed a positive correlation between PCSK9 and sdLDL ($r = 0.263$, $P < .001$). Multiple linear regression analysis showed a significant positive correlation between plasma PCSK9 and sdLDL in the whole population study. sdLDL was used as the dependent variable, and the potential cofounders were adjusted. However, any independent relationship was not observed between circulating PCSK9 and sdLDL in the diabetic subpopulation ($r = 0.269$, $P < .05$, beta = 9.591, $P > .05$).Thus, there is a positive correlation between plasma PCSK9 and sdLDL in a community-dwelling cohort, but not in type 2 diabetic subpopulation, after confounder adjustment.

[56] *Chen ML, Takeda K, Sundrud MS*. **Emerging roles of bile acids in mucosal immunity and inflammation**. Mucosal immunology 2019.

PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=30952999

ABSTRACT

Bile acids are cholesterol-derived surfactants that circulate actively between the liver and ileum and that are classically recognized for emulsifying dietary lipids to facilitate absorption. More recent studies, however, have revealed new functions of bile acids; as pleotropic signaling metabolites that regulate diverse metabolic and inflammatory pathways in multiple cell types and tissues through dynamic interactions with both germline-encoded host receptors and the microbiota. Accordingly, perturbed bile acid circulation and/or metabolism is now implicated in the pathogenesis of cholestatic liver diseases,

metabolic syndrome, colon cancer, and inflammatory bowel diseases (IBDs). Here, we discuss the three-dimensional interplay between bile acids, the microbiota, and the mucosal immune system, focusing on the mechanisms that regulate intestinal homeostasis and inflammation. Although the functions of bile acids in mucosal immune regulation are only beginning to be appreciated, targeting bile acids and their cellular receptors has already proven an important area of new drug discovery.

[57] *Clayton ZS, Fusco E, Schreiber L et al.* **Snack selection influences glucose metabolism, antioxidant capacity and cholesterol in healthy overweight adults: A randomized parallel arm trial**. Nutrition research (New York, N.Y.) 2019.

PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=30952505

ABSTRACT

Including carbohydrate/fructose-rich foods (predominantly fruit) in the diets of overweight individuals can improve chronic disease risk factors. We hypothesized dried plums (DP) would improve nutrient consumption, total antioxidant capacity (TAC), lipid and adipokine profiles, and would decrease adiposity and inflammation. To test this, we studied the effects of 8-weeks of twice-daily snacking of macronutrient-matched 100kcal servings of DP or refined carbohydrate-rich snack (low-fat muffins: LFM) on daily energy and nutrient consumption, and chronic disease risk factors in overweight adults. Body weight/composition, waist circumference, blood pressure, plasma glucose, insulin, c-peptide, lipids, TAC, adipokines and inflammation were measured at baseline and throughout the study. Postprandial glucose and insulin were assessed following assigned test foods at baseline and 8-weeks. Repeated measures ANOVAs were undertaken to examine group and time differences. Post-hoc independent and paired samples t-tests were conducted where necessary. DP increased (P<.05) overall intake of dietary fiber and potassium, and TAC, from baseline to 8-weeks. Baseline postprandial glycemia tended (P=.09) to be lower with DP versus LFM, while both groups had a decreased response after 8-weeks. Postprandial insulinemia was lower (P<.05) for DP at both time-points. No differences in body weight/composition, blood pressure, or fasting glucose, insulin, triglycerides, total cholesterol, HDL-C, inflammation or adipokines were detected. Low-density lipoprotein cholesterol (LDL-C) increased (P<.05) throughout the trial following LFM. Overall, DP lessened postprandial insulinemia, improved nutrient consumption and plasma TAC, and maintained plasma LDL-C compared to a macronutrient-matched refined carbohydrate snack, which could decrease chronic disease risk.

[58] *Garcia-Jaramillo M, Spooner MH, Lohr CV et al.* **Lipidomic and transcriptomic analysis of western diet-induced nonalcoholic steatohepatitis (NASH) in female Ldlr -/- mice**. PloS one 2019; 14:e0214387.

PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=30943218

ABSTRACT

BACKGROUND: Nonalcoholic fatty liver disease (NAFLD) is the most common chronic liver disease worldwide, particularly in obese and type 2 diabetic individuals. NAFLD ranges in severity from benign steatosis to nonalcoholic steatohepatitis (NASH); and NASH can progress to cirrhosis, primary hepatocellular carcinoma (HCC) and liver failure. As such, NAFLD has emerged as a major public health concern. Herein, we used a lipidomic and transcriptomic approach to identify lipid markers associated with western diet (WD) induced NASH in female mice. METHODS: Female mice (low-density lipoprotein receptor null (Ldlr -/-) were fed a reference or WD diet for 38 and 46 weeks. Transcriptomic and lipidomic approaches, coupled with statistical analyses, were used to identify associations between

major NASH markers and transcriptomic & lipidomic markers. RESULTS: The WD induced all major hallmarks of NASH in female Ldlr -/- mice, including steatosis (SFA, MUFA, MUFA-containing di- and triacylglycerols), inflammation (TNFalpha), oxidative stress (Ncf2), and fibrosis (Col1A). The WD also increased transcripts associated with membrane remodeling (LpCat), apoptosis & autophagy (Casp1, CtsS), hedgehog (Taz) & notch signaling (Hey1), epithelial-mesenchymal transition (S1004A) and cancer (Gpc3). WD feeding, however, suppressed the expression of the hedgehog inhibitory protein (Hhip), and enzymes involved in triglyceride catabolism (Tgh/Ces3, Ces1g), as well as the hepatic abundance of C18-22 PUFA-containing phosphoglycerolipids (GpCho, GpEtn, GpSer, GpIns). WD feeding also increased hepatic cyclooxygenase (Cox1 & 2) expression and pro-inflammatory omega6 PUFA-derived oxylipins (PGE2), as well as lipid markers of oxidative stress (8-iso-PGF2alpha). The WD suppressed the hepatic abundance of reparative oxylipins (19, 20-DiHDPA) as well as the expression of enzymes involved in fatty epoxide metabolism (Cyp2C, Ephx). CONCLUSION: WD-induced NASH in female Ldlr -/- mice was characterized by a massive increase in hepatic neutral and membrane lipids containing SFA and MUFA and a loss of C18-22 PUFA-containing membrane lipids. Moreover, the WD increased hepatic pro-inflammatory oxylipins and suppressed the hepatic abundance of reparative oxylipins. Such global changes in the type and abundance of hepatic lipids likely contributes to tissue remodeling and NASH severity.

[59] *Zamora A, Masana L, Plana N, Ramos R*. **Estimated Percentage of Patients With Stable Coronary Heart Disease Candidates for PCSK9 Inhibitors. Response**. Revista espanola de cardiologia (English ed.) 2019.

PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=30930255

ABSTRACT

[60] *Al-Bustan SA, Al-Serri A, Alnaqeeb MA et al.* **Genetic association of LPL rs1121923 and rs258 with plasma TG and VLDL levels**. Scientific reports 2019; 9:5572.

PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=30944368

ABSTRACT

Lipoprotein lipase (LPL) is a rate-limiting enzyme for the hydrolysis of triglycerides (TG). Hundreds of genetic variants including single nucleotide polymorphisms have been identified across the 30Kb gene locus on chromosome 8q22. Several of these variants have been demonstrated to have genetic association with lipid level variation but many remain unresolved. Controversial reports on the genetic association of variants among different populations pose a challenge to which variants are informative. This study aimed to investigate "common" LPL variants (rs1121923, rs258, rs328, rs13702) and their possible role in plasma lipid level. Genotyping was performed using Realtime PCR. Based on the observed genotypes, the minor allele frequencies were A: 0.065 for rs1121923; C: 0.379 for rs258; G: 0.087 for rs328 and C: 0.337 for rs13702. Using linear regression, a lowering effect of rs1121923 ($p = 0.024$) on TG levels (-0.14 B coefficient: CI: -0.27--0.019) and rs258 ($p = 0.013$) on VLDL levels (B: -0.046; CI: -0.082--0.009) was observed indicating a "protective" role for the two variants. Moreover, the findings indicate the potential for including rs1121923 and rs258 in diagnostic panels for use as an estimator of "risk" scores for dyslipidemia.

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