

Literature update week 03 (2018)

[1] *Feng D, Biftu T, Romero FA et al. Discovery of MK-8722: A Systemic, Direct Pan-Activator of AMP-Activated Protein Kinase. ACS medicinal chemistry letters* 2018; 9:39-44.

PM: <http://www.ncbi.nlm.nih.gov/pubmed/?term=29348809>

ABSTRACT

5'-Adenosine monophosphate-activated protein kinase (AMPK) is a key regulator of mammalian energy homeostasis and has been implicated in mediating many of the beneficial effects of exercise and weight loss including lipid and glucose trafficking. As such, the enzyme has long been of interest as a target for the treatment of Type 2 Diabetes Mellitus. We describe the optimization of beta1-selective, liver-targeted AMPK activators and their evolution into systemic pan-activators capable of acutely lowering glucose in mouse models. Identifying surrogates for the key acid moiety in early generation compounds proved essential in improving beta2-activation and in balancing improvements in plasma unbound fraction while avoiding liver sequestration.

[2] *Kukava NG, Titov BV, Osmak GJ et al. Multilocus Analysis of Genetic Susceptibility to Myocardial Infarction in Russians: Replication Study. Acta naturae* 2017; 9:74-83.

PM: <http://www.ncbi.nlm.nih.gov/pubmed/?term=29340220>

ABSTRACT

In search of genetic markers of myocardial infarction (MI) risk, which have prognostic significance for Russians, we performed a replication study of MI association with genetic variants of PCSK9 (rs562556), APOE (epsilon polymorphism, rs7412 and rs429358), LPL (rs320), MTHFR (rs1801133), eNOS (rs2070744), and the 9p21 region (rs1333049) in 405 patients with MI and 198 controls. Significant MI association was observed with variants of the lipid metabolism genes (PCSK9, APOE and LPL), and of eNOS. The SNPs in the MTHFR gene and the 9p21 region were not significantly associated with MI one by one but were included in several different MI-associated allelic combinations identified by multilocus analysis. Since we have not revealed nonlinear epistatic interactions between the components of the identified combinations, we postulate that the cumulative effect of genes that form a combination arises from the summation of their small independent contributions. The prognostic significance of the additive composite model built from the PCSK9, APOE, LPL, and eNOS genes as genetic markers was assessed using ROC analysis. After we included these markers in the previously published composite model of individual genetic risk of MI, the prognostic efficacy in our sample reached AUC = 0.676. However, the results obtained in this study certainly need to be replicated in an independent sample of Russians.

[3] *Fu N, Liang M, Yang S. High Loading Dose of Atorvastatin for the Prevention of Serum Creatinine and Cystatin C-Based Contrast-Induced Nephropathy Following Percutaneous Coronary Intervention. Angiology* 2018:3319717750903.

PM: <http://www.ncbi.nlm.nih.gov/pubmed/?term=29343076>

ABSTRACT

The aim of this study is to assess the efficacy of high-dose atorvastatin on the prevention of contrast-induced nephropathy (CIN) in patients with acute coronary syndrome (ACS) undergoing percutaneous intervention and observe the incidence of cystatin C (CyC)-based CIN. A total of 496 patients with ACS

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were randomly assigned to either the control group (247 patients receiving conventional dose atorvastatin 10 mg daily from 1 day before to 3 days after contrast administration) or the high-dose atorvastatin group (249 patients receiving atorvastatin 40 mg daily for the same perioperative period). The baseline characteristics of the 2 groups were similar. The primary end point of serum creatinine (SCr)-based CIN occurred in 31 patients in the control group and 16 patients in the high-dose atorvastatin group (12.6% vs 6.4%; $P = .02$). Cystatin C-based CIN developed in 90 patients in the control group and 46 patients in the high-dose atorvastatin group (36.4% vs 18.5%; $P < .001$). A multivariable analysis revealed that high-dose atorvastatin was independently associated with a decreased risk of CIN. Our study demonstrated that prophylactic treatment with high-dose atorvastatin reduced the risk of both SCr and CyC-based CIN and suggested that CyC was a more reliable marker for early diagnosis of CIN compared with SCr.

[4] *Wulff AB, Nordestgaard BG, Tybjaerg-Hansen A. APOC3 Loss-of-Function Mutations, Remnant Cholesterol, Low-Density Lipoprotein Cholesterol, and Cardiovascular Risk: Mediation and Meta-Analyses of 137 895 Individuals. Arteriosclerosis, thrombosis, and vascular biology* 2018.

PM: <http://www.ncbi.nlm.nih.gov/pubmed/?term=29348120>

ABSTRACT

OBJECTIVE: Loss-of-function mutations in APOC3 associate with low remnant cholesterol levels and low risk of ischemic vascular disease (IVD). Because some studies show an additional association with low levels of low-density lipoprotein cholesterol (LDL-C), low LDL-C may explain the low risk of IVD in APOC3 loss-of-function heterozygotes. We tested to what extent the low risk of IVD in APOC3 loss-of-function heterozygotes is mediated by low plasma remnant cholesterol and LDL-C. APPROACH AND RESULTS: In APOC3 loss-of-function heterozygotes versus noncarriers, we first determined remnant cholesterol and LDL-C levels in meta-analyses of 137 895 individuals. Second, we determined whether the association with LDL-C was masked by lipid-lowering therapy. Finally, using mediation analysis, we determined the fraction of the low risk of IVD and ischemic heart disease mediated by remnant cholesterol and LDL-C. In meta-analyses, remnant cholesterol was 43% lower (95% confidence interval, 40%-47%), and LDL-C was 4% lower (1%-6%) in loss-of-function heterozygotes ($n=776$) versus noncarriers. In the general population, LDL-C was 3% lower in loss-of-function heterozygotes versus noncarriers, 4% lower when correcting for lipid-lowering therapy, and 3% lower in untreated individuals (P values, 0.06-0.008). Remnant cholesterol mediated 37% of the observed 41% lower risk of IVD and 54% of the observed 36% lower risk of ischemic heart disease; corresponding values mediated by LDL-C were 1% and 2%. CONCLUSIONS: The low risk of IVD observed in APOC3 loss-of-function heterozygotes is mainly mediated by the associated low remnant cholesterol and not by low LDL-C. Furthermore, the contribution of LDL-C to IVD risk was not masked by lipid-lowering therapy. This suggests APOC3 and remnant cholesterol as important new targets for reducing cardiovascular risk.

[5] *Sun B, Zhong Z, Wang F et al. Atorvastatin Impaired Glucose Metabolism in C2C12 Cells Partly via Inhibiting Cholesterol-dependent Glucose Transporter 4 Translocation. Biochem Pharmacol* 2018.

PM: <http://www.ncbi.nlm.nih.gov/pubmed/?term=29338971>

ABSTRACT

Skeletal muscle accounts for approximately 75% of glucose disposal in body and statins impair glucose metabolism. We aimed to investigate the effect of atorvastatin on glucose metabolism in C2C12 cells.

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Glucose metabolism and expression of glucose transporter 4 (GLUT4) and hexokinase II (HXKII) were measured following incubation with atorvastatin or pravastatin. Roles of cholesterol in atorvastatin-induced glucose metabolism impairment were investigated via adding cholesterol or mevalonic acid and confirmed by cholesterol depletion with methyl-beta-cyclodextrin. Hypercholesterolemia mice induced by high fat diet (HFD) feeding, orally received atorvastatin (6 and 12 mg/kg) or pravastatin (12mg/kg) for 22 days. Results showed that atorvastatin not pravastatin concentration-dependently impaired glucose consumption, glucose uptake and GLUT4 membrane translocation in C2C12 cells without affecting expression of HXKII or total GLUT4 protein. The atorvastatin-induced alterations were reversed by cholesterol or mevalonic acid. Cholesterol depletion exerted similar impact to atorvastatin, which could be alleviated by cholesterol supplement. Glucose consumption or GLUT4 translocation was positively associated with cellular cholesterol levels. In HFD mice, atorvastatin not pravastatin significantly increased blood glucose levels following glucose or insulin dose and decreased expression of membrane not total GLUT4 protein in muscle. Glucose exposure following glucose or insulin dose was negatively correlated to muscular free cholesterol concentration. Expression of membrane GLUT4 protein was positively related to free cholesterol in muscle. In conclusion, atorvastatin impaired glucose utilization in muscle cells partly via inhibiting GLUT4 membrane translocation due to inhibition of cholesterol synthesis by atorvastatin, at least, partly contributing to glucose intolerance in HFD mice.

[6] *Deljehier T, Pariente A, Miremont-Salame G et al. Rhabdomyolysis after co-administration of a statin and fusidic acid: an analysis of the literature and of the WHO database of adverse drug reactions. British journal of clinical pharmacology 2018.*

PM: <http://www.ncbi.nlm.nih.gov/pubmed/?term=29337401>

ABSTRACT

Following a severe case of rhabdomyolysis in our University Hospital after a co-administration of atorvastatin and fusidic acid, we describe this interaction as this combination is not clearly contraindicated in some countries, particularly for long-term treatment by fusidic acid. All cases of rhabdomyolysis during a co-administration of a statin and fusidic acid were identified in the literature and in the World and Health Organization database, VigiBase(R). In the literature, 29 cases of rhabdomyolysis were identified; mean age was 66 years, median duration of co-administration before rhabdomyolysis occurrence was 21 days, 28% of cases were fatal. In VigiBase(R), 182 cases were retrieved; mean age was 68 years, median duration of co-administration before rhabdomyolysis was 31 days and 24% of cases were fatal. Owing to the high fatality associated with this co-administration and the long duration of treatment before rhabdomyolysis occurrence, fusidic acid should be used if there is no appropriate alternative, as long as statin therapy is interrupted for the duration of fusidic acid therapy, and perhaps a week longer. Rarely will interruption of this sort have adverse consequences for the patient.

[7] *Marra F, Honer Zu Siederdisen C, Khoo S et al. Clinical impact of pharmacokinetic interactions between the HCV protease inhibitor Simeprevir and frequently used concomitant medications. British journal of clinical pharmacology 2018.*

PM: <http://www.ncbi.nlm.nih.gov/pubmed/?term=29345798>

ABSTRACT

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AIMS: Direct-acting antivirals (DAAs) for the treatment of hepatitis C (HCV) can be associated with drug-drug interactions (DDIs) with concomitant medications. The practical clinical implications of such DDIs are poorly understood. We assessed the clinical impact of possible pharmacokinetic (PK) interactions between simeprevir and frequently prescribed concomitant medications. METHODS: This post-hoc analysis pooled data from 9 studies which evaluated simeprevir (SMV)-based interferon-free HCV treatment. Three classes of frequently used concomitant medication of interest (CMOI) were analysed (antihypertensive drugs (AHD), anxiolytic drugs (AXD), and lipid-lowering drugs (LLD)) and categorized as amber or green according to their DDI potential with SMV (green: no DDIs; amber: potential/known PK interactions). Concomitant medications not recommended to be co-administered with SMV were not included. The composite primary endpoint was defined as the frequency of either discontinuation, interruption or dose modification of the CMOI during 12 weeks of SMV treatment. RESULTS: Few patients met the composite endpoint in the various subgroups. Patients on amber CMOI tended to experience CMOI modification more often (13.4-19.4%) than patients on green CMOI (3.1%-10.8%). There was no difference in frequency of adverse events between patients taking green and patients taking amber CMOI. CONCLUSIONS: In this large pooled analysis, co-administration of the evaluated commonly prescribed medications with known or potential PK interactions with SMV was manageable and resulted in few adjustments of concomitant medications. Our method could serve as a blueprint for the evaluation of the impact of DDIs.

[8] *Borow KM, Mason RP, Vijayaraghavan K. Eicosapentaenoic Acid as a Potential Therapeutic Approach to Reduce Cardiovascular Risk in Patients with End-Stage Renal Disease on Hemodialysis: A Review. Cardiorenal Med 2017; 8:18-30.*

PM: <http://www.ncbi.nlm.nih.gov/pubmed/?term=29344023>

ABSTRACT

Background: Patients with end-stage renal disease on hemodialysis have excess cardiovascular disease (CVD) burden with substantially increased CV event rates compared with the general population. Summary: Traditional interventions that, according to standard clinical guidelines, reduce CV risk such as antihypertensive therapy, diet, exercise, and statins are not similarly effective in the hemodialysis population. This raises the question of whether additional risk factors, such as enhanced inflammation and oxidative stress, may drive the increased CVD burden in hemodialysis patients. Eicosapentaenoic acid (EPA), an omega-3 polyunsaturated fatty acid, is incorporated into the atherosclerotic plaque as well as membrane phospholipid bilayers and produces beneficial effects on inflammatory and oxidative mechanisms involved in atherosclerotic plaque formation and progression. EPA levels and the ratio of EPA to the omega-6 polyunsaturated fatty acid arachidonic acid (AA) are reduced in hemodialysis patients. Serum EPA levels have been inversely correlated with proinflammatory cytokines, and the EPA/AA ratio has been inversely associated with CV events in hemodialysis cohorts. Three recent studies involving over 800 hemodialysis patients and follow-up of 2-3 years suggest that EPA therapy may improve clinical outcomes in this patient population as evidenced by significant reductions in cardiovascular mortality, all-cause mortality, and/or CV events. Key Messages: Further studies with high-purity EPA are warranted in patients on hemodialysis, especially given the fact that other interventions including antihypertensives, diet, exercise, and statins have not provided meaningful benefit.

[9] *Acampa M, Lazzerini PE, Guideri F et al. Previous use of statins and atrial electrical remodeling in patients with cryptogenic stroke. Cardiovascular & hematological disorders drug targets 2018.*

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PM: <http://www.ncbi.nlm.nih.gov/pubmed/?term=29332603>

ABSTRACT

BACKGROUND: In the general population the leading cause of cardioembolic stroke is atrial fibrillation (AF). A silent AF is also the possible cause of many cryptogenic strokes. P wave dispersion (PWD), a predictor of AF, has been proposed as a marker of silent AF occurrence in these strokes. PWD correlates with high-sensitive C-reactive protein levels reflecting the role of inflammation in promoting a slowed and inhomogeneous atrial conduction. Statins have a multitude of additional effects beyond lipid lowering, in particular anti-inflammatory effects that may influence atrial conduction. **OBJECTIVE:** The aim of this study was to evaluate the effects of previous statin use on PWD in patients with cryptogenic stroke, in order to highlight a possible role for statins in preventing atrial conduction alterations that predispose to AF. **METHOD:** We enrolled 131 patients (67 males, 64 females; mean age 69+/-13 years) with cryptogenic stroke. All patients underwent neuroimaging examination, arterial ultrasound examination, echocardiography and ECG. PWD was measured in all subjects. **RESULTS:** Patients previously treated with statins (n: 34) had lower PWD and P index values in comparison with no-statin group (41.7+/-12.2 vs 48.7+/-15.2 ms, p=0.01, and 14.2+/-3.7 vs 16.5+/-5.3 ms, p=0.02, respectively). **CONCLUSIONS:** Our results show lower PWD values in cryptogenic stroke patients previously treated with statins. These findings provide support to the hypothesis that statins may play a role in modulating atrial electrophysiological and structural properties, preventing the occurrence of a slowed and heterogeneous atrial conduction and finally, reducing the occurrence of AF.

[10] *Petri B, Sanz MJ. Neutrophil chemotaxis. Cell and tissue research 2018.*

PM: <http://www.ncbi.nlm.nih.gov/pubmed/?term=29350282>

ABSTRACT

Neutrophils are the primary cells recruited to inflamed sites during an innate immune response to tissue damage and/or infection. They are finely sensitive to inciting stimuli to reach in great numbers and within minutes areas of inflammation and tissue insult. For this effective response, they can detect extracellular chemical gradients and move towards higher concentrations, the so-called chemotaxis process or guided cell migration. This directed neutrophil recruitment is orchestrated by chemoattractants, a chemically diverse group of molecular guidance cues (e.g., lipids, N-formylated peptides, complement, anaphylotoxins and chemokines). Neutrophils respond to these guidance signals in a hierarchical manner and, based on this concept, they can be further subdivided into two groups: "end target" and "intermediary" chemoattractants, the signals of the former dominant over the latter. Neutrophil chemoattractants exert their effects through interaction with heptahelical G protein-coupled receptors (GPCRs) expressed on cell surfaces and the chemotactic response is mainly regulated by the Rho family of GTPases. Additionally, neutrophil behavior might differ and be affected in different complex scenarios such as disease conditions and type of vascular bed in specific organs. Finally, there are different mechanisms to disrupt neutrophil chemotaxis either associated to the resolution of inflammation or to bacterial escape and systemic infection. Therefore, in the present review, we will discuss the different molecular players involved in neutrophil chemotaxis, paying special attention to the different chemoattractants described and the way that they interact intra- and extravascularly for neutrophils to properly reach the target tissue.

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[11] *Houttu N, Morkkala K, Laitinen K. Overweight and obesity status in pregnant women are related to intestinal microbiota and serum metabolic and inflammatory profiles. Clinical nutrition (Edinburgh, Scotland) 2017.*

PM: <http://www.ncbi.nlm.nih.gov/pubmed/?term=29338886>

ABSTRACT

BACKGROUND: Overweight and obesity may predispose women to clinical complications during their pregnancy. We hypothesize that a higher degree of overweight status is related to a range of aberrations in biomarkers already in early pregnancy. Our objective was to investigate whether intestinal microbiota, serum metabolic and inflammatory profiles differ in relation to the degree of overweight status in pregnant women. **METHODS:** This study investigated 52 overweight and 47 obese pregnant women in early pregnancy. Fecal samples were analyzed for intestinal microbiota composition by 16S ribosomal RNA gene sequencing and Qiime pipeline. Circulating serum metabolites, including lipids, amino acids and GlycA, a marker of low-grade inflammation, were analyzed by NMR metabolomics and hsCRP was quantified by immunoassay. Serum zonulin levels were analyzed to depict intestinal permeability by Zonulin ELISA kit and LPS activity for endotoxemia by Limulus amoebocyte lysate assay. The analyses were adjusted for multiple comparisons using Benjamini-Hochberg procedure for false discovery rate controlling. **RESULTS:** The relative abundance of bacterial family Prevotellaceae (adjusted $P = 0.19$) and markers of low-grade inflammation, hsCRP ($P = 0.0015$) and GlycA ($P < 0.001$) and three branched chain amino acids (isoleucine, adjusted $P = 0.024$; leucine, adjusted $P = 0.026$; valine, adjusted $P = 0.10$) and one aromatic amino acid (phenylalanine, adjusted $P = 0.050$) and concentrations of several VLDL particles and lipid measures in several VLDL particles were higher in obese pregnant women compared to their overweight pregnant counterparts (adjusted $P < 0.12$). In contrast, lipid measures in a few HDL particles and many fatty acids were lower in obese compared to overweight pregnant women (adjusted $P < 0.12$). **CONCLUSIONS:** The detected alterations in intestinal microbiota and metabolic and inflammatory profiles related to obesity status may offer new alternative tools to supplement standard clinical measures to predict the risk for metabolic alterations during the early phase of pregnancy.

[12] *Shah B, Ganguzza L, Slater J et al. The Effect of a Vegan versus AHA DiEt in Coronary Artery Disease (EVADE CAD) trial: study design and rationale. Contemporary clinical trials communications 2017; 8:90-98.*

PM: <http://www.ncbi.nlm.nih.gov/pubmed/?term=29333503>

ABSTRACT

Background: Multiple studies demonstrate the benefit of a vegan diet on cardiovascular risk factors when compared to no intervention or usual dietary patterns. The aim of this study is to evaluate the effect of a vegan diet versus the American Heart Association (AHA)-recommended diet on inflammatory and glucometabolic profiles in patients with angiographically defined coronary artery disease (CAD). **Study Design:** This study is a randomized, open label, blinded end-point trial of 100 patients with CAD as defined by $\geq 50\%$ diameter stenosis in a coronary artery ≥ 2 mm in diameter on invasive angiography. Participants are randomized to 8 weeks of either a vegan or AHA-recommended diet (March 2014 and February 2017). Participants are provided weekly groceries that adhere to the guidelines of their diet. The primary endpoint is high sensitivity C-reactive concentrations. Secondary endpoints include anthropometric data, other markers of inflammation, lipid parameters, glycemic markers, endothelial function, quality of life data, and assessment of physical activity. Endpoints are measured at each visit

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(baseline, 4 weeks, and 8 weeks). Dietary adherence is measured by two weekly 24-hour dietary recalls, a 4-day food record during the week prior to each visit, and both plasma and urine levels of trimethylamine-N-oxide at each visit. Conclusion: This study is the first to comprehensively assess multiple indices of inflammation and glucometabolic profile in a rigorously conducted randomized trial of patients with CAD on a vegan versus AHA-recommended diet.

[13] *Biondi-Zoccai G, Mastrangeli S, Romagnoli E et al. What We Have Learned from the Recent Meta-analyses on Diagnostic Methods for Atherosclerotic Plaque Regression. Current atherosclerosis reports* 2018; 20:2.

PM: <http://www.ncbi.nlm.nih.gov/pubmed/?term=29344739>

ABSTRACT

PURPOSE OF REVIEW: Atherosclerosis has major morbidity and mortality implications globally. While it has often been considered an irreversible degenerative process, recent evidence provides compelling proof that atherosclerosis can be reversed. Plaque regression is however difficult to appraise and quantify, with competing diagnostic methods available. Given the potential of evidence synthesis to provide clinical guidance, we aimed to review recent meta-analyses on diagnostic methods for atherosclerotic plaque regression. RECENT FINDINGS: We identified 8 meta-analyses published between 2015 and 2017, including 79 studies and 14,442 patients, followed for a median of 12 months. They reported on atherosclerotic plaque regression appraised with carotid duplex ultrasound, coronary computed tomography, carotid magnetic resonance, coronary intravascular ultrasound, and coronary optical coherence tomography. Overall, all meta-analyses showed significant atherosclerotic plaque regression with lipid-lowering therapy, with the most notable effects on echogenicity, lipid-rich necrotic core volume, wall/plaque volume, dense calcium volume, and fibrous cap thickness. Significant interactions were found with concomitant changes in low density lipoprotein cholesterol, high density lipoprotein cholesterol, and C-reactive protein levels, and with ethnicity. Atherosclerotic plaque regression and conversion to a stable phenotype is possible with intensive medical therapy and can be demonstrated in patients using a variety of non-invasive and invasive imaging modalities.

[14] *Kugo H, Moriyama T, Zaima N. Adipocytes and abdominal aortic aneurysm: Putative potential role of adipocytes in the process of AAA development. Current drug targets* 2018.

PM: <http://www.ncbi.nlm.nih.gov/pubmed/?term=29336260>

ABSTRACT

Background Adipose tissue plays a role in the storage of excess energy as triglycerides (TGs). Excess fat accumulation causes various metabolic and cardiovascular diseases. It has been reported that ectopic fat deposition and excess TG accumulation in non-adipose tissue might be important predictors of cardiometabolic and vascular risk. For example, ectopic fat in perivascular tissue promotes atherosclerotic plaque formation in the arterial wall. Objective Recently, it has been reported that ectopic fat (adipocyte) in the vascular wall of an abdominal aortic aneurysm (AAA) is present in both human and experimental animal models. The pathological significance of adipocytes in the AAA wall has not been fully understood. In this review, we summarized the functions of adipocytes and discussed potential new drugs that target vascular adipocytes for AAA treatment. Result Previous studies suggest that adipocytes in vascular wall play an important role in the development of AAA. Conclusion Adipocytes in the vascular wall could be novel targets for the development of AAA therapeutic drugs.

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[15] Battaggia A, Scalisi A, Donzelli A. **The systematic review of randomized controlled trials of PCSK9 antibodies challenges their "efficacy breakthrough" and the "lower, the better" theory.** Current medical research and opinion 2018:1-6.

PM: <http://www.ncbi.nlm.nih.gov/pubmed/?term=29334796>

ABSTRACT

BACKGROUND: A Cochrane review with meta-analysis showed controversial results about the efficacy of PCSK9 antibodies in the prevention of cardiovascular diseases. This review gives the opportunity to test the relationship between LDL-C levels and cardiovascular events. METHODS: The authors analyzed the relationship between the calculated LDL-C lowering and the risk of all-cause mortality, fatal and non-fatal myocardial infarction, fatal and non-fatal stroke, any adverse event, cardiovascular events and cardiovascular disease mortality. RESULTS: No beneficial relationship was found between LDL-C lowering and cardiovascular events explored by meta-regression; instead, there was a trend toward harm. For any of the other outcomes there was no significant association between LDL-C lowering and risk. Furthermore, the authors calculated the efficacy that would be expected through the LDL-C lowering showed in the meta-analysis, considering widely accepted predictions. These were respected only for stroke, while the observed efficacy on other cardiovascular events was significantly lower than the expected, and no significant result was observed at all for fatal outcomes. A separate meta-analysis of trials recruiting familial hypercholesterolemia patients have showed a tendency to harm for almost all outcomes. CONCLUSIONS: The relationship between LDL-C lowering and cardiovascular events has not showed any significant association (and even a tendency toward harm), challenging the "lower the better" theory. A separate meta-analysis of trials recruiting familial hypercholesterolemia patients has showed a tendency to harm for all outcomes with PCSK9 antibodies. Therefore, at the moment, the data available from randomized trials does not clearly support the use of these antibodies.

[16] Seidah NG, Chretien M, Mbikay M. **The ever-expanding saga of the proprotein convertases and their roles in body homeostasis: emphasis on novel proprotein convertase subtilisin kexin number 9 functions and regulation.** Current opinion in lipidology 2018.

PM: <http://www.ncbi.nlm.nih.gov/pubmed/?term=29342010>

ABSTRACT

PURPOSE OF REVIEW: The nine members of the proprotein convertase family play major physiological roles during development and in the adult, and their dysregulation leads to various diseases. The primary objective of this article is to review recent findings on the clinical importance of some of these convertases concentrating mostly on PCSK9, the ninth member of the convertase family. This includes the transcriptional and translational regulation of PCSK9, its ability to enhance the degradation of LDL receptor (LDLR), and the implication of PCSK9 in inflammation and sepsis. RECENT FINDINGS: PCSK9 levels are upregulated by E2F1 and reduced by specific miRNAs and by Annexin A2 that bind the 3' end of its mRNA. The implication of the LDLR in the clearance of pathogenic bacterial debris in mice and human puts in perspective a new role for PCSK9 in the regulation of sepsis. The specific implication of the LDLR in the clearance of Lp(a) is now confirmed by multiple studies of PCSK9 inhibition in human cohorts. SUMMARY: Emerging data suggest that PCSK9 can be regulated at the transcriptional and translational levels by specific factors and miRNAs. The identification of a novel pocket in the catalytic domain of PCSK9 represents a harbinger for a new class of small inhibitor drugs. The implication of the LDLR in reducing the effects of bacterially induced sepsis has been supported by both human and mouse

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data. Outcome studies confirmed the clinical importance of reducing PCSK9 levels. The present review puts in perspective new developments in the PCSK9 biology and its regulation of the LDLR. VIDEO ABSTRACT.

[17] *Ashraf A, Valaiyapathi B. Hospital Management of Severe Hypertriglyceridemia in Children. Current pediatric reviews 2018.*

PM: <http://www.ncbi.nlm.nih.gov/pubmed/?term=29345595>

ABSTRACT

Severe hypertriglyceridemia (HTG), i.e., triglyceride levels exceeding 1000 mg/dL, is one of the established causes of acute pancreatitis and severe abdominal pain. There are no established pediatric guidelines for treatment of children and adolescents with severe HTG. Management often includes hospital admission, fasting followed by fat free diet until the triglyceride (TG) levels are below 1000 mg/dL. Insulin infusion lowers TG levels in patients, especially in those with diabetes. Plasmapheresis is a limited option due to its restricted availability and scarcity of studies on its efficacy and safety in children. Medications play only an adjunct role in treatment. Low fat diet, lifestyle changes, control of secondary causes of hypertriglyceridemia, and parent education form the mainstay of management once the patient is discharged.

[18] *Ali A, Costanzo P, Hoyer A. Proprotein convertase subtilisin/kexin type 9 inhibition in cardiovascular prevention. Current pharmaceutical design 2018.*

PM: <http://www.ncbi.nlm.nih.gov/pubmed/?term=29332570>

ABSTRACT

Elevated levels of Low Density Lipoprotein cholesterol (LDL-C) are directly associated with increased risk for atherosclerotic cardiovascular and cerebrovascular events. Statins have been used to control serum LDL-C and this has translated into reduction in cardiovascular and cerebrovascular events. However, despite high dose statin therapy, LDL-C control may remain inadequate in some patients, particularly those with familial hypercholesterolemia. A new therapeutic approach has emerged in recent years with proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitors. In this review, we describe the development and the use of this new class of drugs.

[19] *Tsivgoulis G, Katsanos AH, Giannopoulos G et al. The Role of Colchicine in the Prevention of Cerebrovascular Ischemia. Current pharmaceutical design 2018.*

PM: <http://www.ncbi.nlm.nih.gov/pubmed/?term=29336246>

ABSTRACT

INTRODUCTION: Despite the proven efficacy of anti-thrombotic, lipid-lowering, anti-hypertensive therapies and lifestyle modification changes for secondary ischemic stroke prevention, the risk of recurrent stroke, coronary events and vascular death remains substantial even for patients treated with high rates of established secondary preventive medications. METHODS: In the present review, we summarize available literature data on the association between systemic inflammation and symptomatic atherosclerosis including recurrent cerebral ischemia. We also highlight the potential role of colchicine in the suppression of atherosclerosis-induced inflammation, plaque stabilization and thromboembolism

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prevention. RESULTS: Accumulating evidence suggests that inflammation is of key importance in the pathophysiology of atherosclerotic plaque de-stabilization and thromboembolism, with inflammatory cells being involved in all stages of atherosclerosis development. Therefore, anti-inflammatory therapies targeting the atherosclerotic plaque inflammation may be important contributors in plaque stabilization and in the prevention of thromboembolic events. Colchicine is known to have multiple anti-inflammatory properties including inhibition of microtubule polymerization, leading to reduced secretion in monocyte-macrophages. Currently the randomized controlled CONVINCE trial is enrolling stroke patients to evaluate the effect of a daily low-dose of colchicine on reducing the rate of recurrent stroke and major vascular events. CONCLUSION: Inflammatory pathways seem to be key mediators in the development of atherosclerotic process, atheromatous plaque destabilization and thromboembolism. Colchicine as a novel therapeutic agent could be a safe and effective inhibitor of the inflammation cascade in patients with extra- or intracranial atherosclerosis or arteriolosclerosis, resulting in reduced vascular events.

[20] *Al-Kuraishy HM, Al-Gareeb AI, Al-Buhadilly AK. Rosuvastatin Improves Vaspin Serum Levels in Obese Patients with Acute Coronary Syndrome. Diseases (Basel, Switzerland) 2018; 6.*

PM: <http://www.ncbi.nlm.nih.gov/pubmed/?term=29337850>

ABSTRACT

Adipose tissue-derived serine protease inhibitor (vaspin), which has endocrine and local roles in atherosclerosis growth, is also synthesized by adipose tissue; it was found that vaspin was negatively correlated with blood pressure in obese patients, while vaspin levels were decreased in endothelial dysfunction. The aim of the present study was to determine rosuvastatin modulation effects on serum vaspin levels in acute coronary syndrome (ACS) with class I obesity. A total number of seventy patients with acute coronary syndrome previously and currently treated with rosuvastatin was compared to 40 patients with IHD not treated by rosuvastatin as a control. Vaspin serum levels were higher in rosuvastatin-treated patients with acute coronary syndrome compared to the patients with acute coronary syndrome not treated by rosuvastatin, $p < 0.01$. Additionally, in the rosuvastatin-treated group, patients with STEMI showed higher vaspin serum levels compared to NSTEMI $p < 0.01$. CONCLUSION: Rosuvastatin significantly increases vaspin serum levels in acute coronary syndrome.

[21] *Takano J, Maeda K, Kusuhashi H, Sugiyama Y. Organic anion transporting polypeptide 1a4 is responsible for the hepatic uptake of cardiac glycosides in mice. Drug metabolism and disposition: the biological fate of chemicals 2018.*

PM: <http://www.ncbi.nlm.nih.gov/pubmed/?term=29348124>

ABSTRACT

Among organic anion transporting polypeptide (Oatp) family transporters expressed in the rodent liver, such as Oatp1a1, Oatp1a4, Oatp1b2, and Oatp2b1, Oatp1a4 has a unique character to recognize neutral cardiac glycosides as substrate in addition to organic anions. The relative contribution of Oatp1a4 to the substrate uptake into hepatocytes has not been clarified. In this study, we investigated the importance of Oatp1a4 in the hepatic uptake of its substrate drugs using Slco1a4(-/-) mice. The hepatic mRNA expression of Slco1a4 was decreased significantly in Slco1a4(-/-) mice, whereas no differences were seen in other hepatic transporters between wild-type and Slco1a4(-/-) mice. We determined the plasma concentrations, and liver-to-plasma ratio of Oatp1a4 substrates including ouabain, digoxin, BQ-123,

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fexofenadine, rosuvastatin, pravastatin, nafcillin, and telmisartan, after continuous intravenous infusion. The plasma concentrations of ouabain and rosuvastatin were 2.1 and 1.7-fold higher in *Slco1a4(-/-)* mice, and the liver-to-plasma concentration ratios of ouabain and digoxin were 13.4 and 4.3-fold lower in *Slco1a4(-/-)* mice, respectively. Furthermore, the biliary clearance of ouabain and digoxin with regard to plasma concentration were 21.9 and 4.1-fold lower in *Slco1a4(-/-)* mice, respectively, accompanied with a marked reduction in their liver-to-plasma ratios, whereas the systemic clearance of ouabain, but not digoxin, was reduced significantly in *Slco1a4(-/-)* mice. These results suggest that *Oatp1a4* plays a major role in the hepatic accumulation of cardiac glycosides in mice.

[22] *Gencer B, Mach F. So low... so far so good: neurocognitive impact of lowering LDL-C levels with PCSK9 inhibitors. European heart journal* 2018.

PM: <http://www.ncbi.nlm.nih.gov/pubmed/?term=29346544>

ABSTRACT

[23] *Fraga-Silva RA, Seeman H, Montecucco F et al. Apelin-13 treatment enhances the stability of atherosclerotic plaques. European journal of clinical investigation* 2018.

PM: <http://www.ncbi.nlm.nih.gov/pubmed/?term=29336478>

ABSTRACT

BACKGROUND: Apelin is an endogenous peptidergic system which modulates cardiovascular function. Recent studies pointed out a fundamental contribution of apelin on atherosclerosis development; however, such reports revealed contradictory data, and to date, it is difficult to accurately define a beneficial or deleterious role. To better understand apelin function on atherosclerosis, we aimed to investigate apelin-13 treatment effects on atherosclerotic plaques composition. DESIGN: Apolipoprotein E gene-deleted mice were fed on Western-type diet for 11 weeks. Atherosclerotic plaque formation was induced in the carotid artery by a shear stress modifier device, which exposes the same vessel to distinct patterns of shear stress enabling the formation of plaques with different composition. Mice were treated with apelin-13 (2 mg/Kg/day) or vehicle for the last 3 weeks. RESULTS: Apelin-13 treatment did not alter the lipid content of low shear stress- and oscillatory shear stress-induced plaques in the carotid. However, apelin-13 greatly ameliorated plaque stability by increasing intraplaque collagen content and reducing MMP-9 expression. Furthermore, apelin-13 decreased the infiltration of inflammatory cells (neutrophil and macrophage) and intraplaque reactive oxygen species content. Interestingly, apelin-13 treatment reduced total cholesterol, LDL levels and free fatty acid serum levels, while HDL, triglycerides serum levels were not significantly changed. CONCLUSIONS: Apelin-13 treatment for 3 weeks did not alter the lesion size, but it significantly enhanced the stable phenotype of atherosclerotic plaques and improved serum lipid profile. These results indicate that activation of apelin system decreases plaque vulnerability. This article is protected by copyright. All rights reserved.

[24] *Dey D, Gaur S, Ovrehus KA et al. Integrated prediction of lesion-specific ischaemia from quantitative coronary CT angiography using machine learning: a multicentre study. European radiology* 2018.

PM: <http://www.ncbi.nlm.nih.gov/pubmed/?term=29352380>

ABSTRACT

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OBJECTIVES: We aimed to investigate if lesion-specific ischaemia by invasive fractional flow reserve (FFR) can be predicted by an integrated machine learning (ML) ischaemia risk score from quantitative plaque measures from coronary computed tomography angiography (CTA). **METHODS:** In a multicentre trial of 254 patients, CTA and invasive coronary angiography were performed, with FFR in 484 vessels. CTA data sets were analysed by semi-automated software to quantify stenosis and non-calcified (NCP), low-density NCP (LD-NCP, < 30 HU), calcified and total plaque volumes, contrast density difference (CDD, maximum difference in luminal attenuation per unit area) and plaque length. ML integration included automated feature selection and model building from quantitative CTA with a boosted ensemble algorithm, and tenfold stratified cross-validation. **RESULTS:** Eighty patients had ischaemia by FFR (FFR \leq 0.80) in 100 vessels. Information gain for predicting ischaemia was highest for CDD (0.172), followed by LD-NCP (0.125), NCP (0.097), and total plaque volumes (0.092). ML exhibited higher area-under-the-curve (0.84) than individual CTA measures, including stenosis (0.76), LD-NCP volume (0.77), total plaque volume (0.74) and pre-test likelihood of coronary artery disease (CAD) (0.63); $p < 0.006$. **CONCLUSIONS:** Integrated ML ischaemia risk score improved the prediction of lesion-specific ischaemia by invasive FFR, over stenosis, plaque measures and pre-test likelihood of CAD. **KEY POINTS:** * Integrated ischaemia risk score improved prediction of ischaemia over quantitative plaque measures * Integrated ischaemia risk score showed higher prediction of ischaemia than standard approach * Contrast density difference had the highest information gain to identify lesion-specific ischaemia.

[25] Cicero AFG, Colletti A. **An update on the safety of nutraceuticals and effects on lipid parameters.** Expert opinion on drug safety 2018:1-11.

PM: <http://www.ncbi.nlm.nih.gov/pubmed/?term=29338456>

ABSTRACT

INTRODUCTION: Cardiovascular diseases (CVDs) are the leading cause of mortality and disability in developed countries, whereas a large portion of patients in primary prevention have uncontrolled level of CVD risk factors. Dietary supplementation with bioactive natural compounds with demonstrated lipid-lowering effects is currently supported by the international guidelines for CVD prevention and some international expert panels. **Areas covered:** This review provides insights on issues concerning the tolerability and safety of the most commonly used nutraceuticals with demonstrated lipid-lowering effect in humans. They will be then divided into three main categories according to their mechanism of action (cholesterol synthesis inhibitors, intestinal cholesterol absorption inhibitors, and LDL-C excretion stimulants) and their pharmacological profile will be discussed. **Expert opinion:** A growing body of preclinical, epidemiological and clinical evidence has defined the tolerability and safety profile of the most commonly used lipid-lowering nutraceuticals. In the most part of cases, the side effects are mild and reversible. However, detailed knowledge of specific health risks and pharmacological interactions for each individual compound is needed for the management of frail patients, such as children, elderly, patients with liver or renal failure, and patients consuming numerous drugs.

[26] Katsiki N, Reiner Z, Tedeschi Reiner E et al. **Improvement of endothelial function by pitavastatin: a meta-analysis.** Expert opinion on pharmacotherapy 2018:1-8.

PM: <http://www.ncbi.nlm.nih.gov/pubmed/?term=29334477>

ABSTRACT

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OBJECTIVE: Dyslipidemia is commonly associated with endothelial dysfunction and increased cardiovascular risk. Pitavastatin has been shown to reduce total and low-density lipoprotein cholesterol, to increase high-density lipoprotein (HDL)-cholesterol and improve HDL function. Furthermore, several trials explored its effects on flow-mediated dilation (FMD), as an index of endothelial function. The authors evaluated the effect of pitavastatin therapy on FMD. **METHODS:** The authors performed a systematic review and meta-analysis of all clinical trials exploring the impact of pitavastatin on FMD. The search included PubMed-Medline, Scopus, ISI Web of Knowledge and Google Scholar databases. Quantitative data synthesis was performed using a random-effects model, with weighted mean difference (WMD) and 95% confidence interval (CI) as summary statistics. **RESULTS:** Six eligible studies comprising 7 treatment arms were selected for this meta-analysis. Overall, WMD was significant for the effect of pitavastatin on FMD (2.45%, 95% CI: 1.31, 3.60, $p < 0.001$) and the effect size was robust in the leave-one-out sensitivity analysis. **CONCLUSION:** This meta-analysis of all available clinical trials revealed a significant increase of FMD induced by pitavastatin.

[27] *El-Shinnawy NA, Abd Elhalem SS, Haggag NZ, Badr G. Ameliorative role of camel whey protein and rosuvastatin on induced dyslipidemia in mice. Food & function 2018.*

PM: <http://www.ncbi.nlm.nih.gov/pubmed/?term=29349446>

ABSTRACT

The incidence of obesity is rapidly increasing throughout the world. Dyslipidemia is a major risk factor for a number of chronic diseases, including diabetes and cardiovascular diseases. This work presents a novel approach to study the activity of camel whey protein (WP) with antioxidant and anti-inflammatory properties as a cheap dietary protein substance extracted from camel milk to produce satiety and help in building muscles. Mice model suffering from dyslipidemia as a result of feeding on high fat-cholesterol diet for 8 weeks were administrated with either camel WP and/or rosuvastatin for 4 weeks. Dyslipidemia revealed significant increase in anthropometrical measurements, levels of glucose, insulin, cholesterol, triglycerides, low-density lipoprotein, total leucocyte count, inflammatory cytokines and reactive oxygen species, accompanied by a significant elevation in activating transcription factor-3 and inducible nitric oxide synthase expressions. These alterations were correlated with a profound reduction in high-density lipoprotein, peroxisome proliferator-activated receptor alpha and adiponectin along with a decrease in liver and muscle mitochondrial proteins. Rosuvastatin treatment to mice suffering from dyslipidemia in combination with camel WP for 4 weeks ameliorated these parameters. Notably, animals treated with both camel WP and rosuvastatin exhibited a remarkable decrease in the incidence of dyslipidemia. In addition, camel WP succeeded to overcome the therapeutic drawback posed from rosuvastatin therapy alone with minimal side effects.

[28] *Nampijja D, Kumbakumba E, Bajunirwe F, Kiwanuka J. Dyslipidemia and its Correlates among HIV Infected Children on HAART Attending Mbarara Regional Referral Hospital. International clinical pathology journal 2017; 4.*

PM: <http://www.ncbi.nlm.nih.gov/pubmed/?term=29333525>

ABSTRACT

Background: HAART and chronic HIV associated inflammation has been attributed to abnormal lipids in HIV infected people. Little is known about dyslipidemia among children in Uganda in the era of increasing Highly Active Anti Retroviral Therapy (HAART) use. We determined the prevalence of lipid

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abnormalities, the correlation of the lipid abnormalities to CD4 count, HIV clinical stage and duration on HAART among HIV infected children. Methods: This was a cross-sectional, descriptive and analytical study of HIV infected children age 1-17 years receiving HAART for more than 6 months in Mbarara Regional Referral Hospital. Consent and assent were obtained as appropriate. Sociodemographic, clinical and immunological data were collected and recorded in a questionnaire. A blood sample was taken for lipid profiling. Dyslipidemia was defined as any low HDL (≤ 40 mg/dl), high LDL (>130 mg/dl), high TG (>130 mg/dl) and a high total cholesterol (>200 mg/dl) or a combination of these in the study population. The proportion of children with dyslipidemia was calculated and logistic regression analysis for associated factors. Results: The mean age was 118 months (SD 49 months) with 49.5% of the children male and 62.1% had severe HIV disease at initiation of HAART. Mean duration of HAART was 55.6 months (SD 31.2 months). The prevalence of dyslipidemia was 74%. Among the children with dyslipidemia, 56.6% exhibited low HDL, 22% had hypertriglyceridemia, 15.6% had high LDL and 11% had hypercholesterolemia. We found significant association between dyslipidemia and WHO clinical stage at initiation of HAART (AOR 2.9 1.05 - 8.45 $p=0.040$). Conclusion: There was a high prevalence of dyslipidemia associated with severe HIV disease at initiation of HAART among HIV-infected children on HAART.

[29] *Alvarez-Sala A, Lopez-Garcia G, Attanzio A et al. Effects of Plant Sterols or beta-Cryptoxanthin at Physiological Serum Concentrations on Suicidal Erythrocyte Death. Journal of agricultural and food chemistry 2018.*

PM: <http://www.ncbi.nlm.nih.gov/pubmed/?term=29345907>

ABSTRACT

The eryptotic and hemolytic effects of a phytosterol (PS) mixture (beta-sitosterol, campesterol, stigmasterol) or beta-cryptoxanthin (beta-Cx) at physiological serum concentration and their effect against oxidative stress induced by tert-butylhydroperoxide (tBOOH) (75 and 300 μ M) were evaluated. beta-Cryptoxanthin produced an increase in eryptotic cells, cell volume, hemolysis, and glutathione depletion (GSH) without ROS overproduction and intracellular Ca^{2+} influx. Co-incubation of both bioactive compounds protected against beta-Cx-induced eryptosis. Under tBOOH stress, PS prevented eryptosis, reducing Ca^{2+} influx, ROS overproduction and GSH depletion at 75 μ M, and hemolysis at both tBOOH concentrations. beta-Cryptoxanthin showed no cytoprotective effect. Co-incubation with both bioactive compounds completely prevented hemolysis and partially prevented eryptosis as well as GSH depletion induced by beta-Cx plus tBOOH. Phytosterols at physiological serum concentrations help to prevent pro-eryptotic and hemolytic effects and are promising candidate compounds for ameliorating eryptosis-associated diseases.

[30] *D'Erasmus L, Minicocci I, Nicolucci A et al. Autosomal Recessive Hypercholesterolemia: Long-Term Cardiovascular Outcomes. Journal of the American College of Cardiology 2018; 71:279-288.*

PM: <http://www.ncbi.nlm.nih.gov/pubmed/?term=29348020>

ABSTRACT

BACKGROUND: Autosomal recessive hypercholesterolemia (ARH) is a rare lipid disorder characterized by premature atherosclerotic cardiovascular disease (ASCVD). There are sparse data for clinical management and cardiovascular outcomes in ARH. OBJECTIVES: Evaluation of changes in lipid management, achievement of low-density lipoprotein cholesterol (LDL-C) goals and cardiovascular

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outcomes in ARH. **METHODS:** Published ARH cases were identified by electronic search. All corresponding authors and physicians known to treat these patients were asked to provide follow-up information, using a standardized protocol. **RESULTS:** We collected data for 52 patients (28 females, 24 males; 31.1 +/- 17.1 years of age; baseline LDL-C: 571.9 +/- 171.7 mg/dl). During a mean follow-up of 14.1 +/- 7.3 years, there was a significant increase in the use of high-intensity statin and ezetimibe in combination with lipoprotein apheresis; in 6 patients, lomitapide was also added. Mean LDL-C achieved at nadir was 164.0 +/- 85.1 mg/dl (-69.6% from baseline), with a better response in patients taking lomitapide (-88.3%). Overall, 23.1% of ARH patients reached LDL-C of <100 mg/dl. During follow-up, 26.9% of patients had incident ASCVD, and 11.5% had a new diagnosis of aortic valve stenosis (absolute risk per year of 1.9% and 0.8%, respectively). No incident stroke was observed. Age (>=30 years) and the presence of coronary artery disease at diagnosis were the major predictors of incident ASCVD. **CONCLUSIONS:** Despite intensive treatment, LDL-C in ARH patients remains far from targets, and this translates into a poor long-term cardiovascular prognosis. Our data highlight the importance of an early diagnosis and treatment and confirm the fact that an effective treatment protocol for ARH is still lacking.

[31] *Tawakol A, Jaffer F. Imaging the Intersection of Oxidative Stress, Lipids, and Inflammation: Progress Toward Personalized Care of Atherosclerosis. Journal of the American College of Cardiology* 2018; 71:336-338.

PM: <http://www.ncbi.nlm.nih.gov/pubmed/?term=29348026>

ABSTRACT

[32] *Luput L, Licarete E, Drotar DM et al. In Vivo Double Targeting of C26 Colon Carcinoma Cells and Microenvironmental Protumor Processes Using Liposomal Simvastatin. Journal of Cancer* 2018; 9:440-449.

PM: <http://www.ncbi.nlm.nih.gov/pubmed/?term=29344291>

ABSTRACT

Purpose: Besides cholesterol lowering effects, simvastatin (SIM) at very high doses possesses antitumor actions. Moreover our previous studies demonstrated that tumor-targeted delivery of SIM by using long-circulating liposomes (LCL) improved the therapeutic index of this drug in murine melanoma-bearing mice. To evaluate whether this finding can be exploited for future therapy of colorectal cancer the antitumor activity and the underlying mechanisms of long-circulating liposomal simvastatin (LCL-SIM) efficacy for inhibition of C26 murine colon carcinoma growth in vivo were investigated. **Materials and Methods:** To find LCL-SIM dose with the highest therapeutic index, dose-response relationship and side effects of different LCL-SIM doses were assessed in C26 colon carcinoma-bearing mice. The underlying mechanisms of LCL-SIM versus free SIM treatments were investigated with regard to their actions on C26 cell proliferation and apoptosis (via tumor tissues immunostaining for PCNA and Bax markers), tumor inflammation (via western blot analysis of NF-kappaBeta production), angiogenesis (using an angiogenic protein array), and oxidative stress (by HPLC assessment of malondialdehyde). **Results:** Our findings suggest that LCL-SIM antitumor activity on C26 colon carcinoma is a result of the tumor-targeting property of the liposome formulation, as free SIM treatment was ineffective. Moreover, LCL-SIM exerted significant antiproliferative and pro-apoptotic actions on C26 cells, notable suppressive effects on two main supportive processes for tumor development, inflammation and angiogenesis, and only slight anti-oxidant actions. **Conclusion:** Our data proved that LCL-SIM antitumor activity in C26

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colon carcinoma was based on cytotoxic effects on these cancer cells and suppressive actions on tumor angiogenesis and inflammation.

[33] *Mayyas F, Baydoun D, Ibdah R, Ibrahim K. Atorvastatin Reduces Plasma Inflammatory and Oxidant Biomarkers in Patients With Risk of Atherosclerotic Cardiovascular Disease. Journal of cardiovascular pharmacology and therapeutics* 2018:1074248417753677.

PM: <http://www.ncbi.nlm.nih.gov/pubmed/?term=29343081>

ABSTRACT

BACKGROUND: Oxidative stress and inflammation are associated with endothelial injury and coronary artery disease. Inflammatory factors that promote oxidative damage include endothelin-1 (ET-1), myeloperoxidase (MPO), and C-reactive protein (CRP). Current guidelines recommend the use of statins in patients with risk of atherosclerotic cardiovascular disease (ASCVD). AIM: To assess the impact of atorvastatin on plasma inflammatory and oxidant biomarkers in patients with moderate to very high risk of ASCVD. METHOD: Two hundred ten patients presented to the cardiology clinic were included and stratified into low, moderate, high, and very high risk of ASCVD. Moderate- (20 mg/d) to high-intensity (40 mg/d) atorvastatin was prescribed. Plasma levels of lipids, ET-1, CRP, MPO, total nitrite, lipid peroxides (thiobarbituric acid reactive substances [TBARS]), and superoxide dismutase (SOD) activities were measured at baseline and 12 weeks after treatment. RESULT: Relative to low-risk patients, baseline plasma inflammatory markers of CRP, MPO, ET-1, and nitrite were higher in patients with very high risk of ASCVD, whereas plasma SOD was lower (all $P < .05$). Use of high and moderate atorvastatin therapy significantly reduced low-density lipoprotein and total cholesterol levels, as well as plasma levels of CRP, MPO, nitrite, and TBARS, and increased plasma SOD activity in patients with moderate to very high risk of ASCVD, independent of lipid-lowering effects. CONCLUSIONS: Key markers of oxidative stress/inflammation such as CRP, ET-1, total nitrite, and MPO are associated with an increased risk of ASCVD. Moderate- and high-intensity atorvastatin use reduces plasma oxidative stress and inflammation regardless of ASCVD risk and independent of its lipid-lowering effect.

[34] *Lahdentausta L, Leskela J, Winkelmann A et al. Serum MMP-9 Diagnostics, Prognostics, and Activation in Acute Coronary Syndrome and Its Recurrence. Journal of cardiovascular translational research* 2018.

PM: <http://www.ncbi.nlm.nih.gov/pubmed/?term=29349668>

ABSTRACT

Matrix metalloproteinase (MMP)-9 is crucial in atherosclerotic plaque rupture and tissue remodeling after a cardiac event. The balance between MMP-9 and endogenous inhibitor, tissue inhibitors of matrix metalloproteinase 1 (TIMP-1), is important in acute coronary syndrome (ACS). This is an age- and gender-matched case-control study of ACS (N = 669). Patients (45.7%) were resampled after recovery, and all were followed up for 6 years. The molecular forms of MMP-9 were investigated by gelatin zymography. Diagnostically, MMP-9 and the MMP-9/TIMP-1 molar ratio were associated with ACS (OR 5.81, 95% CI 2.65-12.76, and 4.96, 2.37-10.38). The MMP-9 concentrations decreased 49% during recovery ($p < 0.001$). The largest decrease of these biomarkers between acute and recovery phase (DeltaMMP-9) protected the patients from major adverse cardiac events, especially the non-fatal events. The fatal events were associated with in vitro activatable MMP-9 levels ($p = 0.028$). Serum MMP-

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9 and the MMP-9/TIMP-1 molar ratio may be valuable in ACS diagnosis and prognosis. High serum MMP-9 activation potential is associated with poor cardiovascular outcome.

[35] Yu X, Zhang J, Gu Y *et al.* **CHILD Syndrome Mimicking Verrucous Nevus in a Chinese Patient Responded Well to The Topical Therapy of Compound of Simvastatin and Cholesterol.** Journal of the European Academy of Dermatology and Venereology : JEADV 2018.

PM: <http://www.ncbi.nlm.nih.gov/pubmed/?term=29341259>

ABSTRACT

BACKGROUND: Congenital hemidysplasia with ichthyosiform erythroderma and limb defects (CHILD) syndrome is a rare X-linked dominant disorder characterized by peculiar cutaneous presentations and ipsilateral skeletal abnormalities. CHILD syndrome is caused by mutations in NSDHL gene, which involves in cholesterol synthesis. **OBJECTIVES:** To verify the diagnosis of CHILD syndrome and seek effective pathogenesis-based therapy with little side effects. **METHOD:** We comprehensively evaluated the patient's conditions. Pathological biopsy was performed in the lesion location. Genetic tests and real-time quantitative PCR were conducted to further confirm the diagnosis. The topical application of a mixed lotion containing 2% simvastatin and 2% cholesterol to lesion areas based on the pathogenesis as well as the literature review. **RESULTS:** We diagnosed a rare and typical case of CHILD syndrome cooccurring with multiple VX-like lesions. The gene mutation is a large deletion of exon 3 and 4 of the NSDHL gene, which was discovered and reported for the first time in CHILD syndrome. The skin lesions, including the verruciform plaques and VX-like lesions, improved obviously after treatment. **CONCLUSIONS:** Multiple exons deletions or microdeletion were not rare in CHILD syndrome. Classical Sanger sequencing may not be useful enough to find all kinds of mutations. Next Generation Sequencing may be more effective. It is important to conduct genetic counseling to prevent more serious defects in descendants. The excellent therapeutic effect on CHILD syndrome resulted from the topical treatment with simvastatin /cholesterol provides a proof-of-concept for other topical pathogenesis-based therapies for skin disease. This article is protected by copyright. All rights reserved.

[36] Shapiro H, Kolodziejczyk AA, Halstuch D, Elinav E. **Bile acids in glucose metabolism in health and disease.** The Journal of experimental medicine 2018.

PM: <http://www.ncbi.nlm.nih.gov/pubmed/?term=29339445>

ABSTRACT

Bile acids (BAs) are cholesterol-derived metabolites that facilitate the intestinal absorption and transport of dietary lipids. Recently, BAs also emerged as pivotal signaling molecules controlling glucose, lipid, and energy metabolism by binding to the nuclear hormone farnesoid X receptor (FXR) and Takeda G protein receptor 5 (TGR5) in multiple organs, leading to regulation of intestinal incretin secretion, hepatic gluconeogenesis, glycogen synthesis, energy expenditure, inflammation, and gut microbiome configuration. Alterations in BA metabolism and signaling are associated with obesity and type 2 diabetes mellitus (T2DM), whereas treatment of T2DM patients with BA sequestrants, or bariatric surgery in morbidly obese patients, results in a significant improvement in glycemic response that is associated with changes in the BA profile and signaling. Herein, we review the roles of BAs in glucose metabolism in health and disease; highlight the limitations, unknowns, and challenges in understanding the impact of BAs on the glycemic response; and discuss how this knowledge may be harnessed to develop innovative therapeutic approaches for the treatment of hyperglycemia and diabetes.

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[37] *Ikramuddin S, Korner J, Lee WJ et al. Lifestyle Intervention and Medical Management With vs Without Roux-en-Y Gastric Bypass and Control of Hemoglobin A1c, LDL Cholesterol, and Systolic Blood Pressure at 5 Years in the Diabetes Surgery Study. Jama 2018; 319:266-278.*

PM: <http://www.ncbi.nlm.nih.gov/pubmed/?term=29340678>

ABSTRACT

Importance: The Roux-en-Y gastric bypass is effective in achieving established diabetes treatment targets, but durability is unknown. **Objective:** To compare durability of Roux-en-Y gastric bypass added to intensive lifestyle and medical management in achieving diabetes control targets. **Design, Setting, and Participants:** Observational follow-up of a randomized clinical trial at 4 sites in the United States and Taiwan, involving 120 participants who had a hemoglobin A1c (HbA1c) level of 8.0% or higher and a body mass index between 30.0 and 39.9 (enrolled between April 2008 and December 2011) were followed up for 5 years, ending in November 2016. **Interventions:** Lifestyle-intensive medical management intervention based on the Diabetes Prevention Program and LookAHEAD trials for 2 years, with and without (60 participants each) Roux-en-Y gastric bypass surgery followed by observation to year 5. **Main Outcomes and Measures:** The American Diabetes Association composite triple end point of hemoglobin A1c less than 7.0%, low-density lipoprotein cholesterol less than 100 mg/dL, and systolic blood pressure less than 130 mm Hg at 5 years. **Results:** Of 120 participants who were initially randomized (mean age, 49 years [SD, 8 years], 72 women [60%]), 98 (82%) completed 5 years of follow-up. Baseline characteristics were similar between groups: mean (SD) body mass index 34.4 (3.2) for the lifestyle-medical management group and 34.9 (3.0) for the gastric bypass group and had hemoglobin A1c levels of 9.6% (1.2) and 9.6% (1.0), respectively. At 5 years, 13 participants (23%) in the gastric bypass group and 2 (4%) in the lifestyle-intensive medical management group had achieved the composite triple end point (difference, 19%; 95% CI, 4%-34%; $P = .01$). In the fifth year, 31 patients (55%) in the gastric bypass group vs 8 (14%) in the lifestyle-medical management group achieved an HbA1c level of less than 7.0% (difference, 41%; 95% CI, 19%-63%; $P = .002$). Gastric bypass had more serious adverse events than did the lifestyle-medical management intervention, 66 events vs 38 events, most frequently gastrointestinal events and surgical complications such as strictures, small bowel obstructions, and leaks. Gastric bypass had more parathyroid hormone elevation but no difference in B12 deficiency. **Conclusions and Relevance:** In extended follow-up of obese adults with type 2 diabetes randomized to adding gastric bypass compared with lifestyle and intensive medical management alone, there remained a significantly better composite triple end point in the surgical group at 5 years. However, because the effect size diminished over 5 years, further follow-up is needed to understand the durability of the improvement. **Trial Registration:** clinicaltrials.gov Identifier: NCT00641251.

[38] *Salminen P, Helmio M, Ovaska J et al. Effect of Laparoscopic Sleeve Gastrectomy vs Laparoscopic Roux-en-Y Gastric Bypass on Weight Loss at 5 Years Among Patients With Morbid Obesity: The SLEEVEPASS Randomized Clinical Trial. Jama 2018; 319:241-254.*

PM: <http://www.ncbi.nlm.nih.gov/pubmed/?term=29340676>

ABSTRACT

Importance: Laparoscopic sleeve gastrectomy for treatment of morbid obesity has increased substantially despite the lack of long-term results compared with laparoscopic Roux-en-Y gastric bypass. **Objective:** To determine whether laparoscopic sleeve gastrectomy and laparoscopic Roux-en-Y gastric bypass are equivalent for weight loss at 5 years in patients with morbid obesity. **Design, Setting, and**

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Participants: The Sleeve vs Bypass (SLEEVEPASS) multicenter, multisurgeon, open-label, randomized clinical equivalence trial was conducted from March 2008 until June 2010 in Finland. The trial enrolled 240 morbidly obese patients aged 18 to 60 years, who were randomly assigned to sleeve gastrectomy or gastric bypass with a 5-year follow-up period (last follow-up, October 14, 2015). Interventions: Laparoscopic sleeve gastrectomy (n = 121) or laparoscopic Roux-en-Y gastric bypass (n = 119). Main Outcomes and Measures: The primary end point was weight loss evaluated by percentage excess weight loss. Prespecified equivalence margins for the clinical significance of weight loss differences between gastric bypass and sleeve gastrectomy were -9% to +9% excess weight loss. Secondary end points included resolution of comorbidities, improvement of quality of life (QOL), all adverse events (overall morbidity), and mortality. Results: Among 240 patients randomized (mean age, 48 [SD, 9] years; mean baseline body mass index, 45.9, [SD, 6.0]; 69.6% women), 80.4% completed the 5-year follow-up. At baseline, 42.1% had type 2 diabetes, 34.6% dyslipidemia, and 70.8% hypertension. The estimated mean percentage excess weight loss at 5 years was 49% (95% CI, 45%-52%) after sleeve gastrectomy and 57% (95% CI, 53%-61%) after gastric bypass (difference, 8.2 percentage units [95% CI, 3.2%-13.2%], higher in the gastric bypass group) and did not meet criteria for equivalence. Complete or partial remission of type 2 diabetes was seen in 37% (n = 15/41) after sleeve gastrectomy and in 45% (n = 18/40) after gastric bypass (P > .99). Medication for dyslipidemia was discontinued in 47% (n = 14/30) after sleeve gastrectomy and 60% (n = 24/40) after gastric bypass (P = .15) and for hypertension in 29% (n = 20/68) and 51% (n = 37/73) (P = .02), respectively. There was no statistically significant difference in QOL between groups (P = .85) and no treatment-related mortality. At 5 years the overall morbidity rate was 19% (n = 23) for sleeve gastrectomy and 26% (n = 31) for gastric bypass (P = .19). Conclusions and Relevance: Among patients with morbid obesity, use of laparoscopic sleeve gastrectomy compared with use of laparoscopic Roux-en-Y gastric bypass did not meet criteria for equivalence in terms of percentage excess weight loss at 5 years. Although gastric bypass compared with sleeve gastrectomy was associated with greater percentage excess weight loss at 5 years, the difference was not statistically significant, based on the prespecified equivalence margins. Trial Registration: clinicaltrials.gov Identifier: NCT00793143.

[39] *Shubeck S, Dimick JB, Telem DA. Long-term Outcomes Following Bariatric Surgery. Jama* 2018; 319:302-303.

PM: <http://www.ncbi.nlm.nih.gov/pubmed/?term=29340664>

ABSTRACT

[40] *Ozbicer S, Gur M, Kalkan G et al. Chronic statin treatment is a predictor of pre-interventional infarct related artery patency in patients with ST elevation myocardial infarction treated with percutaneous coronary intervention. Kardiol Pol* 2018.

PM: <http://www.ncbi.nlm.nih.gov/pubmed/?term=29350388>

ABSTRACT

BACKGROUND: Beyond lipid-lowering effects, early statin treatment has beneficial effects on prognosis after acute coronary syndrome. Infarct related artery patency before percutaneous coronary intervention is known to be a strong predictor of improved clinical outcome. AIM: We aimed to investigate the effects of chronic statin treatment before admission on the infarct related artery patency after infarction. METHODS: In this study, 938 ST elevation myocardial infarction patients admitted to the hospital within the first 12 hours of symptom onset were prospectively enrolled (682 male, 256 female;

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mean age 58.6 +/- 12.4 years). All patients underwent emergent primary percutaneous coronary intervention. Patients were divided into two groups based upon the angiographic infarct related artery patency. Impaired infarct related artery patency was defined as TIMI grade 0 and 1 flows (non-patent infarct related artery group). Angiographic infarct related artery patency was defined as TIMI 2 and 3 flows (patent infarct related artery group). RESULTS: Previous statin usage was more frequent in the patent infarct related artery group (n=138 71.9%), than the non-patent infarct related artery group (n=110, 14.7%), (p<0.001). Pre-percutaneous coronary interventional infarct related artery patency was independently associated with body mass index (OR=1.087, 95%CI= 1.005-1.176, p<0.001), previous chronic statin use (OR= 0.065, 95%CI=0.043-0.098, p= 0.039), ejection fraction (OR: 1.041, 95%CI= 1.018-1.064, p<0.001) and Syntax score (OR= 0.927, 95%CI=0.899-0.957, p<0.001) in multivariate logistic regression analysis. CONCLUSIONS: Chronic pre-treatment with statin is a significant predictor of the infarct related artery patency in patients with ST elevation myocardial infarction.

[41] Guo W, Gong Y, Gu Y et al. **Circulating PCSK9 levels and 2-hPG are positively correlated in metabolic diseases in a Chinese Han population.** *Lipids in health and disease* 2018; 17:15.

PM: <http://www.ncbi.nlm.nih.gov/pubmed/?term=29343301>

ABSTRACT

BACKGROUND: Proprotein convertase subtilisin/kexin type 9 (PCSK9), which plays a crucial role in lipoprotein metabolism, has been also regarded as an important marker for atherosclerosis. Available evidence indicated that 2-h postchallenge plasma glucose (2-hPG) could be another biomarker for atherosclerosis. However, currently the association between circulating PCSK9 and 2-hPG remains unclear. Here, we explored this potential link in a Chinese Han population. METHODS: Totally, 600 Chinese Han subjects from Nanjing district, China, were enrolled for the 75-g oral glucose tolerance test (OGTT), and they included normal glucose tolerance (NGT, n = 200), impaired glucose regulation (IGR, n = 200), and type 2 diabetes (T2DM, n = 200). Anthropometric and biochemical determinations such as serum lipid measurements were made. A sandwich ELISA assay was performed to measure serum PCSK9 levels in all subjects. RESULTS: Serum PCSK9 concentrations were higher in IGR group (77.63 +/- 28.14 ng/ml) and T2DM group (90.62 +/- 39.96 ng/ml) than in NGT group (65.33 +/- 32.68 ng/ml), and it was significantly higher in T2DM group than in IGR group (p < 0.01). Serum PCSK9 levels positively correlated with 2-hPG and LDL-C in all subgroups, but presented a positive correlation with fasting blood glucose (FBG) only in T2DM group. Using multiple regression model analysis, we also found that PCSK9 levels closely correlated with 2-hPG in all tested groups. According to multinomial logistic regression analysis, PCSK9 levels positively correlated with T2DM (OR = 1.017[1.010-1.025], p < 0.001) even after adjustment for lipid levels. Moreover, in subjects with normal FBG level, 2-hPG gradually and significantly increased across PCSK9 tertiles (6.68 +/- 2.01, 7.48 +/- 2.10 and 8.27 +/- 2.41 mmol/L, respectively, p < 0.01); however, in subjects with normal 2-hPG levels, no such difference was observed. CONCLUSIONS: PCSK9 levels increase as glucose metabolism deteriorated. Serum PCSK9 levels positively correlated with 2-hPG in patients with metabolic diseases.

[42] Han J, Meng Q, Shen L, Wu G. **Interleukin-6 induces fat loss in cancer cachexia by promoting white adipose tissue lipolysis and browning.** *Lipids in health and disease* 2018; 17:14.

PM: <http://www.ncbi.nlm.nih.gov/pubmed/?term=29338749>

ABSTRACT

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BACKGROUND: Cancer cachexia is a progressive and multi-factorial metabolic syndrome characterized by loss of adipose tissue and skeletal muscle. White adipose tissue (WAT) lipolysis and white-to-brown transdifferentiation of WAT (WAT browning) are proposed to contribute to WAT atrophy in cancer cachexia. Chronic inflammation, mediated by cytokines such as tumor necrosis factor alpha (TNF-alpha) and interleukin-6 (IL-6), has been reported to promote cancer cachexia. However, whether chronic inflammation promotes cancer cachexia by regulating WAT metabolism and the underlying mechanism remains unclear. **METHODS:** In this study, we first analyzed the association between chronic inflammation and WAT metabolism in gastric and colorectal cancer cachectic patients. In cachectic mice treated with anti-IL-6 receptor antibody, we clarified whether WAT lipolysis and browning were regulated by IL-6. **RESULTS:** Clinical analyses showed positive significant association between serum IL-6 and free fatty acid (FFA) both in early- and late-stage cancer cachexia. However, serum TNF-alpha was positively associated with serum FFA in the early- but not late-stage cachexia. WAT lipolysis was increased in early- and late-stage cachexia, while WAT browning was detected only in late-stage cachexia. Anti-IL-6 receptor antibody inhibited WAT lipolysis and browning in cachectic mice. **CONCLUSIONS:** Based on these findings, we conclude that chronic inflammation (especially that mediated by IL-6) might promote cancer cachexia by regulating WAT lipolysis in early-stage cachexia and browning in late-stage cachexia.

[43] *Busygina K, Parhofer KG. [PCSK9 inhibitors: For which patients? For which indication? What to consider?]. MMW Fortschritte der Medizin 2018; 160:43-46.*

PM: <http://www.ncbi.nlm.nih.gov/pubmed/?term=29335943>

ABSTRACT

[44] *Klose G. [Statin-associated muscle symptoms]. MMW Fortschritte der Medizin 2018; 160:40-43.*

PM: <http://www.ncbi.nlm.nih.gov/pubmed/?term=29335944>

ABSTRACT

[45] *Al-Qatati A, Aliwaini S. Combined pitavastatin and dacarbazine treatment activates apoptosis and autophagy resulting in synergistic cytotoxicity in melanoma cells. Oncology letters 2017; 14:7993-7999.*

PM: <http://www.ncbi.nlm.nih.gov/pubmed/?term=29344241>

ABSTRACT

Melanoma is an aggressive skin cancer and its incidence is increasing faster than any other type of cancer. Whilst dacarbazine (DTIC) is the standard chemotherapy for metastatic melanoma, it has limited success. Statins, including pitavastatin, have been demonstrated to have a range of anti-cancer effects in a number of human cancer cell lines. The present study therefore explored the anti-cancer activity of combined DTIC and pitavastatin in A375 and WM115 human melanoma cells. Cell survival assays demonstrated that combined DTIC and pitavastatin treatment resulted in synergistic cell death. Cell cycle analyses further revealed that this combined treatment resulted in a G1 cell cycle arrest, as well as a sub-G1 population, indicative of apoptosis. Activation of apoptosis was confirmed by Annexin V-fluorescein isothiocyanate/propidium iodide double-staining and an increase in the levels of active caspase 3 and cleaved poly (ADP-ribose) polymerase. Furthermore, it was demonstrated that apoptosis occurs through the intrinsic pathway, evident from the release of cytochrome c. Finally, combined DTIC

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and pitavastatin treatment was demonstrated to also activate autophagy as part of a cell death mechanism. The present study provides novel evidence to suggest that the combined treatment of DTIC and pitavastatin may be effective in the treatment of melanoma.

[46] Duni A, Liakopoulos V, Rapsomanikis KP, Dounousi E. **Chronic Kidney Disease and Disproportionally Increased Cardiovascular Damage: Does Oxidative Stress Explain the Burden?** Oxidative medicine and cellular longevity 2017; 2017:9036450.

PM: <http://www.ncbi.nlm.nih.gov/pubmed/?term=29333213>

ABSTRACT

Chronic kidney disease (CKD) patients are among the groups at the highest risk for cardiovascular disease and significantly shortened remaining lifespan. CKD enhances oxidative stress in the organism with ensuing cardiovascular damage. Oxidative stress in uremia is the consequence of higher reactive oxygen species (ROS) production, whereas attenuated clearance of pro-oxidant substances and impaired antioxidant defenses play a complementary role. The pathophysiological mechanism underlying the increased ROS production in CKD is at least partly mediated by upregulation of the intrarenal angiotensin system. Enhanced oxidative stress in the setting of the uremic milieu promotes enzymatic modification of circulating lipids and lipoproteins, protein carbamylation, endothelial dysfunction via disruption of nitric oxide (NO) pathways, and activation of inflammation, thus accelerating atherosclerosis. Left ventricular hypertrophy (LVH) and heart failure are hallmarks of CKD. NADPH oxidase activation, xanthine oxidase, mitochondrial dysfunction, and NO-ROS are the main oxidative pathways leading to LVH and the cardiorenal syndrome. Finally, a subset of antioxidant enzymes, the paraoxonases (PON), deserves special attention due to abundant clinical evidence accumulated regarding reduced serum PON1 activity in CKD as a contributor to the increased burden of cardiovascular disease. Future, meticulously designed studies are needed to assess the effects of antioxidant therapy on patients with CKD.

[47] Liu Z, Zhang X, Xiao Q et al. **Pretreatment Donors after Circulatory Death with Simvastatin Alleviates Liver Ischemia Reperfusion Injury through a KLF2-Dependent Mechanism in Rat.** Oxidative medicine and cellular longevity 2017; 2017:3861914.

PM: <http://www.ncbi.nlm.nih.gov/pubmed/?term=29348789>

ABSTRACT

Objective: Severe hepatic ischemia reperfusion injury (IRI) can result in poor short- and long-term graft outcome after transplantation. The way to improve the viability of livers from donors after circulatory death (DCD) is currently limited. The aim of the present study was to explore the protective effect of simvastatin on DCD livers and investigate the underlying mechanism. Methods: 24 male rats randomly received simvastatin or its vehicle. 30 min later, rat livers were exposed to warm ischemia in situ for 30 min. Livers were removed and cold-stored in UW solution for 24 h, subsequently reperfused for 60 min with an isolated perfused rat liver system. Liver injury was evaluated during and after warm reperfusion. Results: Pretreatment of DCD donors with simvastatin significantly decreased IRI liver enzyme release, increased bile output and ATP, and ameliorated hepatic pathological changes. Simvastatin maintained the expression of KLF2 and its protective target genes (eNOS, TM, and HO-1), reduced oxidative stress, inhibited innate immune responses and inflammation, and increased the expression of Bcl-2/Bax to suppress hepatocyte apoptosis compared to DCD control group. Conclusion: Pretreatment of DCD

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donors with simvastatin improves DCD livers' functional recovery probably through a KLF2-dependent mechanism. These data suggest that simvastatin may provide a potential benefit for clinical DCD liver transplantation.

[48] *Krysiak R, Szkrobka W, Okopien B. Moderate-dose simvastatin therapy potentiates the effect of vitamin D on thyroid autoimmunity in levothyroxine-treated women with Hashimoto's thyroiditis and vitamin D insufficiency. Pharmacological reports : PR 2017; 70:93-97.*

PM: <http://www.ncbi.nlm.nih.gov/pubmed/?term=29331793>

ABSTRACT

BACKGROUND: Vitamin D preparations reduce titers of thyroid antibodies in women with autoimmune thyroiditis. The same effect was induced by high-dose, but not moderate-dose-, statin therapy. No previous study has investigated the impact of concomitant treatment with a statin and vitamin D on thyroid autoimmunity. **METHODS:** The study included three matched groups of women with Hashimoto's thyroiditis and low vitamin D status. Groups B (n=19) and C (n=20) were treated with vitamin D (2000 IU daily). Because of coexistent hypercholesterolemia, groups A (n=18) and B received simvastatin (40mg daily). Plasma lipids, serum levels of thyrotropin, free thyroid hormones and 25-hydroxyvitamin D, as well as titers of thyroid peroxidase and thyroglobulin antibodies were measured at the beginning of the study and 6 months later. **RESULTS:** At baseline, 25-hydroxyvitamin D levels inversely correlated with titers of thyroid antibodies. In groups A and B, simvastatin reduced plasma levels of total and LDL cholesterol. Simvastatin produced no effect on thyroid antibody titers. Vitamin D decreased titers of thyroid peroxidase antibodies, as well as tended to decrease titers of thyroglobulin antibodies. Simvastatin-vitamin D combination therapy reduced serum titers of thyroid peroxidase and thyroglobulin antibodies and this effect was stronger than the effect of simvastatin and vitamin D administered alone. Treatment-induced changes in thyroid antibody titers correlated with baseline antibody titers, baseline levels of 25-hydroxyvitamin and treatment-induced changes in 25-hydroxyvitamin. **CONCLUSIONS:** The obtained results indicate that simvastatin may potentiate the impact of vitamin D on thyroid autoimmunity in vitamin D-deficient women with Hashimoto's thyroiditis.

[49] *Daly B, Toulis KA, Thomas N et al. Increased risk of ischemic heart disease, hypertension, and type 2 diabetes in women with previous gestational diabetes mellitus, a target group in general practice for preventive interventions: A population-based cohort study. PLoS medicine 2018; 15:e1002488.*

PM: <http://www.ncbi.nlm.nih.gov/pubmed/?term=29337985>

ABSTRACT

BACKGROUND: Gestational diabetes mellitus (GDM) is associated with developing type 2 diabetes, but very few studies have examined its effect on developing cardiovascular disease. **METHODS AND FINDINGS:** We conducted a retrospective cohort study utilizing a large primary care database in the United Kingdom. From 1 February 1990 to 15 May 2016, 9,118 women diagnosed with GDM were identified and randomly matched with 37,281 control women by age and timing of pregnancy (up to 3 months). Adjusted incidence rate ratios (IRRs) with 95% confidence intervals (CIs) were calculated for cardiovascular risk factors and cardiovascular disease. Women with GDM were more likely to develop type 2 diabetes (IRR = 21.96; 95% CI 18.31-26.34) and hypertension (IRR = 1.85; 95% CI 1.59-2.16) after adjusting for age, Townsend (deprivation) quintile, body mass index, and smoking. For ischemic heart

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disease (IHD), the IRR was 2.78 (95% CI 1.37-5.66), and for cerebrovascular disease 0.95 (95% CI 0.51-1.77; p-value = 0.87), after adjusting for the above covariates and lipid-lowering medication and hypertension at baseline. Follow-up screening for type 2 diabetes and cardiovascular risk factors was poor. Limitations include potential selective documentation of severe GDM for women in primary care, higher surveillance for outcomes in women diagnosed with GDM than control women, and a short median follow-up postpartum period, with a small number of outcomes for IHD and cerebrovascular disease. CONCLUSIONS: Women diagnosed with GDM were at very high risk of developing type 2 diabetes and had a significantly increased incidence of hypertension and IHD. Identifying this group of women in general practice and targeting cardiovascular risk factors could improve long-term outcomes.

[50] *Kenny TA, Hu XF, Kuhnlein HV et al. Dietary sources of energy and nutrients in the contemporary diet of Inuit adults: results from the 2007-08 Inuit Health Survey. Public health nutrition 2018:1-13.*

PM: <http://www.ncbi.nlm.nih.gov/pubmed/?term=29331158>

ABSTRACT

OBJECTIVE: To characterize the major components of the contemporary Inuit diet and identify the primary sources of energy and essential nutrients. DESIGN: Dietary data were derived from the 24 h recall collected by the Inuit Health Survey (IHS) from 2007 to 2008. The population proportion method was used to determine the percentage contribution of each group. Unique food items/preparations (ninety-three country foods and 1591 market foods) were classified into eight country food groups and forty-one market food groups. Nutrient composition of each food item was obtained from the Canadian Nutrient File. SETTING: Thirty-six communities across three Inuit regions of northern Canada. SUBJECTS: A representative sample (n 2095) of non-pregnant Inuit adults (>/=18 years), selected through stratified random sampling. RESULTS: Despite their modest contribution to total energy intake (6.4-19.6 %, by region) country foods represented a major source of protein (23-52 %), Fe (28-54 %), niacin (24-52 %) and vitamins D (up to 73 %), B6 (18-55 %) and B12 (50-82 %). By contrast, the three most popular energy-yielding market foods (i.e. sweetened beverages, added sugar and bread) collectively contributed approximately 20 % of total energy, while contributing minimally to most micronutrients. A notable exception was the contribution of these foods to Ca (13-21 %) and vitamins E (17-35 %) and C (as much as 50 %). Solid fruits were consumed by less than 25 % of participants while vegetables were reported by 38-59 % of respondents. CONCLUSIONS: Country foods remain a critical dimension of the contemporary Inuit diet.

[51] *Boovarahan SR, Kurian GA. Mitochondrial dysfunction: a key player in the pathogenesis of cardiovascular diseases linked to air pollution. Reviews on environmental health 2018.*

PM: <http://www.ncbi.nlm.nih.gov/pubmed/?term=29346115>

ABSTRACT

Air pollution has become an environmental burden with regard to non-communicable diseases, particularly heart disease. It has been reported that air pollution can accelerate the development of heart failure and atrial fibrillation. Air pollutants encompass various particulate matters (PMs), which change the blood composition and heart rate and eventually leads to cardiac failure by triggering atherosclerotic plaque ruptures or by developing irreversible ischemia. A series of major epidemiological and observational studies have established the noxious effect of air pollutants on cardiovascular diseases (CVD), but the underlying molecular mechanisms of its susceptibility and the pathological

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disease events remain largely elusive and are predicted to be initiated in the cell organelle. The basis of this belief is that mitochondria are one of the major targets of environmental toxicants that can damage mitochondrial morphology, function and its DNA (manifested in non-communicable diseases). In this article, we review the literature related to air pollutants that adversely affect the progression of CVD and that target mitochondrial morphological and functional activities and how mitochondrial DNA (mtDNA) copy number variation, which reflects the airborne oxidant-induced cell damage, correlates with heart failure. We conclude that environmental health assessment should focus on the cellular/circulatory mitochondrial functional copy number status, which can predict the outcome of CVD.

[52] *Packard CJ. LDL cholesterol: How low to go? Trends in cardiovascular medicine* 2017.

PM: <http://www.ncbi.nlm.nih.gov/pubmed/?term=29336946>

ABSTRACT

Epidemiology and the results of large-scale outcome trials indicate that the association of LDL with atherosclerotic cardiovascular disease is causal, and continuous not only across levels seen in the general population but also down to sub-physiological values. There is no scientific basis, therefore, to set a target or 'floor' for LDL cholesterol lowering, and this presents a clinical and conceptual dilemma for prescribers, patients, and payers. With the advent of powerful agents such as proprotein convertase/subtilisin kexin type 9 (PCSK9) inhibitors, LDL cholesterol can be lowered profoundly but health economic constraints mandate that this therapeutic approach needs to be selective. Based on the need to maximize the absolute risk reduction when prescribing combination lipid-lowering therapy, it is appropriate to prioritize patients with the highest risk (aggressive and established CVD) who will obtain the highest benefit, that is, those with elevated LDL cholesterol on optimized statin therapy.