

Literature update week 47 (2018)

[1] Bagheri MJ, Talebpour M, Sharifi A et al. **Lipid profile change after bariatric surgeries: laparoscopic gastric plication versus mini gastric bypass.** *Acta chirurgica Belgica* 2018:1-6.

PM: <http://www.ncbi.nlm.nih.gov/pubmed/?term=30451582>

ABSTRACT

INTRODUCTION: Bariatric surgeries are known to have profound effects on lipid profile. Laparoscopic gastric plication (LGP) has been shown to have a comparable effect on weight loss rather than Roux-en-Y gastric bypass (RYGB) and mini gastric bypass (MGB). But the post-operative effect on lipid profile is not well-compared. We aimed to compare post-operative lipid profile change after LGP and MGB. METHODS: In a retrospective analysis, we reviewed 91 patients for at least 12 months. Patients were assigned to undergo either LGP (71 patients) or MGB (20 patients). Preoperative and postoperative visits were accomplished and weight, BMI, fasting blood glucose (FBG) and lipid profile including triglyceride (TG), and total cholesterol (TC) levels were repeatedly measured. Follow up rate for the first year was 100%. RESULTS: LGP significantly decreased both TG and TC levels in each follow up (all p values < .05). The same trends were observed in BMI reduction, total body weight loss percentage, and FBG. When comparing either TC or TG level between LGP and MGB, there was just one statistically significant result in TG reduction at 6 months (p value = .042) while MGB showed more reduction. All other variables in different follow up visits were not significantly different between two techniques. CONCLUSIONS: LGP would result in lipid profile improvement lasting at least for one year. Lipid-lowering effect seems to be similar between LGP and MGB. This lipid-lowering property and weight reduction might be indicative that LGP is an alternative for RYGB and MGB in selective patients.

[2] Nikolova-Karakashian M. **Alcoholic and non-alcoholic fatty liver disease: Focus on ceramide.** *Advances in biological regulation* 2018; 70:40-50.

PM: <http://www.ncbi.nlm.nih.gov/pubmed/?term=30455063>

ABSTRACT

Sphingolipids are class of metabolically distinct lipids that play structural and signaling functions in all organisms. Sphingolipid metabolism is deregulated during various diseases such as cancer, neurological and immune disorders, and metabolic syndrome. With the advancement of sphingo-lipidomics and sphingo-genomics, an understanding of the specific roles of ceramide, the quintessential bioactive sphingolipid, in fatty liver disease has taken shape. Two major pathways for ceramide generation, the de novo pathway and the sphingomyelinase pathway are activated in the course of both, the non-alcoholic and the alcoholic, forms of fatty liver disease. The mechanisms of activation of these two pathways are distinct and reflect the different disease etiology in each case; at the same time, common processes impacted by the resulting ceramide overproduction involve lipotoxicity, ER/mitochondrial stress, inflammation, and de-regulation of hepatic lipid metabolism. Studies in human patients and animal models have delineated specific enzymes and ceramide species that are involved at the different stages of the disease, and represent novel pharmaceutical targets for successful management of fatty liver disease.

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[3] *Cakir SS, Ozcan L, Polat EC et al. Statins are effective in the treatment of benign prostatic hyperplasia with metabolic syndrome. The aging male : the official journal of the International Society for the Study of the Aging Male* 2018;1-6.

PM: <http://www.ncbi.nlm.nih.gov/pubmed/?term=30463466>

ABSTRACT

OBJECTIVE: To compare the efficacy of statins and a blockers drug therapies for benign prostatic hyperplasia (BPH) in patients with metabolic syndrome (MetS). MATERIALS AND METHOD: A total of three hundred patients were randomly distributed into three groups of one hundred patients each. Group 1 received only a-adrenoceptor antagonist (a-blocker, AB) (Tamsulosin), group 2 received only statin (atorvastatin), and group 3 received AB plus statin (Tamsulosin + Atorvastatin). The efficacy measurement was assessed by analyzing the changes from baseline in the total International Prostate Symptom Score (IPSS), disease-specific QoL question score and maximum urinary flow rate at the end of 6 months in each group and between the three groups. RESULTS: Pre-treatment and post-treatment value of triglycerides (TG), high-density lipoprotein (HDL), and prostate volume (PV) were not significantly different in AB group, while TG and PV were significantly lower in patients taking statin and combined therapy. The significant decrease was demonstrated in maximum urinary flow rate (Qmax) in three groups. However, the most significant decrease was observed in the combination therapy group. IPSS, postvoid residual urine volume (PVR), and Quality of Life score (QoL) significantly changed in three groups. CONCLUSION: We recommend of the use of statins in those men with BPH accompanied by MetS in which AB is ineffective alone.

[4] *Borgo MV, Baldo MP, Alvim RO et al. Lipid disorders among Black Africans non-users of lipid-lowering medication. Archives of endocrinology and metabolism* 2018; 62:552-559.

PM: <http://www.ncbi.nlm.nih.gov/pubmed/?term=30462809>

ABSTRACT

OBJECTIVE: Angola is a sub-Saharan African country where the population has scarce access to lipidlowering medication. We sought to determine the frequency of lipid disorders among Angolan nonusers of lipid-lowering medication. MATERIAL AND METHODS: A cross-sectional descriptive study was carried out in a sample of 604 workers from the public sector. Blood pressure and anthropometric data were measured along with biochemical parameters including total cholesterol (TC), triglycerides (TG), low-density lipoprotein cholesterol (LDL-C) and high-density lipoprotein cholesterol (HDL-C). LDL-C to HDL-C ratio (LDL-C/HDL-C) was obtained from LDL-C and HDL-C levels. RESULTS: High frequencies of elevated blood pressure (44.8%), metabolic syndrome (20.2%), increased TC (39.2%) and increased LDL-C (19.3%) were found. Low HDL-C was more frequent in women (62.4% vs. 36.1%, $p < 0.001$). Isolated hypercholesterolemia was more frequent in men (9.6% vs. 2.5%, $p < 0.001$). Among men TC, TG, LDL-C and LDL-C/HDL-C ratio were higher and HDL-C was lower in obese than in low-weight and normal-weight participants. Among women TC, TG, LDL-C and LDL-C/HDL-C ratio were higher in obese than in normal-weight participants. Significant linear trend of increasing TC and LDL-C levels as age increased was detected for both genders (p for trend < 0.05). CONCLUSION: The results of our study showed a high frequency of lipid disorders in Angolan non-users of lipid-lowering medication.

[5] Yorulmaz H, Ozkok E, Demir G et al. **Pretreatment of simvastatin on liver trace element levels during endotoxemia.** *Archives of physiology and biochemistry* 2018:1-5.

PM: <http://www.ncbi.nlm.nih.gov/pubmed/?term=30450988>

ABSTRACT

There are a number of studies investigating anti-inflammatory effects of simvastatin in patients with sepsis and animal models. There are a few studies which investigated effect of simvastatin on elements in sepsis. In the present study, the impact of pretreatment with simvastatin on element levels was evaluated in liver during endotoxemia. Rats were divided into control, LPS, simvastatin, and simvastatin + LPS. The histopathologic examination of the liver was performed using hematoxylin and eosin. Selenium, zinc, iron, manganese, magnesium, and copper were analyzed using inductively coupled plasma - optical emission spectroscopy. In the LPS, the hepatocyte cell structure was damaged. In the simvastatin + LPS, hepatocyte, and sinusoidal cord damage were partially smaller than LPS. Levels of selenium, and copper significantly decreased in both of LPS and simvastatin + LPS. In the LPS group, iron was found to increase. In the simvastatin + LPS, zinc was increased. Simvastatin partially smaller liver damage by increasing zinc levels during endotoxemia.

[6] Bojanin D, Vekic J, Milenkovic T et al. **Association between proprotein convertase subtilisin/kexin 9 (PCSK9) and lipoprotein subclasses in children with type 1 diabetes mellitus: Effects of glycemic control.** *Atherosclerosis* 2018; 280:14-20.

PM: <http://www.ncbi.nlm.nih.gov/pubmed/?term=30453116>

ABSTRACT

BACKGROUND AND AIMS: Dyslipidemia in type 1 diabetes mellitus (T1DM) is characterised by altered distributions of low-density lipoprotein (LDL) and high-density lipoprotein (HDL) subclasses. Recent studies suggested that proprotein convertase subtilisin/kexin 9 (PCSK9) may contribute to the development of dyslipidemia in T1DM. In this cross-sectional study, we investigated the association between PCSK9 and lipoprotein subclasses in young T1DM patients, with respect to glycemic control. METHODS: Plasma PCSK9 and lipoprotein subclasses were determined in 207 patients with T1DM (106 boys and 101 girls), aged 13.9+/-3.0 years and treated by intensive insulin therapy. RESULTS: Plasma PCSK9 levels significantly increased with worsening of glycemic control ($p<0.001$). T1DM patients with poor glucoregulation had the highest proportion of small, dense LDL (sdLDL) and smaller HDL particles, as well. PCSK9 was positively associated with markers of glucose homeostasis and serum lipid parameters only in patients with suboptimal/poor glucoregulation. In well-controlled T1DM, plasma PCSK9 level was inversely associated with a relative proportion of sdLDL particles ($p<0.01$) and this association remained significant in multivariate analysis. In T1DM patients with suboptimal/poor glycemic control, PCSK9 was positively associated with the proportion of the smallest HDL3c particles ($p<0.001$), but negatively with HDL size ($p<0.05$). CONCLUSIONS: The extent of achieved metabolic control modifies the association between PCSK9 and lipoprotein subclasses in T1DM. Further investigations are needed to reveal whether the observed effects of glycemic control on PCSK9 and sdLDL levels have causal consequences on CVD risk in young patients with T1DM.

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[7] *Humphries SE, Cooper JA, Capps N et al. Coronary heart disease mortality in severe vs. non-severe familial hypercholesterolaemia in the Simon Broome Register. Atherosclerosis 2018.*

PM: <http://www.ncbi.nlm.nih.gov/pubmed/?term=30458964>

ABSTRACT

BACKGROUND AND AIMS: The International Atherosclerosis Society (IAS) has proposed that patients with "severe" FH (SFH) would warrant early and more aggressive cholesterol-lowering treatment such as with PCSK9 inhibitors. SFH is diagnosed if LDL-cholesterol (LDLC) >10mmol/L, or LDLC >8.0mmol/L plus one high-risk feature, or LDLC >5mmol/L plus two high-risk features. Here we compare CHD mortality in SFH and non-SFH (NSFH) patients in the UK prospective Simon Broome Register since 1991, when statin use became routine. **METHODS:** 2929 definite or possible PFH patients (51% women) aged 20-79 years were recruited from 21 UK lipid clinics and followed prospectively between 1992 and 2016. The excess CHD standardised mortality ratio (SMR) compared to the England and Wales population was calculated (with 95% confidence intervals). **RESULTS:** 1982 (67.7%) patients met the SFH definition. Compared to the non-SFH, significantly ($p < 0.001$) more SFH patients had diagnosed CHD at baseline (24.6% vs. 17.5%), were current smokers (21.9% vs 10.2%) and had a BMI >30kg/m² (14.9% vs. 7.8%). The SMR for CHD mortality was significantly ($p=0.007$) higher for SFH (220 (184-261) (34,134 person years, 129 deaths observed, vs. 59 expected) compared to NSFH of 144 (98-203) (15,432 person years, 32 observed vs. 22 expected). After adjustment for traditional risk factors, the Hazard Ratio for CHD mortality in SFH vs. NSFH was 1.22 (0.80-1.87) $p=0.36$, indicating that the excess risk was largely accounted for by these factors. **CONCLUSIONS:** CHD mortality remains elevated in treated FH, especially for SFH, emphasising the importance of optimal lipid-lowering and management of other risk factors.

[8] *Pirro M, Francisci D, Bianconi V et al. NUtraceutical TReatment for hYpercholesterolemia in HIV-infected patients: The NU-TRY(HIV) randomized cross-over trial. Atherosclerosis 2018; 280:51-57.*

PM: <http://www.ncbi.nlm.nih.gov/pubmed/?term=30471555>

ABSTRACT

BACKGROUND AND AIMS: Despite hypercholesterolemia has been recognized to increase cardiovascular risk in human immunodeficiency virus (HIV)-infected patients, cholesterol-lowering therapy is underused in this population, due to fear of drug-drug interactions with antiretroviral therapy (ART). We investigated the effects of a nutraceutical combination (NC) on lipid profile, proprotein convertase subtilisin/kexin type 9 (PCSK9), subclinical inflammation and arterial stiffness in ART-treated HIV-infected patients. **METHODS:** This was a prospective randomized open-label trial with a cross-over design including 30 stable HIV-infected patients on ART with low-density lipoprotein cholesterol (LDL-C) >115mg/dL, not taking lipid-lowering treatment. After a 3-week lipid stabilization period, the effects associated with 3 months of an oral NC containing red yeast rice and berberine vs. no active treatment (noNC) were assessed for plasma total cholesterol (TC), LDL-C, high-density lipoprotein cholesterol (HDL-C), triglyceride (TG), lipoprotein(a), PCSK9, high-sensitivity C-reactive protein (hs-CRP) levels and aortic pulse wave velocity (aPWV). **RESULTS:** At baseline, significant correlations between PCSK9 levels, age ($\rho=-0.51$, $p=0.004$), waist circumference ($\rho=0.36$, $p=0.005$) and CD4(+) cell count ($\rho=-0.40$, $p=0.027$) were observed. NC treatment effects corrected for noNC were

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significant for TC (-14%, $p<0.001$), LDL-C (-19%, $p<0.001$), PCSK9 (-12%, $p=0.02$), hs-CRP (-14%, $p=0.03$) and aPWV (-6%, $p=0.005$). No significant effects were observed for HDL-C, TG and lipoprotein(a). NC treatment was safe and no significant alterations in muscle, liver and immunovirological parameters were observed. No carry over effect was recorded.

CONCLUSIONS: The tested NC significantly reduced plasma cholesterol and PCSK9 levels, attenuated subclinical inflammation and improved arterial stiffness in stable HIV-infected patients on ART.

[9] *Hu LL, Zhang KQ, Tian T et al. Probucol improves erectile function via Activation of Nrf2 and coordinates the HO-1 / DDAH / PPAR-gamma/ eNOS pathways in streptozotocin-induced diabetic rats. Biochem Biophys Res Commun* 2018.

PM: <http://www.ncbi.nlm.nih.gov/pubmed/?term=30454888>

ABSTRACT

BACKGROUND: Diabetic erectile dysfunction (DMED) is mainly attributed to oxidative stress, and Nrf2 plays an important role in cellular antioxidation and regulates NO production in the vascular endothelium. Probucol maintains endothelial function through its antioxidant activity. This study investigated the efficacy and mechanism of probucol in improving erectile function in streptozotocin-induced diabetic rats. METHODS: In our study, thirty 12-week-old Sprague-Dawley male rats were fasted for 12h. All rats received a 1-time injection of intraperitoneal streptozotocin(60mg/kg) or vehicle. After 72h, STZ-treated rats (with random blood glucose concentrations consistently greater than 16.7mmol/L) were considered diabetic. The diabetic rats were randomly assigned into 2 groups and treated with daily gavage feedings of probucol at doses of 0 and 500mg/kg for 12 weeks. A positive control group underwent intraperitoneal injection of normal saline followed by daily gavage of saline solution. Erectile function was assessed by electrical stimulation of the cavernous nerves with real-time intracavernous pressure measurement. After euthanasia, penile tissue was investigated using immunohistochemistry, Western blot, and ELISA to assess the proteins of Nrf2/HO-1/DDAH/PPAR-gamma/eNOS pathways. RESULTS: After treatment, the rats in the probucol group presented significantly improved erectile function ($P<0.05$) than that of the diabetic group without probucol treatment (DM). Also, protein expression of Nrf2, DDAH, PPAR-gamma, HO-1 and eNOS was significantly higher than that of the DM group ($P<0.05$). CGMP concentrations and SOD concentrations of probucol-treated rats were higher than those of DM group ($P<0.05$). The MDA levels and ADMA levels were significantly lower than those of DM group rats ($P<0.05$). CONCLUSION: Probucol can improve erectile function via activation of Nrf2, which coordinates the HO-1/DDAH/PPAR-gamma/eNOS pathways in streptozotocin-induced diabetic rats.

[10] *Knecht T, Borlongan C, Dela Pena I. Combination therapy for ischemic stroke: Novel approaches to lengthen therapeutic window of tissue plasminogen activator. Brain circulation* 2018; 4:99-108.

PM: <http://www.ncbi.nlm.nih.gov/pubmed/?term=30450415>

ABSTRACT

Tissue plasminogen activator (tPA) thrombolysis continues to be the gold standard therapy for ischemic stroke. Due to the time-limited treatment window, within 4.5 h of stroke onset, and a

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variety of potentially deadly complications related to delayed administration, particularly hemorrhagic transformation (HT), clinical use of tPA is limited. Combination therapies with other interventions, drug or nondrug, have been hypothesized as a logical approach to enhancing tPA effectiveness. Here, we discuss various potential pharmacological and nondrug treatments to minimize adverse effects, primarily HT, associated with delayed tPA administration. Pharmacological interventions include many that support the integrity of the blood-brain barrier (i.e., atorvastatin, batimastat, candesartan, cilostazol, fasudil, and minocycline), promote vascularization and preserve cerebrovasculature (i.e., coumarin derivative IMM-H004 and granulocyte-colony stimulating factor), employing other mechanisms of action (i.e., oxygen transporters and ascorbic acid). Nondrug treatments are comprised of stem cell transplantation and gas therapies with multi-faceted approaches. Combination therapy with tPA and the aforementioned treatments demonstrated promise for mitigating the adverse complications associated with delayed tPA treatment and rescuing stroke-induced behavioral deficits. Therefore, the conjunctive therapy method is a novel therapeutic approach that can attempt to minimize the limitations of tPA treatment and possibly increase the therapeutic window for ischemic stroke treatment.

[11] *Waters DD. Cholesterol Lowering Guidelines: From Whence We Came and Where We Are Now. The Canadian journal of cardiology* 2018.

PM: <http://www.ncbi.nlm.nih.gov/pubmed/?term=30454967>

ABSTRACT

Treatment guidelines have proliferated in cardiology, although most guideline recommendations are not supported by clinical trial evidence. What is considered to be a normal cholesterol level has progressively declined over the past 50 years, with the increasing realization that "normal" is far from optimal and that lower is better. The first important United States and Canadian cholesterol guidelines were published in 1988, and recommended diet for 6 months to be followed by consideration of bile acid sequestrants or nicotinic acid. Over the ensuing 25 years guidelines have changed rapidly and dramatically in response to a large number of definitive clinical trials, usually with statins. Low-density lipoprotein cholesterol targets have moved progressively lower, and in some guidelines, have been abandoned entirely. The concept of selecting patients for treatment according to the absolute risk reduction expected from treatment on the basis of clinical trial data seems to be a rational approach. For secondary prevention, some patients are still untreated or undertreated, presenting an opportunity for improving outcomes.

[12] *Maki KC, Palacios OM, Buggia MA et al. Effects of a Self-micro-emulsifying Delivery System Formulation Versus a Standard omega-3 Acid Ethyl Ester Product on the Bioavailability of Eicosapentaenoic Acid and Docosahexaenoic Acid: A Study in Healthy Men and Women in a Fasted State. Clinical therapeutics* 2018.

PM: <http://www.ncbi.nlm.nih.gov/pubmed/?term=30454850>

ABSTRACT

PURPOSE: Intakes of eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) are associated with several potential health benefits, but standard ethyl ester (EE) formulations of these omega-3 fatty acids require the co-ingestion of fat for adequate absorption. The objective

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of this research was to assess the relative bioavailability of EPA and DHA administered in a proprietary self-micro-emulsifying delivery system (SMEDS) formulation compared with EPA and DHA in a standard omega-3 acid EE product in healthy men and women in a fasted state. METHODS: This randomized crossover study investigated the bioavailability of 2 encapsulated formulations of EPA and DHA, a capsule containing 500 mg EPA + DHA administered in a SMEDS formulation (SMEDS treatment), and a capsule containing 840 mg EPA + DHA in a standard omega-3 acid EE formulation (EE treatment). Subjects consumed a single dose of their assigned capsule in a fasting state, and plasma was collected before and for 24 h after dosing. Subjects underwent a ≥ 14 -day washout and were crossed over to the other treatment condition. Plasma concentrations of EPA, DHA, and EPA + DHA were assessed. FINDINGS: Twenty-three subjects (11 women, 12 men; mean [SEM] age, 33.8 [2.1] years; and body mass index, 24.9 [0.7] kg/m²) completed the trial. The baseline-adjusted, dose-normalized, arithmetic means (SD) of the incremental (i)-AUC_{0-24h} for EPA + DHA were 543 (266) and 102 (88.2) h . mug/mL/g for the SMEDS and EE formulations, respectively (P < 0.001). The iAUC_{0-24h} least-squares geometric mean ratio (90% CI) for SMEDS:standard EE was 475/58 = 8.2 (4.8-13.9), indicating markedly higher bioavailability of EPA + DHA with the SMEDS formulation compared to the standard EE formulation. This finding was also true for EPA (geometric mean ratio [90% CI], 18.2 [11.3-29.3]) and DHA (geometric mean ratio [90% CI], 4.5 [2.9-7.0]). IMPLICATIONS: The SMEDS delivery system markedly enhanced appearance in plasma of EPA and DHA, compared to a standard EE formulation, when ingested in the fasting state. ClinicalTrials.gov identifier: NCT03443076.

[13] Aziz F, Garg N, Parajuli S et al. **Lipid lowering in dialysis patients with cardiovascular disease who are awaiting kidney transplantation.** *Clinical transplantation* 2018:e13452.

PM: <http://www.ncbi.nlm.nih.gov/pubmed/?term=30466167>

ABSTRACT

Dyslipidemias are highly prevalent in chronic kidney disease, end-stage renal disease and kidney transplant patients. These dyslipidemias are associated with high cardiovascular risk and mortality. Many clinical trials have shown that statin therapy can significantly reduce adverse cardiovascular events in chronic kidney disease patients and kidney transplant recipients. However, three major trials did not show a benefit of statin therapy in end-stage renal disease patients on dialysis. Major guidelines either recommend against the use of statins in patients on dialysis or provide no recommendations about statin use for this complex patient population. As a result, we suspect many patients on dialysis are not on statins, even if they have known atherosclerotic cardiovascular disease. When these patients receive kidney transplants, the risk of adverse cardiovascular events increases in the peri-operative period. Although, there are no randomized clinical trials looking at statin use in these patients, we suggest that statin use be considered in patients with a history of atherosclerotic cardiovascular disease, to potentially minimize peri-operative cardiovascular complications. We also recommend further research to determine whether statin therapy in dialysis patients awaiting kidney transplant is associated with better survival. This article is protected by copyright. All rights reserved.

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[14] Lwin EMP, Leggett C, Ritchie U et al. **Transfer of rosuvastatin into breast milk: liquid chromatography-mass spectrometry methodology and clinical recommendations.** *Drug design, development and therapy* 2018; 12:3645-3651.

PM: <http://www.ncbi.nlm.nih.gov/pubmed/?term=30464396>

ABSTRACT

Introduction: Rosuvastatin reduces concentrations of total cholesterol (TC) and is used for the management of hypercholesterolemia and prevention of acute coronary syndromes. There are no published reports estimating infant exposure to rosuvastatin through breast milk. Purpose: The aims of this study were to quantify concentrations of rosuvastatin in human milk and plasma from a lactating woman taking rosuvastatin and to investigate potential infant exposure. Materials and methods: A 38-year-old breastfeeding mother was commenced on rosuvastatin 20 mg daily for secondary prevention of an acute coronary syndrome. Eight maternal breast milk samples and a single plasma sample were collected over a 24-hour period. The samples were quantified using a sensitive liquid chromatography-mass spectrometry (LC-MS/MS) method. Results: The average concentration of rosuvastatin in breast milk was 30.84 ng/mL, and a peak concentration of 58.59 ng/mL occurred at 17 hours after oral administration. Although the milk-to-plasma (M/P) ratio was 16.49 at 14 hours, the theoretical infant dosage (TID) and relative infant dose (RID) were 0.005 mg/kg/day and 1.50%, respectively. Conclusion: The findings suggest that only small amounts of rosuvastatin pass into breast milk. Should the maternal condition necessitate treatment, consideration could be given to the use of rosuvastatin during breastfeeding provided the infant is monitored.

[15] Zhang J, Guo Y, Jin Q et al. **Meta-analysis of rosuvastatin efficacy in prevention of contrast-induced acute kidney injury.** *Drug design, development and therapy* 2018; 12:3685-3690.

PM: <http://www.ncbi.nlm.nih.gov/pubmed/?term=30464400>

ABSTRACT

Background: Contrast-induced nephropathy (CIN) is a complication after the intravascular administration of a contrast medium injection. Previous studies have investigated statins as therapy for CIN due to its positive results in the prevention of contrast-induced acute kidney injury (CI-AKI). Nevertheless, the beneficial effects of rosuvastatin pretreatment in preventing CIN in patients with acute coronary syndromes still remain controversial. In this study, we performed a meta-analysis of randomized controlled trials (RCTs) to evaluate the beneficial impact of rosuvastatin in the prevention of CI-AKI in acute coronary syndrome patients. Methods: PubMed, Embase, and Cochrane library were searched, for RCTs, updated on January 2018. The method was to evaluate rosuvastatin prior to angiography for the prevention of CI-AKI in patients undergoing coronary angiography, of which the main outcome was the incidence of CIN. Results: A total of five RCTs were included in this analysis. Patients treated with rosuvastatin prior to invasive angiography had a significantly lower incidence of CI-AKI than controls (odds ratio [OR]: 0.53, 95% CI: 0.40-0.71, $P < 0.0001$). Moreover, the subgroup analysis also showed that the benefit of rosuvastatin for patients with chronic kidney disease (OR: 0.49, 95% CI: 0.26-0.92, $P = 0.03$) and diabetes mellitus (OR: 0.56, 95% CI: 0.38-0.83, $P = 0.004$) which was consistent in compared with the respective control groups. Conclusion: The findings of this meta-analysis suggest that the preoperative rosuvastatin treatment significantly

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reduces the risk of renal insufficiency of CIN in at-risk patients with chronic kidney disease or diabetes mellitus. Additional studies are needed to identify at-risk patients, provide optimum dose peri-procedural treatment, and reduce the incidence of CIN.

[16] *Sampalis JS, Psaradellis E, Stutz M et al. Post Hoc Analysis of the CONFIDENCE II, PROTECT I, SHAKE THE HABIT I and SHAKE THE HABIT II Observational Studies in Mild to Moderate Hypertensive Patients Treated with Perindopril and Atorvastatin Concomitantly. Drugs in R&D 2018.*

PM: <http://www.ncbi.nlm.nih.gov/pubmed/?term=30448890>

ABSTRACT

BACKGROUND AND OBJECTIVES: Management of hypertension and dyslipidemia is important when considering cardiovascular disease risk; however, achievement of optimal lipid and blood pressure (BP) targets in clinical practice remains inadequate. This analysis sought to estimate the frequency, effectiveness, and safety of co-administrated atorvastatin and perindopril in routine care. **METHODS:** We conducted a post hoc analysis of four Canadian, prospective, multi-center, observational studies assessing real-life effectiveness and safety of perindopril + atorvastatin in mild-to-moderate hypertensive patients with concomitant dyslipidemia over 16 weeks. The safety population comprised patients receiving one or more doses of free combination perindopril + atorvastatin; the full analysis set (FAS) received perindopril + atorvastatin at baseline, with one or more post-baseline systolic BP measurements while on treatment. **RESULTS:** A total of 3541 and 3172 patients were included in the safety population and FAS, respectively. At the last observation carried forward, significant reductions in mean systolic BP (- 18.0 mmHg; $p < 0.001$) and diastolic BP (- 8.9 mmHg; $p < 0.001$) were observed; target BP was achieved by 73.1% of patients. Emergent adverse events (AEs) were reported in 8.0% of patients, the most common being cough (4.5% of patients), headache (0.9%), and dizziness (0.8%). Four serious AEs were reported among three (0.1%) patients. No differences were observed in effectiveness or safety between studies. **CONCLUSIONS:** Concomitant perindopril + atorvastatin therapy demonstrated similar efficacy across all studies, with significant reductions in BP and achievement of target BP levels observed in a real-world setting. Results align with known safety profiles of atorvastatin and perindopril, with no unexpected AEs observed when compared with data from treatment with the individual drugs.

[17] *Zhang Z, Zhang HY, Zhang Y, Li H. Inactivation of the Ras/MAPK/PPARgamma signaling axis alleviates diabetic mellitus-induced erectile dysfunction through suppression of corpus cavernosal endothelial cell apoptosis by inhibiting HMGCS2 expression. Endocrine 2018.*

PM: <http://www.ncbi.nlm.nih.gov/pubmed/?term=30460485>

ABSTRACT

PURPOSE: Diabetic mellitus-induced erectile dysfunction (DMED) represents a significant complication associated with diabetes mellitus (DM) that greatly affects human life quality. Various reports have highlighted the involvement of mitochondrial 3-hydroxy-3-methylglutaryl-CoA synthase 2 (HMGCS2) in the regulation of mitochondrial fatty acid oxidation, which has also been linked with DM. Through bioinformatics analysis, HMGCS2 was determined to be a novel target among DM patients suffering from erectile dysfunction (ED), and enriched in the Ras/ERK/PPAR signaling axis. Owing to the fact that the key mechanism HMGCS2 involved in

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DM remains largely unknown, we set out to investigate the role of the Ras/MAPK/PPARgamma signaling axis and HMGCS2 in the corpus cavernosal endothelial cells (CCECs) of rats with DMED. METHODS: Firstly, bioinformatics analysis was used to screen out differentially expressed genes in DMED. Then, to investigate the influence of the Ras/MAPK/PPARgamma signaling axis and HMGCS2 on DMED, a rat model of DMED was established and injected with Simvastatin and si-Hmgcs2. The individual expression patterns of Ras, MAPK, PPARgamma and HMGCS2 were determined by RT-qPCR, immunohistochemistry and western blot analysis methods. Afterwards, to investigate the mechanism of Ras/MAPK/PPARgamma signaling axis and HMGCS2, CCECs were isolated from DMED rats and transfected with agonists and inhibitors of the Ras/MAPK/PPARgamma signaling axis and siRNA of HMGCS2, with their respective functions in apoptosis and impairment of CCECs evaluated using TUNEL staining and flow cytometry. RESULTS: Microarray analysis and KEGG pathway enrichment analysis revealed that Ras/ERK/PPAR signaling axis mediated HMGCS2 in DMED. Among the DMED rats, the Ras/MAPK/PPAR signaling axis was also activated while the expression of HMGCS2 was upregulated. The activation of Ras was determined to be capable of upregulating ERK expression which resulted in the inhibition of the transcription of PPARgamma and subsequent upregulation of HMGCS2 expression. The inhibited activation of the Ras/ERK/PPAR signaling axis and silencing HMGCS2 were observed to provide an alleviatory effect on the injury of DMED while acting to inhibit the apoptosis of CCECs. CONCLUSION: Collectively, the key findings suggested that suppression of the Ras/MAPK/PPARgamma signaling axis could downregulate expression of HMGCS2, so as to alleviate DMED. This study defines the potential treatment for DMED through inhibition of the Ras/MAPK/PPARgamma signaling axis and silencing HMGCS2.

[18] *Xu S, Luo S, Zhu Z, Xu J. Small molecules as inhibitors of PCSK9: Current status and future challenges. European journal of medicinal chemistry* 2018; 162:212-233.

PM: <http://www.ncbi.nlm.nih.gov/pubmed/?term=30448414>

ABSTRACT

Proprotein convertase subtilisin/kexin type 9 (PCSK9) plays an important role in regulating lipoprotein metabolism by binding to low-density lipoprotein receptors (LDLRs), leading to their degradation. LDL cholesterol (LDL-C) lowering drugs that operate through the inhibition of PCSK9 are being pursued for the management of hypercholesterolemia and reducing its associated atherosclerotic cardiovascular disease (CVD) risk. Two PCSK9-blocking monoclonal antibodies (mAbs), alirocumab and evolocumab, were approved in 2015. However, the high costs of PCSK9 antibody drugs impede their prior authorization practices and reduce their long-term adherence. Given the potential of small-molecule drugs, the development of small-molecule PCSK9 inhibitors has attracted considerable attention. This article provides an overview of the recent development of small-molecule PCSK9 inhibitors disclosed in the literature and patent applications, and different approaches that have been pursued to modulate the functional activity of PCSK9 using small molecules are described. Challenges and potential strategies in developing small-molecule PCSK9 inhibitors are also discussed.

[19] *Soulele K, Karalis V. Development of a joint population pharmacokinetic model of ezetimibe and its conjugated metabolite. Eur J Pharm Sci* 2018.

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PM: <http://www.ncbi.nlm.nih.gov/pubmed/?term=30465817>

ABSTRACT

Ezetimibe (EZE) is an extensively used antihyperlipidemic drug with an important cholesterol lowering activity. It undergoes extensive first-pass metabolism to form its active glucuronide metabolite (EZEG). Both drugs exhibit complex pharmacokinetic profiles attributed mainly to repetitive enterohepatic kinetics. The aim of the present study was the investigation of EZE and EZEG pharmacokinetics (PK), through the development of a joint population pharmacokinetic model able to characterize their kinetic processes and enterohepatic recirculation simultaneously. Concentration-time data derived from a bioequivalence study in 28 healthy subjects were used for the analysis. Population PK modeling was performed on the obtained data using nonlinear mixed effect modeling approach, where different methodologies were applied for the description of the complex metabolism and recirculation processes of the two compounds. EZE and EZEG concentrations were best described by a population PK model incorporating first-pass metabolism and an enterohepatic recirculation loop, accounting for the recycling process of the two moieties. This is the first joint population pharmacokinetic model describing the kinetics of both EZE and EZEG.

[20] *Osuna-Ramos JF, Reyes-Ruiz JM, Del Angel RM. The Role of Host Cholesterol During Flavivirus Infection. Frontiers in cellular and infection microbiology 2018; 8:388.*

PM: <http://www.ncbi.nlm.nih.gov/pubmed/?term=30450339>

ABSTRACT

In recent years the emergence and resurgence of arboviruses have generated a global health alert. Among arboviruses, Dengue (DENV), Zika (ZIKV), Yellow Fever (YFV), and West Nile (WNV) virus, belong to the genus Flavivirus, cause high viremia and occasionally fatal clinical disease in humans. Given the genetic austerity of the virus, they depend on cellular factors and organelles to complete its replication. One of the cellular components required for flavivirus infection is cholesterol. Cholesterol is an abundant lipid in biomembranes of eukaryotes cells and is necessary to maintain the cellular homeostasis. Recently, it has been reported, that cholesterol is fundamental during flavivirus infection in both mammal and insect vector models. During infection with DENV, ZIKV, YFV, and WNV the modulation of levels of host-cholesterol facilitates viral entry, replicative complexes formation, assembly, egress, and control of the interferon type I response. This modulation involves changes in cholesterol uptake with the concomitant regulation of cholesterol receptors as well as changes in cholesterol synthesis related to important modifications in cellular metabolism pathways. In view of the flavivirus dependence of cholesterol and the lack of an effective anti-flaviviral treatment, this cellular lipid has been proposed as a therapeutic target to treat infection using FDA-approved cholesterol-lowering drugs. This review aims to address the dependence of cholesterol by flaviviruses as well as the basis for anti flaviviral therapy using drugs which target is cholesterol synthesis or uptake.

[21] *Seghieri M, Christensen AS, Andersen A et al. Future Perspectives on GLP-1 Receptor Agonists and GLP-1/glucagon Receptor Co-agonists in the Treatment of NAFLD. Frontiers in endocrinology 2018; 9:649.*

PM: <http://www.ncbi.nlm.nih.gov/pubmed/?term=30459715>

ABSTRACT

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Along the obesity pandemic, the prevalence of non-alcoholic fatty liver disease (NAFLD), often regarded as the hepatic manifestation of the metabolic syndrome, increases worldwide representing now the prevalent liver disease in western countries. No pharmacotherapy is approved for the treatment of NAFLD and, currently, the cornerstone treatment is lifestyle modifications focusing on bodyweight loss, notoriously difficult to obtain and even more difficult to maintain. Thus, novel therapeutic approaches are highly demanded. Glucagon-like peptide-1 (GLP-1) receptor agonists (GLP-1RAs) are approved for the treatment of type 2 diabetes and obesity. They exert their body weight-lowering effect by reducing satiety and food intake. GLP-1RAs have also been shown to reduce liver inflammation and fibrosis. Furthermore, glucagon receptor agonism is being investigated for the treatment of NAFLD due to its appetite and food intake-reducing effects, as well as its ability to increase lipid oxidation and thermogenesis. Recent studies suggest that glucagon receptor signaling is disrupted in NAFLD, indicating that supra-physiological glucagon receptor agonism might represent a new NAFLD treatment target. The present review provides (1) an overview in the pathophysiology of NAFLD, including the potential involvement of GLP-1 and glucagon, (2) an introduction to the currently available GLP-1RAs and (3) outlines the potential of emerging GLP-1RAs and GLP-1/glucagon receptor co-agonists in the treatment of NAFLD.

[22] Jang H, Lee J, Park S et al. **Pravastatin Attenuates Acute Radiation-Induced Enteropathy and Improves Epithelial Cell Function.** *Frontiers in pharmacology* 2018; 9:1215.

PM: <http://www.ncbi.nlm.nih.gov/pubmed/?term=30459609>

ABSTRACT

Background and Aim: Radiation-induced enteropathy is frequently observed after radiation therapy for abdominal and pelvic cancer or occurs secondary to accidental radiation exposure. The acute effects of irradiation on the intestine might be attributed to inhibition of mitosis in the crypts, as the loss of proliferative functions impairs development of the small intestinal epithelium and its barrier function. Especially, oxidative damage to intestinal epithelial cells is a key event in the initiation and progression of radiation-induced enteropathy. Pravastatin is widely used clinically to lower serum cholesterol levels and has been reported to have anti-inflammatory effects on endothelial cells. Here, we investigated the therapeutic effects of pravastatin on damaged epithelial cells after radiation-induced enteritis using in vitro and in vivo systems. **Materials and Methods:** To evaluate the effects of pravastatin on intestinal epithelial cells, we analyzed proliferation and senescence, oxidative damage, and inflammatory cytokine expression in an irradiated human intestinal epithelial cell line (InEpC). In addition, to investigate the therapeutic effects of pravastatin in mice, we performed histological analysis, bacterial translocation assays, and intestinal permeability assays, and also assessed inflammatory cytokine expression, using a radiation-induced enteropathy model. **Results:** Histological damage such as shortening of villi length and impaired intestinal crypt function was observed in whole abdominal-irradiated mice. However, damage was attenuated in pravastatin-treated animals, in which normalization of intestinal epithelial cell differentiation was also observed. Using in vitro and in vivo systems, we also showed that pravastatin improves the proliferative properties of intestinal epithelial cells and decreases radiation-induced oxidative damage to the intestine. In addition, pravastatin inhibited levels of epithelial-derived inflammatory cytokines including IL-6, IL-1beta, and TNF-alpha in irradiated InEpC cells.

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We also determined that pravastatin could rescue intestinal barrier dysfunction via anti-inflammatory effects using the mouse model. Conclusion: Pravastatin has a therapeutic effect on intestinal lesions and attenuates radiation-induced epithelial damage by suppressing oxidative stress and the inflammatory response.

[23] Guan S, Zhang Y, Wang B, Li W. **Medical Therapy Induced Regression of Plaque in a Female Patient with ASCVD.** *Int Heart J* 2018.

PM: <http://www.ncbi.nlm.nih.gov/pubmed/?term=30464115>

ABSTRACT

The initiation and progression of atherosclerotic cardiovascular disease (ASCVD) has always been associated with a series of risk factors. Evidences of statin therapy from randomized clinical trials are abundant, whereas discussions regarding patients with ASCVD without evidence-based risk factors are rare. Here, we describe a case of a 58-year-old woman who was diagnosed with ASCVD with none of these evidence-based risk factors. After four years of medical interventions, including atorvastatin, the patient recovered completely from severe chest pain with significant regression of atherosclerotic plaques in coronary arteries.

[24] Parisi V, Petraglia L, D'Esposito V et al. **Statin therapy modulates thickness and inflammatory profile of human epicardial adipose tissue.** *International journal of cardiology* 2019; 274:326-330.

PM: <http://www.ncbi.nlm.nih.gov/pubmed/?term=30454723>

ABSTRACT

BACKGROUND: Epicardial adipose tissue (EAT) thickness and pro-inflammatory status has been shown to be associated with several cardiac diseases, including aortic stenosis (AS). Thus, cardiac visceral fat could represent a potential new target for drugs. In the present study we evaluate the effect of statin therapy on EAT accumulation and inflammation. METHODS: Echocardiographic EAT thickness was assessed in 193 AS patients taking (n.87) and not taking (n.106) statins, undergoing cardiac surgery. To explore the association between statin therapy and EAT inflammation, EAT biopsies were obtained for cytokines immunoassay determination in EAT secretomes. An in vitro study was also conducted and the modulation of EAT and subcutaneous adipose tissue (SCAT) secretomes by atorvastatin was assessed in paired biopsies. RESULTS: Statin therapy was significantly associated with lower EAT thickness ($p < 0.0001$) and with lower levels of EAT-secreted inflammatory mediators ($p < 0.0001$). Of note, there was a significant correlation between EAT thickness and its pro-inflammatory status. In vitro, atorvastatin showed a direct anti-inflammatory effect on EAT which was significantly higher compared to the SCAT response to statin incubation ($p < 0.0001$). CONCLUSIONS: The present study indicates a robust association between statin therapy and reduced EAT accumulation in patients with AS. The present data also suggest a direct relationship between EAT thickness and its inflammatory status, both modulated by statin therapy. The in vitro results support the hypothesis of a direct action of statins on EAT secretory profile. Overall our data suggest EAT as a potential new therapeutic target for statin therapy.

[25] Wadsack D, Sattler H, Kleber ME et al. **Recurrent tendosynovitis as a rare manifestation of a lipid disorder.** *Journal of clinical lipidology* 2018.

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PM: <http://www.ncbi.nlm.nih.gov/pubmed/?term=30459115>

ABSTRACT

A 33-year-old female had suffered from spontaneously recurrent bursitis and tendosynovitis/enthesitis of the patellar and Achilles tendons for about 10 years. The episodes of immobilization increased. Ultrasound imaging of the swollen and painful tendons showed chronic inflammation with neoangiogenesis within the tendons and hypoechoic lesions. Clinical and laboratory tests did not provide evidence for a rheumatic disease. Low density lipoprotein cholesterol was elevated. Biopsies of skin lesions did not confirm the suspicion of cutaneous xanthomas. Genetic testing for familial hypercholesterolemia was negative. Campesterol and sitosterol were elevated 7- to 12-fold and 20- to 38-fold over the upper limit of normal on two occasions. There was no relevant mutation in ABCG5. In ABCG8, we identified a missense mutation c.1267G>A in exon 9 changing glutamic acid 423 into lysine within the transmembrane domain, and an insertion of adenine (c.1487insA) leading to a frameshift and a premature stop codon (Ile497Aspfs*105). The patient had no clinical evidence of premature atherosclerosis. Therapeutic approaches with nonsteroidal antirheumatic drugs, prednisone, statins, and ezetimibe accompanied by a diet poor in plant sterols led to a relief of symptoms. This case report shows that tendon xanthoma along with tendosynovitis, especially on extensor areas, is suspicious for hypercholesterolemia as the underlying cause. The absence of atherosclerotic plaques in the abdominal aorta and in the carotid arteries on ultrasound may suggest that phytosterolemia is not necessarily accompanied by premature vascular disease.

[26] *Vaishya R, Agarwal AK, Shah A et al. Current status of top 10 nutraceuticals used for Knee Osteoarthritis in India. Journal of clinical orthopaedics and trauma* 2018; 9:338-348.

PM: <http://www.ncbi.nlm.nih.gov/pubmed/?term=30449982>

ABSTRACT

Knee Osteoarthritis (OA) is a progressive degenerative joint disease affecting the quality of life of the elderly population. There is considerable evidence that nutraceuticals from natural herbs may play a significant role in inflammation and joint destruction in OA. We review the current status of some of the commonly used nutraceuticals in Indian market - Boswellia, Aflapin, Chondroitin sulphate, Glucosamine sulphate, Collagen peptide, Curcumin, Fish Oil, Ginger, Green tea, and Rosehip extract. We have summarized their mechanism of action, biological effects, toxicities and efficacy in the management of Knee OA. These supplements have been found to be effective in knee OA in various studies. No serious side effects have been reported for any of these supplements. Overall, our study identifies and support the use of these nutraceuticals to provide symptomatic relief to patients with knee OA and justify their use as an adjunct therapy for the management. More good quality trials are needed to provide definitive answers to questions related to their efficacy and safety for OA prevention and treatment.

[27] *Ermini G, Tosetti C, Zocchi D et al. Type 2 diabetes treatment and progression of chronic kidney disease in Italian family practice. Journal of endocrinological investigation* 2018.

PM: <http://www.ncbi.nlm.nih.gov/pubmed/?term=30465248>

ABSTRACT

AIMS: Progressive chronic kidney disease represents a dreadful complication of type 2 diabetes mellitus (T2DM). We tested the pattern of use and the renal effects of old glucose-lowering

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drugs in T2DM patients cared for by Italian general practitioners (GPs). METHODS: Data of 2606 T2DM patients were extracted from the databases of GPs, who do not have access to the most recent glucose-lowering drugs in Italy. The rate of kidney function decline was calculated by CKD-EPI_{Cr}, based on two consecutive creatinine values. RESULTS: Metformin was used in 55% of cases, either alone or with sulfonylureas/repaglinide, across the whole spectrum of CKD (from 66% in stage G1 to only 8% in G4). Sulfonylurea use peaked at 21-22% in stage G2-G3a, whereas repaglinide use significantly increased from 8% in G1 to 22% in G4. The median rate of CKD decline was - 1.64 mL/min/1.73 m² per year; it was higher in G1 (- 3.22 per year) and progressively lower with CKD severity. 826 cases (31.7%) were classified as fast progressors (eGFR decline more negative than - 5 mL/min/1.73 m² per year). The risk of fast progressing CKD was associated with increasing BMI, albuminuria, and sulfonylurea use, alone (OR, 1.47; 95% confidence interval, 1.16-1.85), or in association with metformin (OR, 1.40; 95% CI 1.04-1.88). No associations were demonstrated for metformin, cardiovascular and lipid lowering drug use. CONCLUSION: In the setting of Italian family practice, sulfonylurea use is associated with progressive CKD in patients with T2DM. Metformin, at doses progressively reduced according to CKD stages, as recommended by guidelines, is not associated with fast progression.

[28] Galvan AM, Chorba JS. **Cell-associated, Heparin-like Molecules Modulate the Ability of LDL to Regulate PCSK9 Uptake.** *Journal of lipid research* 2018.

PM: <http://www.ncbi.nlm.nih.gov/pubmed/?term=30463987>

ABSTRACT

Proprotein convertase subtilisin/kexin type 9 (PCSK9) targets the LDL receptor (LDLR) for degradation, increasing plasma LDL and, consequently, cardiovascular risk. Uptake of secreted PCSK9 is required for its effect on the LDLR, and LDL itself inhibits this uptake, though how it does so remains unclear. In this study, we investigated the relationship between LDL, the PCSK9:LDLR interaction, and PCSK9 uptake. We show that LDL inhibits binding of PCSK9 to the LDLR in vitro more impressively than it inhibits PCSK9 uptake in cells. Furthermore, cell-surface, heparin-like molecules (HLMs) can partly explain this difference, consistent with heparan sulfate proteoglycans (HSPGs) acting as co-receptors for PCSK9. We also show that HLMs can interact with either PCSK9 or LDL to modulate the inhibitory activity of LDL on PCSK9 uptake, with such inhibition rescued by competition with the entire PCSK9 prodomain, but not its truncated variants. Additionally, we show that the gain-of-function (GOF) PCSK9 variant S127R, located in the prodomain near the HSPG binding site, exhibits increased affinity for HLMs, potentially explaining its phenotype. Overall, our findings suggest a model where LDL acts as a negative regulator of PCSK9 function by decreasing its uptake via direct interactions with either the LDLR or HLMs.

[29] Staverosky T. **Ketogenic Weight Loss: The Lowering of Insulin Levels Is the Sleeping Giant in Patient Care.** *The Journal of medical practice management : MPM* 2016; 32:63-66.

PM: <http://www.ncbi.nlm.nih.gov/pubmed/?term=30452850>

ABSTRACT

Research conducted by members of the American Society of Bariatric Physicians (recently renamed the Obesity Medicine Association) and others shows remarkable health benefits

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associated with wellness protocols that limit the intake of carbohydrates and sugars, which results in lower insulin demand and levels. The research demonstrates that the lowering of insulin levels dramatically improves diabetes⁵ and the factors associated with metabolic syndrome,⁶⁻⁸ including central obesity, high blood pressure, and elevated blood lipids, which, of course, are risk factors associated with cardiovascular disease. Other conditions that have shown improvement under the influence of reduced insulin levels include fatty liver disease,⁹ polycystic ovary syndrome,¹⁰ gastroesophageal reflux disease,¹¹ irritable bowel syndrome with diarrhea,¹³ and other maladies. Significantly, dietary carbohydrate restriction induces ketosis, a state in which the body is forced to burn fat instead of sugar as its primary source of fuel. When in ketosis, patients are able to lose weight safely, effectively, and relatively quickly.

[30] Wang Y, Wang X, Yang W et al. **Effect of Simvastatin on the Intestinal Rho/ROCK Signaling Pathway in Rats With Sepsis.** *J Surg Res* 2018; 232:531-538.

PM: <http://www.ncbi.nlm.nih.gov/pubmed/?term=30463769>

ABSTRACT

BACKGROUND: Simvastatin may alleviate the intestinal barrier dysfunction induced by sepsis. This study aimed to investigate the role of the Ras homolog (Rho)/Rho-associated coiled-coil forming protein kinase (ROCK) signaling pathway in the intestinal barrier of simvastatin-treated rats with sepsis. **MATERIALS AND METHODS:** Male Wistar rats were pretreated with simvastatin (0.2 mg/kg of body weight) for 1 week before cecal ligation and puncture. Twenty-four hours after cecal ligation and puncture, the condition of bacterial translocation was evaluated. Plasma levels of intestinal fatty acid binding protein, D-lactic acid and inflammatory factors, and oxidative stress in the intestine were determined. The intestinal injury scores, as well as the protein levels of Rho, ROCK1, and tight junction proteins ZO-1 and occludin were analyzed. **RESULTS:** Treatment with simvastatin alleviated the sepsis-induced increases in the plasma concentration of intestinal fatty acid binding protein and D-lactic acid, as well as the number of colony-forming units in the bacterial culture of the blood, liver, spleen, and kidney. In addition, simvastatin effectively reduced the intestinal levels of tumor necrosis factor alpha, interleukin-6, high-mobility group box 1, and malondialdehyde and increased the activity of superoxide dismutase in rats with sepsis. Staining with hematoxylin and eosin showed that severe intestinal injury occurred in the sepsis group, which was reduced by the treatment of simvastatin. Furthermore, the expression of Rho and ROCK1 was significantly downregulated and the protein expression levels of ZO-1 and occludin were significantly increased in simvastatin-treated rats ($P < 0.05$). **CONCLUSIONS:** Simvastatin can ameliorate the intestinal barrier dysfunction caused by sepsis by inhibiting the Rho/ROCK signaling pathway and reducing the levels of inflammatory factors and oxidative stress in the intestine, which also increase the expression of tight junction proteins.

[31] Miname MH, Bittencourt MS, Moraes SR et al. **Coronary Artery Calcium and Cardiovascular Events in Patients With Familial Hypercholesterolemia Receiving Standard Lipid-Lowering Therapy.** *JACC. Cardiovascular imaging* 2018.

PM: <http://www.ncbi.nlm.nih.gov/pubmed/?term=30448145>

ABSTRACT

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OBJECTIVES: The aim of this study was to evaluate the role of coronary artery calcium (CAC) as a predictor of atherosclerotic cardiovascular disease (ASCVD) (fatal or not myocardial infarction, stroke, unstable angina requiring revascularization, and elective myocardial revascularization) events in asymptomatic primary prevention molecularly proven heterozygous familial hypercholesterolemia (FH) subjects receiving standard lipid-lowering therapy. **BACKGROUND:** FH is associated with premature ASCVD. However, the clinical course of ASCVD in subjects with FH is heterogeneous. CAC score, a marker of subclinical atherosclerosis burden, may optimize ASCVD risk stratification in FH. **METHODS:** Subjects with FH underwent CAC measurement and were followed prospectively. The association of CAC with ASCVD was evaluated using multivariate analysis. **RESULTS:** A total of 206 subjects (mean age 45 +/- 14 years, 36.4% men, baseline and on-treatment low-density lipoprotein cholesterol 269 +/- 70 mg/dl and 150 +/- 56 mg/dl, respectively) were followed for a median of 3.7 years (interquartile range: 2.7 to 6.8 years). CAC was present in 105 (51%), and 15 ASCVD events (7.2%) were documented. Almost half of events were hard outcomes, and the others were elective myocardial revascularizations. The annualized rates of events per 1,000 patients for CAC scores of 0 (n = 101 [49%]), 1 to 100 (n = 62 [30%]) and >100 (n = 43 [21%]) were, respectively, 0, 26.4 (95% confidence interval: 12.9 to 51.8), and 44.1 (95% confidence interval, 26.0 to 104.1). In multivariate Cox regression analysis, log(CAC score + 1) was independently associated with incident ASCVD events (hazard ratio: 3.33; 95% CI: 1.635 to 6.790; p = 0.001). **CONCLUSIONS:** CAC was independently associated with ASCVD events in patients with FH receiving standard lipid-lowering therapy. This may help further stratify near-term risk in patients who might be candidates for further treatment with newer therapies.

[32] Shapiro MD, Blankstein R. **Reclassifying Risk in Familial Hypercholesterolemia: The Power of a Coronary Artery Calcium Score of Zero.** *JACC. Cardiovascular imaging* 2018.

PM: <http://www.ncbi.nlm.nih.gov/pubmed/?term=30448142>

ABSTRACT

[33] Wu NQ, Guo YL, Zhu CG et al. **Comparison of statin plus ezetimibe with double-dose statin on lipid profiles and inflammation markers.** *Lipids in health and disease* 2018; 17:265.

PM: <http://www.ncbi.nlm.nih.gov/pubmed/?term=30470229>

ABSTRACT

BACKGROUND: Achievement of low-density lipoprotein cholesterol (LDL-C) goal is the most important for the patients with atherosclerotic cardiovascular diseases (ASCVD) who received lipid-lowering therapy. It is unclear that whether combination of ezetimibe with statin is superior to double-dose of statin regarding both of the lipid-lowering efficacy and improvement of inflammation in Chinese patients with ASCVD. Therefore, this study was performed to compare the effects of these two regimes on lipid profiles and inflammation markers.

METHODS: In this randomized control study, ninety eight patients with ASCVD, who were naive to statins or other lipid-lowering agents, were enrolled into the study, and randomly assigned into two groups, A40 group (atorvastatin 40 mg/d, n = 50), A20E10 group (atorvastatin 20 mg/d combined with ezetimibe 10 mg/d, n = 48). The patients were followed up at week 4 and week 12 after treatment. The lipid profiles and oxidative low-density lipoprotein cholesterol (ox-LDL) were measured at the end of study. **RESULTS:** There were no differences in clinical

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characteristics including lipid, ox-LDL and hypersensitive C reactive protein (Hs-CRP) among groups at baseline. However, the average level of LDL-C was lower in group A20E10 than that in group A40 significantly (1.59 +/- 0.44 mmol/L vs 1.99 +/- 0.56 mmol/L, p = 0.001) during follow-up at week 12 after treatment. Importantly, the higher rate of achievement of LDL-C goal was attained at group of combination statin with ezetimibe (79.2% in group A20E10 vs 50.0% in group A40, p = 0.016). The difference of the level of ox-LDL between both the groups after 12 weeks treatment had not statistical significance (3.63 +/- 1.13 U/L in group A20E10 vs 4.14 +/- 1.32 U/L in group A40, p = 0.077). Similarly, the level of Hs-CRP between both the groups after treatment was not significantly different (p > 0.05). CONCLUSIONS: In this randomized study, the data showed that a combination of moderate statin and ezetimibe achieved more reduction of LDL-C compared to the double-dose statin but similar impact on inflammation markers.

[34] *Mo R, Zhang X, Yang Y. Effect of probiotics on lipid profiles in hypercholesterolaemic adults: A meta-analysis of randomized controlled trials. Medicina clinica* 2018.

PM: <http://www.ncbi.nlm.nih.gov/pubmed/?term=30467077>

ABSTRACT

BACKGROUND: Recent clinical studies have yielded controversial results regarding the effect of probiotics on lipid profiles. To assess the efficacy of probiotics in lowering serum lipid concentrations, we conducted a meta-analysis of randomized controlled trials (RCTs).

METHODS: Literature from the PubMed, Embase and Cochrane databases were searched and screened. The effects of probiotics on lipid profiles were assessed by mean difference (MD) and 95% confidence interval (CI). All included studies were analyzed using Review Manager 5.3 (Cochrane Collaboration, 2014). RESULTS: A total of 19 RCTs, including 967 participants, met the inclusion criteria. Probiotic interventions reduced total cholesterol (TC) and low-density lipoprotein cholesterol (LDL-C) compared to controls (placebo or no treatment) by -0.25mmol/L (95% CI: -0.39, -0.12) and -0.17mmol/L (95% CI: -0.25, -0.09), respectively. No significant effects of probiotics on triglyceride (TG) and high-density lipoprotein cholesterol (HDL-C) levels were found. The effects of probiotics on decreasing TC and LDL-C levels were greater for longer intervention times, certain probiotic strains, and in younger mildly hypercholesterolaemic subjects. CONCLUSION: This meta-analysis revealed that the use of probiotics can significantly lower TC and LDL-C levels in hypercholesterolaemic adults, which brings hope for reducing the risk factors for developing cardiovascular disease.

[35] *Ong KL, Hui N, Januszewski AS et al. High plasma FGF21 levels predicts major cardiovascular events in patients treated with atorvastatin (from the treating to new targets [TNT] study). Metabolism* 2018.

PM: <http://www.ncbi.nlm.nih.gov/pubmed/?term=30452928>

ABSTRACT

BACKGROUND: Higher plasma fibroblast growth factor 21 (FGF21) levels predict incident cardiovascular events in type 2 diabetes patients. However, whether FGF21 levels predict cardiovascular events in statin-treated patients in the general population is unknown. We investigated whether FGF21 levels predict major cardiovascular event (MCVE) in the Treating to New Targets (TNT) trial participants. METHODS: After 8-week run-in on atorvastatin 10mg/day, 10,001 patients with stable coronary disease in the TNT trial were randomized to 10mg or

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80mg/day of atorvastatin for a median of 4.9years. We analyzed data from 1996 patients with plasma FGF21 levels measured at randomization. Among them, 1835 patients had FGF21 measured one-year post-randomization. RESULTS: Higher ln-transformed FGF21 levels at randomization were associated with higher risk of incident MCVE (adjusted hazards ratio per SD increase=1.18, P=0.019). At 1-year post-randomization, FGF21 levels were lower in patients randomized to receive 80mg versus 10mg atorvastatin (186.9 versus 207.5pg/mL respectively, P=0.006). Higher ln-transformed FGF21 levels at 1-year post-randomization were also associated with higher subsequent risk of MCVEs (adjusted hazards ratio per SD increase=1.24, P=0.009). However, changes in FGF21 levels over 1-year were not related to subsequent MCVE risk. FGF21 levels had significant incremental value in net reclassification improvement in MCVE risk prediction. CONCLUSIONS: Higher plasma FGF21 levels are associated with higher CVD risk in statin-treated high-risk patients. Higher dose atorvastatin is associated with a reduction in FGF21 levels. FGF21 provides incremental value in CVD risk prediction in statin-treated patients.

[36] *Khoshnejad M, Patel A, Wojtak K et al. Development of Novel DNA-Encoded PCSK9 Monoclonal Antibodies as Lipid-Lowering Therapeutics. Molecular therapy : the journal of the American Society of Gene Therapy 2018.*

PM: <http://www.ncbi.nlm.nih.gov/pubmed/?term=30449662>

ABSTRACT

Elevated low-density lipoprotein cholesterol (LDL-C) is one of the major contributors to cardiovascular heart disease (CHD), the leading cause of death worldwide. Due to severe side effects of statins, alternative treatment strategies are required for statin-intolerant patients. Monoclonal antibodies (mAbs) targeting proprotein convertase subtilisin/kexin type 9 (PCSK9) have shown great efficacy in LDL-C reduction. Limitations for this approach include the need for multiple injections as well as increased costs associated with patient management. Here, we engineered a DNA-encoded mAb (DMAb) targeting PCSK9 (daPCSK9), as an alternative approach to protein-based lipid-lowering therapeutics, and we characterized its expression and activity. A single intramuscular administration of mouse daPCSK9 generated expression in vivo for over 42 days that corresponded with a substantial decrease of 28.6% in non-high-density lipoprotein cholesterol (non-HDL-C) and 10.3% in total cholesterol by day 7 in wild-type mice. Repeated administrations of the DMAb plasmid led to increasing expression, with DMAb levels of 7.5 mug/mL at day 62. daPCSK9 therapeutics may provide a novel, simple, less frequent, cost-effective approach to reducing LDL-C, either as a stand-alone therapy or in combination with other LDL-lowering therapeutics for synergistic effect.

[37] *Chen C, Zhai H, Huang G et al. Is lower low-density lipoprotein cholesterol associated with lower androgen and erectile dysfunction in men? Nutrition, metabolism, and cardiovascular diseases : NMCD 2018; 28:1304-1310.*

PM: <http://www.ncbi.nlm.nih.gov/pubmed/?term=30459056>

ABSTRACT

BACKGROUND AND AIMS: Therapeutic possibilities now exist to lower low-density lipoprotein cholesterol (LDL-C) to very low levels. However, substantial controversy remains in clinical practice with regard to its safety, and the question of whether low LDL-C levels per se may provoke adverse effects in humans arises. We aimed to explore the association of LDL-C with

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androgen and erectile dysfunction (ED) in a general population of men. **METHODS AND RESULTS:** A total of 4203 men without hormone replacement therapy were enrolled from 22 sites in East China. Total testosterone (T) and Free T were assessed. Free androgen index (FAI) was calculated. The IIEF-5 questionnaire was used to assess ED. We found that free T and FAI gradually and markedly increased with increasing LDL-C levels. Using linear regression, after adjusting for age, educational level, economic status, smoking status, drinking status, BMI, diabetes, and use of lipid-lowering medication, LDL-C was positively associated with free T ($B = 0.175$, 95% CI: 0.084, 0.266) and FAI ($B = 0.064$, 95% CI: 0.016, 0.112). Meanwhile, there was a U-shaped curvilinear relationship between LDL-C and prevalence of ED. In the logistic regression analysis, compared to those with LDL-C among the 10th-90th percentile, the ORs of ED in men in the lowest and highest deciles were 1.938 (95% CI: 1.121, 3.349) and 1.804 (95% CI: 1.117, 2.916), respectively. **CONCLUSION:** Lower LDL-C levels were significantly associated with lower free T and lower FAI in a general population of men. Moreover, both low and high levels of LDL-C might be risk factors for ED.

[38] *Robertson MD, Pedersen C, Hinton PJ et al. Elevated high density lipoprotein cholesterol and low grade systemic inflammation is associated with increased gut permeability in normoglycemic men. Nutrition, metabolism, and cardiovascular diseases : NMCD 2018; 28:1296-1303.*

PM: <http://www.ncbi.nlm.nih.gov/pubmed/?term=30459055>

ABSTRACT

BACKGROUND & AIMS: Serum lipids and lipoproteins are established biomarkers of cardiovascular disease risk that could be influenced by impaired gut barrier function via effects on the absorption of dietary and biliary cholesterol. The aim of this study was to examine the potential relationship between gut barrier function (gut permeability) and concentration of serum lipids and lipoproteins, in an ancillary analysis of serum samples taken from a previous study. **METHODS AND RESULTS:** Serum lipids, lipoproteins and functional gut permeability, as assessed by the percentage of the urinary recovery of (51)Cr-labelled EDTA absorbed within 24 h, were measured in a group of 30 healthy men. Serum lipopolysaccharide, high sensitivity C-reactive protein and interleukin-6 were also measured as markers of low-grade inflammation. The group expressed a 5-fold variation in total gut permeability (1.11-5.03%). Gut permeability was unrelated to the concentration of both serum total and low density lipoprotein (LDL)-cholesterol, but was positively associated with serum high density lipoprotein (HDL)-cholesterol ($r = 0.434$, $P = 0.015$). Serum HDL-cholesterol was also positively associated with serum endotoxaemia ($r = 0.415$, $P = 0.023$). **CONCLUSION:** The significant association between increased gut permeability and elevated serum HDL-cholesterol is consistent with the role of HDL as an acute phase reactant, and in this situation, potentially dysfunctional lipoprotein. This finding may have negative implications for the putative role of HDL as a cardio-protective lipoprotein.

[39] *Torres-Adorno AM, Vitrac H, Qi Y et al. Eicosapentaenoic acid in combination with EPHA2 inhibition shows efficacy in preclinical models of triple-negative breast cancer by disrupting cellular cholesterol efflux. Oncogene 2018.*

PM: <http://www.ncbi.nlm.nih.gov/pubmed/?term=30459358>

ABSTRACT

Triple-negative breast cancer (TNBC), the most aggressive breast cancer subtype, currently lacks effective targeted therapy options. Eicosapentaenoic acid (EPA), an omega-3 fatty acid and constituent of fish oil, is a common supplement with anti-inflammatory properties. Although it is not a mainstream treatment, several preclinical studies have demonstrated that EPA exerts anti-tumor activity in breast cancer. However, against solid tumors, EPA as a monotherapy is clinically ineffective; thus, we sought to develop a novel targeted drug combination to bolster its therapeutic action against TNBC. Using a high-throughput functional siRNA screen, we identified Ephrin type-A receptor 2 (EPHA2), an oncogenic cell-surface receptor tyrosine kinase, as a therapeutic target that sensitizes TNBC cells to EPA. EPHA2 expression was uniquely elevated in TNBC cell lines and patient tumors. In independent functional expression studies in TNBC models, EPHA2 gene-silencing combined with EPA significantly reduced cell growth and enhanced apoptosis compared with monotherapies, both in vitro and in vivo. EPHA2-specific inhibitors similarly enhanced the therapeutic action of EPA. Finally, we identified that therapy-mediated apoptosis was attributed to a lethal increase in cancer cell membrane polarity due to ABCA1 inhibition and subsequent dysregulation of cholesterol homeostasis. This study provides new molecular and preclinical evidence to support a clinical evaluation of EPA combined with EPHA2 inhibition in patients with TNBC.

[40] *Liping Z, Xiufang L, Tao Y et al. Efficacy comparison of rosuvastatin and atorvastatin in the treatment of atherosclerosis and drug safety analysis. Pak J Pharm Sci* 2018; 31:2203-2208.

PM: <http://www.ncbi.nlm.nih.gov/pubmed/?term=30463813>

ABSTRACT

Previous studies have shown that the commonly used statin lipid lowering drugs can delay the progression of atherosclerotic plaque. Atorvastatin can stabilize atherosclerotic plaque, but it can not reverse atheromatous plaque. This study will compare the efficacy of rosuvastatin and atorvastatin in the treatment of atherosclerosis and try to prove that the use of statins can improve peripheral atherosclerosis and reverse atherosclerotic plaque. The results showed that 10 mg rosuvastatin was more effective than 20 mg atorvastatin in lowering serum lipid level and elevating ABI index, ABI as rosuvastatin group (0.782±0.236) and atorvastatin group(0.541±0.196). After 6 months of treatment, the carotid artery IMT in rosuvastatin group and atorvastatin group decreased compared with before treatment, and the difference was statistically significant (P<0.05). The TC/mmolL-1 is 2.83±0.56 in rosuvastatin group and 3.24±0.71 in atorvastatin group. In addition, rosuvastatin did not increase the risk of adverse reactions compared with atorvastatin. The results confirm that statin therapy can improve peripheral atherosclerosis and reverse atherosclerotic plaques.

[41] *Kosmas CE, Silverio D, Ovalle J et al. Patient adherence, compliance, and perspectives on evolocumab for the management of resistant hypercholesterolemia. Patient preference and adherence* 2018; 12:2263-2266.

PM: <http://www.ncbi.nlm.nih.gov/pubmed/?term=30464416>

ABSTRACT

Evolocumab is a PCSK9 inhibitor which is administered subcutaneously, and when added to statin therapy it has been shown to cause a significant incremental LDL-C reduction, leading to

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a reduction of cardiovascular risk. Evolocumab has a favorable side effect profile, and its self-administration at home appears to be safe and effective with the appropriate training and instructions from a health care provider. Current studies are showing encouraging results regarding adherence to evolocumab in real-life settings, and adherence rates to evolocumab appear to be better than those to statins. However, further larger studies are needed for a more definitive assessment of the short- and long-term patient adherence rates to evolocumab. In addition, reductions in the price of evolocumab may also be necessary to improve cost-effectiveness of the drug.

[42] *Krysiak R, Szkrobka W, Okopien B. Different effects of fenofibrate on cardiometabolic risk factors in young women with and without hyperprolactinemia. Pharmacological reports : PR 2018; 71:61-66.*

PM: <http://www.ncbi.nlm.nih.gov/pubmed/?term=30469130>

ABSTRACT

BACKGROUND: Elevated prolactin levels are associated with increased cardiometabolic risk. No previous study has compared the effect of hypolipidemic therapy on plasma levels of lipids and other cardiometabolic risk factors in patients with and without hyperprolactinemia. **METHODS:** The study included three age-, weight-, blood pressure- and lipid-matched groups of premenopausal women: 18 women with untreated hyperprolactinemia, 19 women with bromocriptine-treated hyperprolactinemia and 20 drug-naive women with normal prolactin levels. Because of concomitant atherogenic dyslipidemia, all patients were treated with fenofibrate (200 mg daily) for 12 weeks. Plasma lipids, glucose homeostasis markers, as well as plasma levels of uric acid, high-sensitivity C-reactive protein (hsCRP), homocysteine and fibrinogen were assessed at baseline and at the end of hypolipidemic treatment. **RESULTS:** Unlike similar baseline lipid levels, plasma concentrations of the remaining investigated cardiometabolic risk factors were higher in women with elevated prolactin levels than in patients with normal prolactin levels. The impact of fenofibrate on total cholesterol, LDL cholesterol, HDL cholesterol and triglyceride levels, as well as on uric acid, hsCRP, homocysteine, and fibrinogen was less pronounced in women with untreated hyperprolactinemia than in women with bromocriptine-treated hyperprolactinemia and drug-naive women with normal prolactin levels. **CONCLUSIONS:** The results of our study indicate that cardiometabolic effects of fenofibrate depend on plasma prolactin levels.

[43] *Ju J, Li J, Lin Q, Xu H. Efficacy and safety of berberine for dyslipidaemias: A systematic review and meta-analysis of randomized clinical trials. Phytomedicine : international journal of phytotherapy and phytopharmacology 2018; 50:25-34.*

PM: <http://www.ncbi.nlm.nih.gov/pubmed/?term=30466986>

ABSTRACT

BACKGROUND: In recent years, berberine has become widely used as an effective alternative to treat dyslipidaemias; much clinical evidence has emerged. It is important to systematically and critically evaluate the existing evidence. **PURPOSE:** This study aims to evaluate the efficacy and safety of berberine in patients with dyslipidaemias. **STUDY DESIGN:** A systematic review and meta-analysis of randomized clinical trials. **METHODS:** Five electronic databases were searched up to Apr 15, 2018 to identify randomized controlled trials (RCTs) of berberine in treatment of

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dyslipidaemias. The outcomes were lipid profile parameters and adverse events. Study selection, data collection, risk of bias assessment, data analyses and interpretations were conducted according to the Cochrane handbook. RESULTS: Sixteen trials with total of 2147 participants were judged to be eligible and were included in the meta-analysis. The included trials were assessed to be of high clinical heterogeneity. The methodological quality of the majority of the trials was generally low in terms of random sequence generation, allocation concealment, blinding and incomplete outcome data. Thus, selection bias, performance bias, detection bias, attrition bias and confounding bias might exist. Meta-analysis showed that berberine significantly reduced levels of total cholesterol (TC) (MD=-0.47 mmol/l 95% CI [-0.64, -0.31], $p<0.00001$), low-density lipoprotein cholesterol (LDL-C) (MD =-0.38 mmol/l 95% CI [-0.53, -0.22], $p<0.00001$) and triglycerides (TG) (MD=-0.28 mmol/l 95% CI [-0.46, -0.10], $p=0.002$). Berberine also increased the level of high-density lipoprotein cholesterol (HDL-C) when used alone (MD=0.08 mmol/l 95% CI [0.03, 0.12], $p=0.001$). No significant differences were found between groups in terms of incidence of adverse events (RR=0.64 95% CI [0.31, 1.30], $p=0.22$). No severe adverse effects were reported in either group. CONCLUSION: Berberine improves lipid profiles in dyslipidaemias with satisfactory safety. Nevertheless, these findings should be interpreted with caution because of the high clinical heterogeneity and high risk of bias in the included trials. Rigorous clinical trials should be carried out to provide more reliable evidence.

[44] *Gafson AR, Thorne T, McKechnie CIJ et al. Lipoprotein markers associated with disability from multiple sclerosis. Scientific reports 2018; 8:17026.*

PM: <http://www.ncbi.nlm.nih.gov/pubmed/?term=30451923>

ABSTRACT

Altered lipid metabolism is a feature of chronic inflammatory disorders. Increased plasma lipids and lipoproteins have been associated with multiple sclerosis (MS) disease activity. Our objective was to characterise the specific lipids and associated plasma lipoproteins increased in MS and to test for an association with disability. Plasma samples were collected from 27 RRMS patients (median EDSS, 1.5, range 1-7) and 31 healthy controls. Concentrations of lipids within lipoprotein sub-classes were determined from NMR spectra. Plasma cytokines were measured using the MesoScale Discovery V-PLEX kit. Associations were tested using multivariate linear regression. Differences between the patient and volunteer groups were found for lipids within VLDL and HDL lipoprotein sub-fractions ($p < 0.05$). Multivariate regression demonstrated a high correlation between lipids within VLDL sub-classes and the Expanded Disability Status Scale (EDSS) ($p < 0.05$). An optimal model for EDSS included free cholesterol carried by VLDL-2, gender and age ($R(2) = 0.38$, $p < 0.05$). Free cholesterol carried by VLDL-2 was highly correlated with plasma cytokines CCL-17 and IL-7 ($R(2) = 0.78$, $p < 0.0001$). These results highlight relationships between disability, inflammatory responses and systemic lipid metabolism in RRMS. Altered lipid metabolism with systemic inflammation may contribute to immune activation.

[45] *Liu Z, Xiang Q, Zhao X et al. Candidate gene and pathway analyses identifying genetic variations associated with prasugrel pharmacokinetics and pharmacodynamics. Thrombosis research 2018; 173:27-34.*

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PM: <http://www.ncbi.nlm.nih.gov/pubmed/?term=30458339>

ABSTRACT

AIM: We aimed to investigate the genetic polymorphisms and pharmacogenetic variability associated with the pharmacodynamics (PD) and pharmacokinetics (PK) of prasugrel, in healthy Han Chinese subjects. **PATIENTS & METHODS:** Healthy, native, Han Chinese subjects (n=36) aged 18 to 45years with unknown genotypes were included. All subjects received a loading dose (LD) on day 1 and a maintenance dose (MD) from day 2 until day 11. Candidate gene association and gene-set analysis of biological pathways related to prasugrel and platelet activity were analyzed. **RESULTS:** 28 SNPs of 17 candidate genes previously associated with prasugrel or platelet activity were selected after a literature search. In the 30mg LD groups (n=24), ITGA2-rs28095 was found to be significantly associated with the P2Y12 reaction unit (PRU) value at 24h after the LD (p=0.015). 165 study genes related to platelet activation-related processes and prasugrel activity were selected from the MSigDB database, including curated gene sets from KEGG, Bio Carta, and Gene Cards. 14 SNPs of 9 genes were found to be significantly correlated both at 24h and 12days after LD: ADAMTSL1, PRKCA, ITPR2, P2RY12, P2RY14, PLCB4, PRKG1, ADCY1, and LYN. Seven SNPs of 6 protein-coding genes associated with area under the concentration-time curve (AUC0-tlast) were significantly identified among the 47 selected genes, including ADAMTSL1, CD36, P2RY1, PCSK9, PON1, and SCD. **CONCLUSION:** These results show that genetic variation affects the PK and PD of prasugrel in normal individuals. Further studies with larger sample sizes are required to explore whether the SNPs are associated only with prasugrel activity or also with cardiovascular events and all-cause mortality.

[46] *Perrotta I. Occurrence and characterization of lipofuscin and ceroid in human atherosclerotic plaque. Ultrastructural pathology* 2018:1-12.

PM: <http://www.ncbi.nlm.nih.gov/pubmed/?term=30465462>

ABSTRACT

Atherosclerotic plaque formation starts early in life, develops silently over decades, and often displays clear evidence of accelerated biological aging. Lipofuscin has been classically defined as "the most consistent and phylogenetically conserved cellular morphologic change of aging," however, despite this traditional view different lines of evidence have recently demonstrated that, besides aging, various noxious influences can engender its accumulation in cells and also that specific experimental conditions can revert this effect. Lipofuscin has been also proven to interact with disease-related factors to enhance cell loss. Along with lipofuscin, ceroid, another autofluorescent lipopigment usually produced under various pathological conditions unrelated to aging, has been suggested to jeopardize cell performance and viability by inducing membrane fragility, mitochondrial dysfunction, DNA damage, and oxidative stress-induced apoptosis. With regard to atherosclerosis, very few investigations have been conducted to assess whether a link could exist between lipofuscin/ceroid accumulation and the progression of the disease and no information still exist regarding the anatomy and the ultrastructural diversification of lipofuscin and ceroid in the lesional vascular tissue. At the same time, data concerning their potential toxicity at the cellular level are fragmentary, dated, and scarce. The present study investigates the occurrence and distribution of lipofuscin and ceroid in human

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atherosclerotic plaque and adjacent healthy tissues and analyzes the ultrastructural changes associated with their accumulation within the cell.

[47] Tang CH, Lin CY, Tsai YL et al. **Lipidomics as a diagnostic tool of the metabolic and physiological state of managed whales: A correlation study of systemic metabolism.** Zoo biology 2018.

PM: <http://www.ncbi.nlm.nih.gov/pubmed/?term=30457161>

ABSTRACT

Integrating multifactor blood analysis is a key step toward a precise diagnosis of the health status of marine mammals. Variations in the circulating lipid profile reflect changes in the metabolism and physiology of an individual. To demonstrate the practicability of lipid profiling for physiological assessment, the phosphorylcholine-containing lipids in the plasma of long-term managed beluga whales (*Delphinapterus leucas*) were profiled using a lipidomics methodology. Using a multivariate analysis, the mean corpuscular volume, cholesterol, potassium, and gamma-glutamyltranspeptidase levels were well modeled with the lipid profile of the female whales. In the models, the correlated lipids provided information about blood parameter-related metabolism and physiological regulation, in particular relating to cholesterol and inflammation. In the males, the levels of cholesterol, triglycerides, blood urea nitrogen, creatinine, plasma iron, and segmented neutrophil were well modeled with the lipid profile. In addition to providing information about the related metabolism and regulation, through a cross-linked analysis of the blood parameters, the correlated lipids indicated a parallel regulation involved in the energy metabolism of the male whales. Lipidomics as a method for revealing the context of physiological change shows practical potential for the health care of managed whales.