

Literature update week 37 (2019)

[1] *Das UN. Bioactive Lipids in Shoulder Tendon Tears. The American journal of pathology* 2019.

PM: <http://www.ncbi.nlm.nih.gov/pubmed/?term=31526772>

ABSTRACT

This commentary highlights the article by Dakin et al that demonstrates critical roles of bioactive lipids in the resolution of inflammation in shoulder tendon tears.

[2] *Mueller PA, Yang L, Ubele M et al. Coronary Artery Disease Risk-Associated Plpp3 Gene and Its Product Lipid Phosphate Phosphatase 3 Regulate Experimental Atherosclerosis.*

Arteriosclerosis, thrombosis, and vascular biology 2019:Atvbaha119313056.

PM: <http://www.ncbi.nlm.nih.gov/pubmed/?term=31533471>

ABSTRACT

OBJECTIVE: Genome-wide association studies identified novel loci in PLPP3 (phospholipid phosphatase 3) that associate with coronary artery disease risk independently of traditional risk factors. PLPP3 encodes LPP3 (lipid phosphate phosphatase 3), a cell-surface enzyme that can regulate the availability of bioactive lysophospholipids including lysophosphatidic acid (LPA). The protective allele of PLPP3 increases LPP3 expression during cell exposure to oxidized lipids, however, the role of LPP3 in atherosclerosis remains unclear. **Approach and Results:** In this study, we sought to validate LPP3 as a determinant of the development of atherosclerosis. In experimental models of atherosclerosis, LPP3 is upregulated and co-localizes with endothelial, smooth muscle cell, and CD68-positive cell markers. Global post-natal reductions in Plpp3 expression in mice substantially increase atherosclerosis, plaque-associated LPA, and inflammation. Although LPP3 expression increases during ox-LDL (oxidized low-density lipoprotein)-induced phenotypic modulation of bone marrow-derived macrophages, myeloid Plpp3 does not appear to regulate lesion formation. Rather, smooth muscle cell LPP3 expression is a critical regulator of atherosclerosis and LPA content in lesions. Moreover, mice with inherited deficiency in LPA receptor signaling are protected from experimental atherosclerosis. **CONCLUSIONS:** Our results identify a novel lipid signaling pathway that regulates inflammation in the context of atherosclerosis and is not related to traditional risk factors. Pharmacological targeting of bioactive LPP3 substrates, including LPA, may offer an orthogonal approach to lipid-lowering drugs for mitigation of coronary artery disease risk.

[3] *Ramaswami U, Humphries SE, Priestley-Barnham L et al. Current management of children and young people with heterozygous familial hypercholesterolaemia - HEART UK statement of care. Atherosclerosis* 2019; 290:1-8.

PM: <http://www.ncbi.nlm.nih.gov/pubmed/?term=31536851>

ABSTRACT

This consensus statement on the management of children and young people with heterozygous familial hypercholesterolaemia (FH) addresses management of paediatric FH in the UK, identified by cascade testing when a parent is diagnosed with FH and for those diagnosed following incidental lipid tests. Lifestyle and dietary advice appropriate for children with FH; suggested low density lipoprotein cholesterol (LDL-C) targets and the most appropriate lipid-lowering therapies to achieve these are discussed in this statement of care. Based on the population prevalence of FH as ~1/250 and the UK paediatric population, there are

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approximately 50,000 FH children under 18 years. Currently only about 550 of these children and young people have been identified and are under paediatric care.

[4] Wang EQ, Bukowski JF, Yunis C et al. **Assessing the Potential Risk of Cross-Reactivity Between Anti-Bococizumab Antibodies and Other Anti-PCSK9 Monoclonal Antibodies.**

BioDrugs : clinical immunotherapeutics, biopharmaceuticals and gene therapy 2019.

PM: <http://www.ncbi.nlm.nih.gov/pubmed/?term=31529318>

ABSTRACT

BACKGROUND: Anti-drug antibodies (ADAs) to bococizumab were detected in > 40% of subjects in the SPIRE lipid-lowering trials. The risk of cross-reactivity between anti-bococizumab antibodies and other approved anti-protein convertase subtilisin/kexin type-9 (PCSK9) monoclonal antibodies (mAbs) was investigated using a single-assay approach. **METHODS:** Bococizumab immunogenicity was assessed in SPIRE-HR, a 52-week study. The highest ADA titer sample from each ADA-positive subject (n = 155) was tested in vitro for cross-reactivity to alirocumab and evolocumab using a novel ADA assay approach. Additional specificity tiers within the bococizumab ADA assay against each drug were validated using recombinant PCSK9 as a surrogate cross-reactive positive control. If the highest ADA titer sample showed cross-reactivity, additional samples from that subject were analyzed. Cross-reactivity was determined by the ability of alirocumab or evolocumab to inhibit the sample signal greater than or equal to the cross-reactivity cut-points. **RESULTS:** ADAs were detected in 44.0% (155/352) of bococizumab-treated subjects, and 27.0% also developed neutralizing antibodies (NAb). Median ADA and NAb titers ranged from 276 to 526 and 8 to 12 over the course of the study, respectively. From 155 ADA-positive subjects tested for cross-reactivity, one (0.6%) subject showed weak cross-reactivity to both alirocumab and evolocumab. This cross-reactivity signal was transient (from Days 337 to 373) and undetectable at the last ADA-positive timepoint (Day 407). **CONCLUSION:** A novel, single-assay approach was validated to assess the potential cross-reactivity of anti-bococizumab antibodies to alirocumab and evolocumab. In subjects who developed ADAs to bococizumab, the likelihood of clinically relevant cross-reactivity to marketed anti-PCSK9 mAbs is remote, based on the low frequency of cross-reactivity observed, which was weak in signal inhibition and transient in nature. **CLINICAL TRIAL REGISTRATION:** The SPIRE-HR study is registered on ClinicalTrials.gov under the identifier NCT01968954.

[5] Fang Y, Duan C, Chen S et al. **Increased Legumain/Smad3 expression in atherosclerotic plaque of rat thoracic aorta.** Biomedicine & pharmacotherapy = Biomedecine & pharmacotherapie 2019; 119:109353.

PM: <http://www.ncbi.nlm.nih.gov/pubmed/?term=31521890>

ABSTRACT

OBJECTIVES: The purpose of this study was to investigate the role of legumain in the formation and stability of atherosclerotic plaque, as well as to explore the association between legumain with Smad3 pathway in a rat atherosclerosis model. **METHODS:** Rat with thoracic aorta atherosclerosis was established and received treatment with statin (n=15 each) or controls (n=10). Serum level of legumain was determined by enzyme-linked immunosorbent assay. Legumain and Smad3 aortic expression levels were assessed by immunohistochemistry and fluorescence microscopy. Protein and mRNA levels were analyzed using Western blot analysis

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and reverse transcriptase coupled polymerase chain reaction, respectively. RESULTS: The atherosclerotic group showed higher serum legumain level than control and statin group. Expression of legumain and Smad3 in macrophages and foam cells was increased in atherosclerotic group compared to control and statin group. The protein and mRNA levels of legumain and Smad3 were significantly attenuated by statin treatment ($p < 0.05$). For all groups, legumain expression was correlated linearly with Smad3 at mRNA (coefficient: 0.94) and protein (coefficient: 0.97) level. CONCLUSIONS: Legumain and Smad3 expression is highly expressed in mainly atherosclerotic plaque macrophages and linearly related, which is attenuated by statin therapy, suggesting legumain a potential Smad3 pathway-related marker of atherosclerosis.

[6] *Das UN. Bioactive lipids in intervertebral disc (IVD) degeneration and its therapeutic implications. Bioscience reports* 2019.

PM: <http://www.ncbi.nlm.nih.gov/pubmed/?term=31533969>

ABSTRACT

Intervertebral disc (IVD) degeneration is not uncommon. It is estimated that approximately > 60% of individuals above the age of 40 years suffer from IVD degeneration. Shan et al showed that hyperglycemia can enhance apoptosis of anulus fibrosis cells in a JNK pathway and p38 MAPK pathway dependent fashion. Recent studies showed that IVD degeneration could be an inflammatory condition characterized by increased production of matrix metalloproteinases, tumor necrosis factor-alpha, nitric oxide, interleukin-6, interleukin-17, interleukin-9, and prostaglandin E2 and decreased formation of anti-inflammatory molecules such as lipoxin A4. This imbalance between pro- and anti-inflammatory molecules seem to activate JNK pathway and p38 MAPK pathway to induce apoptosis of anulus fibrosis and nucleus pulposus cells. The activation of production of PGE2 (due to activation of COX-2 pathway) seems to be dependent on p38/c-Fos and JNK/c-Jun activation in an AP-1-dependent manner. These results imply that suppressing pro-inflammatory events in the disc by either augmenting anti-inflammatory events or suppressing production of pro-inflammatory molecules or both may form a logical step in the prevention and management of IVD degeneration.

[7] *Guirgis FW, Black LP, Rosenthal MD et al. LIPid Intensive Drug therapy for Sepsis Pilot (LIPIDS-P): Phase I/II clinical trial protocol of lipid emulsion therapy for stabilising cholesterol levels in sepsis and septic shock. BMJ open* 2019; 9:e029348.

PM: <http://www.ncbi.nlm.nih.gov/pubmed/?term=31537565>

ABSTRACT

INTRODUCTION: Sepsis is a life-threatening, dysregulated response to infection. Both high-density lipoprotein and low-density lipoprotein cholesterol should protect against sepsis by several mechanisms; however, for partially unknown reasons, cholesterol levels become critically low in patients with early sepsis who experience poor outcomes. An anti-inflammatory lipid injectable emulsion containing fish oil is approved by the Food and Drug Administration as parenteral nutrition for critically ill patients and may prevent this decrease in serum cholesterol levels by providing substrate for cholesterol synthesis and may favourably modulate inflammation. This LIPid Intensive Drug therapy for Sepsis Pilot clinical trial is the first study to attempt to stabilise early cholesterol levels using lipid emulsion as a treatment modality for

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sepsis. **METHODS AND ANALYSIS:** This is a two-centre, phase I/II clinical trial. Phase I is a non-randomised dose-escalation study using a Bayesian optimal interval design in which up to 16 patients will be enrolled to evaluate the safest and most efficacious dose for stabilising cholesterol levels. Based on phase I results, the two best doses will be used to randomise 48 patients to either lipid injectable emulsion or active control (no treatment). Twenty-four patients will be randomised to one of two doses of the study drug, while 24 control group patients will receive no drug and will be followed during their hospitalisation. The control group will receive all standard treatments mandated by the institutional sepsis alert protocol. The phase II study will employ a permuted blocked randomisation technique, and the primary endpoint will be change in serum total cholesterol level (48 hours - enrolment). Secondary endpoints include change in cholesterol level from enrolment to 7 days, change in Sequential Organ Failure Assessment score over the first 48 hours and 7 days, in-hospital and 28-day mortality, lipid oxidation status, inflammatory biomarkers, and high-density lipoprotein function. **ETHICS AND DISSEMINATION:** Investigators are trained and follow good clinical practices, and each phase of the study was reviewed and approved by the institutional review boards of each institution. Results of each phase will be disseminated through presentations at national meetings and publication in peer-reviewed journals. If promising, data from the pilot study will be used for a larger, multicentre, phase II clinical trial. **TRIAL REGISTRATION NUMBER:** NCT03405870.

[8] *Nguyen LT, Pham VN, Chau PMN et al. Association between carotid intima-media thickness and bone mineral density: a cross-sectional study in Vietnamese men and women aged 50 years and older. BMJ open* 2019; 9:e028603.

PM: <http://www.ncbi.nlm.nih.gov/pubmed/?term=31530594>

ABSTRACT

OBJECTIVES: The association between osteoporosis and atherosclerosis remains controversial. We sought to define the relationship between carotid intima-media thickness and bone mineral density (BMD) in individuals of Vietnamese background. **DESIGN AND SETTING:** Cross-sectional study in Ho Chi Minh City, Vietnam. **PARTICIPANTS:** The study involved 1460 individuals (559 men) aged 50 years and older (average age 59 years) who were randomly recruited from the community. **OUTCOME MEASURES:** BMD at the femoral neck and lumbar spine was measured by dual-energy X-ray absorptiometry (Hologic, Waltham, Massachusetts, USA). Carotid intima-media thickness (cIMT) was measured using a Philips Ultrasonography (HD7XE). The presence of atherosclerotic plaque was ascertained for each individual. The association between cIMT and BMD was analysed by a multiple linear regression model. **RESULTS:** In unadjusted analysis, cIMT was positively associated with femoral neck BMD in men ($p=0.005$), but not in women ($p=0.242$). After adjusting for age, smoking, diabetes and hypertension, the association remained statistically significant in men (partial $R(2)=0.005$; $p=0.015$) but not in women (partial $R(2)=0.008$; $p=0.369$). When the analysis was limited to individuals aged 60 years and older, the association between cIMT and BMD was no longer statistically significant. There was no statistically significant association between cIMT and lumbar spine BMD in either men or women. **CONCLUSIONS:** In Vietnamese individuals aged 50 years and older, there is a clinically non-significant but statistically significant association between carotid intima-media thickness and BMD in men, not in women.

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[9] *Lazarte J, Hegele RA. Dyslipidemia Management in Adults With Diabetes. Canadian journal of diabetes* 2019.

PM: <http://www.ncbi.nlm.nih.gov/pubmed/?term=31521544>

ABSTRACT

Lipid abnormalities beyond elevated low-density lipoprotein (LDL) cholesterol contribute to increased risk of atherosclerotic cardiovascular disease (ASCVD) in type 2 diabetes. We searched for English language randomized controlled trials of lipid-lowering therapies primarily since 2012 that included patients with diabetes. Diet and lifestyle advice are always a starting point for ASCVD prevention in diabetes. After almost 30 years of widespread clinical use in diabetes, statin treatment to reduce LDL cholesterol remains the cornerstone of drug therapy to prevent ASCVD. Ezetimibe appears to be particularly beneficial for high-risk statin-treated patients with diabetes. Similarly, currently available proprotein convertase subtilisin kexin type 9 inhibitors-alirocumab and evolocumab-both reduce ASCVD risk in statin-treated patients with diabetes. High-dose icosapent ethyl is another worthwhile add-on treatment, especially in statin-treated patients with diabetes in whom triglyceride levels remain elevated. Fibrates might reduce ASCVD risk in patients with diabetes with high triglyceride and low high-density lipoprotein cholesterol; however, fibrates are more strongly recommended for prophylaxis of pancreatitis in patients with severe hypertriglyceridemia and may also slow progression of diabetic retinopathy. Several existing and newer drug treatments reduce ASCVD risk through LDL cholesterol and/or triglyceride reduction in patients with diabetes. Novel approaches using antisense oligonucleotides and monoclonal antibodies may provide potential future therapies for diabetic dyslipidemia.

[10] *Beita AKV, Whayne TF, Jr. The Superior Mesenteric Artery: from Syndrome in the Young to Vascular Atherosclerosis in the Old. Cardiovascular & hematological agents in medicinal chemistry* 2019.

PM: <http://www.ncbi.nlm.nih.gov/pubmed/?term=31538906>

ABSTRACT

This review is directed at increasing awareness of two diverse rare upper gastrointestinal problems that occur at opposite ends of the age spectrum and are difficult to diagnose and treat. The superior mesenteric artery syndrome (SMAS) likely involves a young patient, especially female, and is especially associated with rapid weight loss, resulting in relative strangulation of the duodenum by a narrowing of the angle between the superior mesenteric artery (SMA) and the aorta. On the other hand, atherosclerosis of the SMA is associated most likely with postprandial upper intestinal ischemia and abdominal pain occurs in the elderly at high risk for cardiovascular (CV) disease. Medical management of the SMAS in the young involves good alimentation and weight gain to overall increase the intestinal fat pad. Medical management of SMA atherosclerotic ischemia in the elderly is directed at marked lipid lowering with atherosclerotic plaque stabilization or even regression. If needed, surgery for SMAS can be attempted laparoscopically with duodenojejunostomy the most popular procedure but there are also more conservative possibilities that avoid division of the duodenum. Also, sometimes direct vision is needed to successfully operate on SMAS. If surgery is needed for SMA atherosclerotic ischemia, it is usually attempted endoscopically with angioplasty and stent

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placement. Most important, in the case of these two rare clinical entities, is that the clinician have a suspicion of their presence when indicated so that the young or old patient can be spared unnecessary suffering and return to good health in a timely fashion.

[11] *Berry JD, Mehta A, Lin K et al. Association of Long-Term Risk Factor Levels With Carotid Atherosclerosis: The Chicago Healthy Aging Magnetic Resonance Imaging Plaque Study (CHAMPS). Circulation. Cardiovascular imaging 2019; 12:e009226.*

PM: <http://www.ncbi.nlm.nih.gov/pubmed/?term=31522549>

ABSTRACT

BACKGROUND: Absence of cardiovascular risk factors (RF) in young adulthood is associated with a lower risk for cardiovascular disease. However, it is unclear if low RF burden in young adulthood decreases the quantitative burden and qualitative features of atherosclerosis. **METHODS:** Multi-contrast carotid magnetic resonance imaging was performed on 440 Chicago Healthy Aging Study participants in 2009 to 2011, whose RF (total cholesterol, blood pressure, diabetes mellitus, and smoking) were measured in 1967 to 1973. Participants were divided into 4 groups: low-risk (with total cholesterol <200 mg/dL and no treatment, blood pressure <120/80 mm Hg and no treatment, no smoking, and no diabetes mellitus), 0 high RF but some RF unfavorable (≥ 1 RF above low-risk threshold but below high-risk threshold), 1 high RF (total cholesterol ≥ 240 mg/dL or treated, blood pressure $\geq 140/90$ or treated, diabetes mellitus, or smoking), and 2 or more high RF. Association of baseline RF status with carotid atherosclerosis (overall mean carotid wall thickness and lipid-rich necrotic core) at follow-up was assessed. **RESULTS:** Among 424 participants with evaluable carotid magnetic resonance images, the mean age was 32 years at baseline and 73 years at follow-up; 67% were male, 86% white, and 36% were low-risk at baseline. Two or more high RF status was associated with higher carotid wall thickness (0.99 \pm 0.11 mm) and lipid-rich necrotic core prevalence (30%), as compared with low-risk group (0.94 \pm 0.09 mm and 17%, respectively). Each increment in baseline RF status was associated with higher carotid wall thickness (beta-coefficient, 0.015; 95% CI, 0.004-0.026) and with higher lipid-rich necrotic core prevalence at older age (odds ratio, 1.26; 95% CI, 1.00-1.58) in models adjusted for baseline RF and demographics. **CONCLUSIONS:** RF status in young adulthood is associated with the burden and quality of carotid atherosclerosis in older age suggesting that the decades-long protective effect of low-risk status might be mediated through a lower burden of quantitative and qualitative features of atherosclerotic plaque.

[12] *Marston NA, Giugliano RP, Im K et al. Association Between Triglyceride Lowering and Reduction of Cardiovascular Risk Across Multiple Lipid-Lowering Therapeutic Classes: A Systematic Review and Meta-Regression Analysis of Randomized Controlled Trials. Circulation 2019.*

PM: <http://www.ncbi.nlm.nih.gov/pubmed/?term=31530008>

ABSTRACT

Background: Randomized trials of therapies that primarily lowered triglycerides have not consistently shown reductions in cardiovascular events. **Methods:** We performed a systematic review and trial-level meta-regression analysis of 3 classes of lipid-lowering therapies that reduce triglycerides to a greater extent than they do LDL-C: fibrates, niacin, and marine-derived

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omega-3 fatty acids. Key inclusion criteria were a randomized controlled trial that reported on major vascular events. We also incorporated data from a previous meta-regression of 25 statin trials. The main outcome measure was the risk ratio (RR) for major vascular events associated with absolute reductions in lipid parameters. Results: A total of 197,270 participants from 24 trials of non-statin therapy with 25,218 major vascular events and 177,088 participants from 25 trials of statin therapy with 20,962 major vascular events were included, for a total of 374,358 patients and 46,180 major CV events. Starting with non-HDL-C, a surrogate for VLDL and LDL, the RR (95%CI) per 1 mmol/L reduction in non-HDL-C was 0.79 (0.76-0.82, $P < 0.0001$) (0.78 per 40 mg/dl). In a multivariable meta-regression model that included terms for both LDL-C and triglyceride (surrogates for LDL and VLDL), the RR (95%CI) was 0.80 (0.76-0.85, $P < 0.0001$) per 1 mmol/L (0.79 per 40 mg/dl) reduction in LDL-C and 0.84 (0.75-0.94, $P = 0.0026$) per 1 mmol/L (0.92 per 40 mg/dl) reduction in triglycerides. REDUCE-IT was a significant outlier and strongly influential trial in the meta-regression. When removed, the RRs became 0.79 (0.76-0.83, $P < 0.0001$) per 1 mmol/L (0.78 per 40 mg/dl) reduction in LDL-C and 0.91 (0.81-1.006, $P = 0.06$) per 1 mmol/L (0.96 per 40 mg/dL) reduction in triglycerides. In regard to omega-3 dose, each 1 gram/day of EPA administered was associated with a 7% relative risk reduction in major vascular events (RR 0.93 [0.91-0.95], $P < 0.0001$) whereas there was no significant reduction in major vascular events with DHA (RR 0.96 [0.89-1.03]). Conclusions: In randomized controlled trials, triglyceride lowering is associated with lower risk of major vascular events, even after adjusting for LDL-C lowering, although the effect is attenuated when REDUCE-IT is excluded. Furthermore, the benefits of marine-derived omega-3 fatty acids, particularly high-dose EPA, appear to exceed their lipid-lowering effects.

[13] *Khoury S, Soleman M, Margolis G et al. Incidence, characteristics and outcomes in very young patients with ST segment elevation myocardial infarction. Coronary artery disease 2019.*

PM: <http://www.ncbi.nlm.nih.gov/pubmed/?term=31524668>

ABSTRACT

OBJECTIVE: ST-segment elevation acute myocardial infarction (STEMI) in very young adults is uncommon. Many studies have focused on the cutoff of 45-50 years old to define young patients with STEMI leaving limited data on the group of very young patients aged less than 35 years old. We investigated the incidence of STEMI in different subgroups of young patients and focused on the characteristics, possible pathogenesis and outcomes in very young patients aged less than 35 years old. **METHODS:** We retrospectively studied 792 STEMI patients aged less than 55 years who underwent successful primary PCI. We categorized patients as very young if they were or less 35 years old and as young if they were between 36 and 55 years old. Baseline characteristics, angiographic findings, as well as short- and long-term outcomes were compared between the two groups. **RESULTS:** There were 46 (6%) very young patients (age \leq 35 years) and 748 (94%) young patients (36 < age \leq 55 years). Very young patients had fewer atherosclerotic risk factors than young patients, but there was no difference in short- or long-term outcomes. Overt hypercoagulable state was evident serologically (antiphospholipid antibodies) in 2/7 (29%) of screened patients and clinically (left ventricular thrombus or acute coronary thrombosis without an atherosclerotic plaque) in 6/46 patients (13%). **CONCLUSION:** Very young patients with STEMI constitute a distinct subset of young patients with fewer

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atherosclerotic risk factors yet comparable outcomes. More efforts should be made screening for serologic and clinical evidence of hypercoagulability in this group of patients.

[14] *Tinahones FJ, Laufs U, Cariou B et al. Alirocumab efficacy and safety by body mass index: A pooled analysis from 10 Phase 3 ODYSSEY trials. Diabetes Metab* 2019;101120.

PM: <http://www.ncbi.nlm.nih.gov/pubmed/?term=31533069>

ABSTRACT

AIMS: Increased body mass index (BMI) contributes to cardiovascular risk and may influence efficacy of therapeutic antibodies. We investigated the effect of baseline BMI on efficacy and safety of alirocumab, a PCSK9 monoclonal antibody. METHODS: In a post-hoc analysis, data were pooled from 10 Phase 3 trials (n=4975) of alirocumab vs. placebo/ezetimibe controls. Alirocumab dose was 150mg every 2 weeks in two trials, and 75mg with possible increase to 150mg at 12 weeks (based on Week 8 low-density lipoprotein cholesterol [LDL-C]) in eight trials. Efficacy/safety data were assessed in baseline BMI subgroups of ≤ 25 , >25 to 30, >30 to 35, and >35 kg/m². RESULTS: Baseline LDL-C levels were lower among patients in the higher BMI subgroups. Significant LDL-C reductions from baseline were observed at Weeks 12 and 24 for alirocumab vs. controls, of similar magnitude regardless of baseline BMI (interaction P-value=0.7119). LDL-C <1.81 mmol/L (<70 mg/dL) was achieved at Week 24 by 69.8-76.4% of alirocumab-treated patients and 9.7-18.4% of control-treated patients, with no pattern by BMI. A greater proportion of patients in higher vs. lower BMI subgroups required alirocumab dose increase (P=0.0343); proportions were 22.5%, 24.9%, 31.7%, and 27.2% of patients across BMI subgroups of ≤ 25 , >25 to 30, >30 to 35, and >35 kg/m², respectively. Adverse event frequencies were similar regardless of BMI; injection-site reaction frequency was higher with alirocumab (5.1-8.2% across BMI categories) vs. controls (3.6-4.8%). CONCLUSIONS: Alirocumab provided consistent LDL-C reductions, with similar safety findings across BMI subgroups.

[15] *Yang XQ, Mao YQ, Wang DX. More consideration of beta-cell function and PCSK9/LDLR axis. European heart journal* 2019.

PM: <http://www.ncbi.nlm.nih.gov/pubmed/?term=31539051>

ABSTRACT

[16] *Danchin N, Simon T. High-intensity lipid lowering regimens in patients with stable coronary artery disease: the intriguing question of all-cause mortality. European heart journal. Cardiovascular pharmacotherapy* 2019.

PM: <http://www.ncbi.nlm.nih.gov/pubmed/?term=31539045>

ABSTRACT

[17] *Jia Q, Cao H, Shen D et al. Quercetin protects against atherosclerosis by regulating the expression of PCSK9, CD36, PPARgamma, LXRA and ABCA1. International journal of molecular medicine* 2019; 44:893-902.

PM: <http://www.ncbi.nlm.nih.gov/pubmed/?term=31524223>

ABSTRACT

The aim of this study was to investigate the mechanisms through which quercetin protects against atherosclerosis (AS) in apoE^{-/-} mice by regulating the expression of proprotein

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convertase subtilisin/kexin type 9 (PCSK9), cluster of differentiation 36 (CD36), peroxisome proliferator-activated receptor gamma (PPARgamma), liver X receptor alpha (LXRalpha) and ATP binding cassette transporter A1 (ABCA1). We established an animal model of highfat diet induced AS using apoE^{-/-} mice. H&E, Oil Red O and Masson's trichrome staining were performed on aortic sinus and liver tissue sections to evaluate the histopathology, lipid accumulation and collagen deposition, respectively. Filipin staining was performed to detect free cholesterol (FC) in the aortic sinus. ELISA was performed to measure the serum levels of lipids including total cholesterol (TC), triglyceride (TG), highdensity lipoproteincholesterol (HDL), lowdensity lipoproteincholesterol (LDL) and oxidized lowdensity lipoprotein (oxLDL), as well as the levels of inflammatory cytokines, including tumor necrosis factor (TNF)alpha, interleukin (IL)6 and IL10. Western blot analysis was performed to analyze the protein expression levels of PCSK9, CD36, PPARgamma, LXRalpha and ABCA1 in both the aorta and liver tissue. H&E staining revealed the presence of atherosclerotic plaques in the aortic sinus. Oil Red O staining revealed the existence of massive redstained lipids in the aortic sinus and Masson's trichrome staining revealed decreased collagen fibers and increased plaque instability. Filipin staining revealed that free cholesterol levels in the aorta sinus were increased. In addition, H&E staining suggested hepatocyte structural disorder in the model group, and Oil Red O staining revealed a cytoplasm filled with lipid droplets, which contained a large amount of redstained lipids. Masson's trichrome staining revealed that the liver tissue of the model group had fewer collagen fibers compared with that of the control group. Moreover, the mice in the model group had higher serum TC, LDL, oxLDL, TNFalpha and IL6 levels, and lower IL10 levels. The protein expression levels of PCSK9 and CD36 were increased, while those of PPARgamma, LXRalpha and ABCA1 were decreased in the aortas and livers of the model group mice. However, treatment with quercetin attenuated all these effects. On the whole, these results demonstrate that quercetin prevents the development of AS in apoE^{-/-} mice by regulating the expression of PCSK9, CD36, PPARgamma, LXRalpha and ABCA1.

[18] *Giri B, Belanger K, Seamon M et al. Niacin Ameliorates Neuro-Inflammation in Parkinson's Disease via GPR109A. International journal of molecular sciences* 2019; 20.

PM: <http://www.ncbi.nlm.nih.gov/pubmed/?term=31540057>

ABSTRACT

In this study, we used macrophage RAW264.7 cells to elucidate the molecular mechanism underlying the anti-inflammatory actions of niacin. Anti-inflammatory actions of niacin and a possible role of its receptor GPR109A have been studied previously. However, the precise molecular mechanism of niacin's action in reducing inflammation through GPR109A is unknown. Here we observed that niacin reduced the translocation of phosphorylated nuclear kappa B (p-NF-kappaB) induced by lipopolysaccharide (LPS) in the nucleus of RAW264.7 cells. The reduction in the nuclear translocation in turn decreased the expression of pro-inflammatory cytokines IL-1beta, IL-6 in RAW264.7 cells. We observed a decrease in the nuclear translocation of p-NF-kappaB and the expression of inflammatory cytokines after knockdown of GPR109A in RAW264.7 cells. Our results suggest that these molecular actions of niacin are mediated via its receptor GPR109A (also known as HCAR2) by controlling the translocation of p-NF-kappaB to the nucleus. Overall, our findings suggest that niacin treatment may have potential in reducing inflammation by targeting GPR109A.

[19] *Yaghchiyan M, Roshangar L, Farhangi MA et al. Histologic, Metabolic, and Inflammatory Changes in the Liver of High-fat Diet-induced Obese Rats before and after Vitamin D Administration. Iranian journal of allergy, asthma, and immunology* 2019; 18:402-411.

PM: <http://www.ncbi.nlm.nih.gov/pubmed/?term=31522448>

ABSTRACT

The current study aimed to investigate the effects of vitamin D administration on the markers of inflammation and metabolic damages in the liver of high-fat diet-induced obese rats. Forty male Wistar rats were divided into two groups of control receiving a normal diet (ND) and intervention receiving a high-fat diet (HFD). After 16 weeks, each group was divided into two groups including ND, ND + vitamin D, HFD, and HFD + vitamin D. Vitamin D was administered by oral gavage for five weeks at the dose of 500 IU/kg. Hepatic MCP-1, TGF-beta, and NF-kappaB levels, serum liver enzymes, and serum lipids, and histological and structural changes in the liver were determined. Vitamin D administration significantly reduced the monocyte chemoattractant protein (MCP)-1 concentrations in the HFD + vitamin D group compared with the HFD group and reduced liver Transforming growth factor beta (TGF-beta) levels in both vitamin D-treated groups ($p < 0.05$). Moreover, a significant reduction in the serum levels of aspartate amino transferase (AST) and alanine amino transferase (ALT) in vitamin D treated groups was identified ($p < 0.05$). A significant improvement in lipids and a pronounced improvement in the markers of liver histology damage including fat accumulation, aggregation of inflammatory cells, pre-apoptotic changes, hepatic sinusoidal dilatation, and necrotic pyknosis in the Kupffer cells were also identified. Our results demonstrated that vitamin D has potential effects in ameliorating the inflammatory, metabolic, and histologic changes in the liver of these animals.

[20] *Zartab S, Abbassian H, Nassiri Koopaei N, Hajimolaali M. Despite Affordability, Low Utilization of Lipid Lowering Drugs in Iran: Trend Analysis and Benchmarking 2005-2016. Iranian journal of pharmaceutical research : IJPR* 2019; 18:1117-1125.

PM: <http://www.ncbi.nlm.nih.gov/pubmed/?term=31531093>

ABSTRACT

Dyslipidemia is responsible for great mortality and morbidity each year. Little data are available on the availability and affordability of Dyslipidemia medications in low and middle incomes countries. In a retrospective time-series study, we examined the utilization pattern and affordability of lipid-lowering medications in Iran as a lower middle-income country. We initially calculated the defined daily dose for 1000 inhabitants (DID) in different years and compared the results with OECD member countries in the same year. We also used 90% Drug Utilization method to rank and compare lipid lowering drugs with the WHO Essential Medicines List (EML). We measured the affordability by the minimum daily wage for one-month course of treatment. The use of lipid-lowering medications increased from 6.31 to 45.98 DID between 2005 and 2016. The utilization share of the subgroup of statins was above 80% of total utilization. Compared to OECD countries, Iran utilized 40% of the average utilization in 2015. In 2015, Atorvastatin was on 90% of DU medications. At the beginning of the study, only Lovastatin and Nicotinic acid were affordable in 2005, but at the end of the study, all lipid-lowering medications were affordable. The utilization of lipid-lowering medications, despite being

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affordable, was low. One of its possible reasons is the lack of proper management of patients with Dyslipidemia and low adherence of patients. Another possible cause is the high percentage of undiagnosed patients in the community. Therefore, comprehensive planning and policy-making should be taken to increase utilization and eliminate the related obstacles.

[21] *Naeimi Eshkaleti M, Kordbacheh P, Hashemi SJ et al. In Vitro Activity of Amphotericin B in Combination with Statins against Clinical and Environmental Rhizopus oryzae Strains. Iranian journal of public health* 2019; 48:943-948.

PM: <http://www.ncbi.nlm.nih.gov/pubmed/?term=31523652>

ABSTRACT

Background: Mucormycosis is an acute and invasive fungal infection with a high mortality rate. Mucorales are less sensitive than other types of fungi to most antifungal agents. Amphotericin B (AMB) is one treatment option for this infection, but in recent studies, the antifungal activity of statins against Mucorales was shown. Therefore, therapy that combines AMB with these agents may have better effects in management of patients with mucormycosis. We evaluated the in vitro activity of AMB alone and in combination with statins, against Mucorales. Methods: Susceptibility profiles of AMB alone and in combination with two statins, atorvastatin (ATO) and lovastatin (LOV) determined against clinical (n: 15) and environmental (n: 5) *Rhizopus oryzae* isolates, obtained between Jan 2009 and Oct 2016 from patients with uncontrolled diabetes mellitus and cancer referred to the Department of Parasitology and Medical Mycology of Tehran University of Medical Sciences, Tehran, Iran. It was performed by microdilution method, based on the Clinical and Laboratory Standard Institute (CLSI) M38-A2 guideline. Results: All clinical and environmental isolates were susceptible to AMB (MIC \leq 1 mug/mL). The results of the interactions between AMB and the two statins were positive. The AMB-ATO (GM: 0.13 mug/MI) combination produced greater activity than the AMB-LOV (GM: 0.26 mug/mL) combination. AMB, in combination with ATO and LOV, reacts positively against clinical and environmental *R. oryzae* isolates. Conclusion: This combination strategy may lead to more effective treatment of mucormycosis and fewer side effects using low dose of AMB.

[22] *Ahmadi A, Argulian E, Leipsic J et al. From Subclinical Atherosclerosis to Plaque Progression and Acute Coronary Events: JACC State-of-the-Art Review. Journal of the American College of Cardiology* 2019; 74:1608-1617.

PM: <http://www.ncbi.nlm.nih.gov/pubmed/?term=31537271>

ABSTRACT

It has been believed that most acute coronary events result from the rupture of mildly stenotic plaques, based on studies in which angiographic information was available from many months to years before the event. However, serial studies in which angiographic data were available from the past as also within 1 to 3 months of myocardial infarction have clarified that nonobstructive lesions progressively enlarged relatively rapidly before the acute event occurred. Noninvasive computed tomography angiography imaging data have confirmed that lesions that did not progress voluminously over time rarely led to events, regardless of the extent of luminal stenosis or baseline high-risk plaque morphology. Therefore, plaque progression could be proposed as a necessary step between early, uncomplicated atherosclerosis and plaque rupture. On the other hand, it has been convincingly demonstrated

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that intensive lipid-lowering therapy (to a low-density lipoprotein cholesterol level of <70 mg/dl) halts plaque progression. Given the current ability to noninvasively detect the presence of early atherosclerosis, the importance of plaque progression in the pathogenesis of myocardial infarction, and the efficacy of maximum lipid-lowering therapy, it has been suggested that plaque progression is a modifiable step in the evolution of atherosclerotic plaque. A personalized approach based on the detection of early atherosclerosis can trigger the necessary treatment to prevent plaque progression and hence plaque instability. Therefore, this approach can redefine the traditional paradigm of primary and secondary prevention based on population-derived risk estimates and can potentially improve long-term outcomes.

[23] *Libby P, Hansson GK. From Focal Lipid Storage to Systemic Inflammation: JACC Review Topic of the Week. Journal of the American College of Cardiology* 2019; 74:1594-1607.

PM: <http://www.ncbi.nlm.nih.gov/pubmed/?term=31537270>

ABSTRACT

Concepts of atherogenesis have evolved considerably with time. Early animal experiments showed that a cholesterol-rich diet could induce fatty lesion formation in arteries. The elucidation of lipoprotein metabolism ultimately led to demonstrating the clinical benefits of lipid lowering. The view of atheromata as bland accumulations of smooth muscle cells that elaborated an extracellular matrix that could entrap lipids then expanded to embrace inflammation as providing pathways that could link risk factors to atherogenesis. The characterization of leukocyte adhesion molecules and their control by proinflammatory cytokines, the ability of chemokines to recruit leukocytes, and the identification of inflammatory cell subtypes in lesions spurred the unraveling of innate and adaptive immune pathways that contribute to atherosclerosis and its thrombotic complications. Such pathophysiologic insights have led to the identification of biomarkers that can define categories of risk and direct therapies and to the development of new treatments.

[24] *Palacios OM, Maki KC, Xiao D et al. Effects of Consuming Almonds on Insulin Sensitivity and Other Cardiometabolic Health Markers in Adults With Prediabetes. Journal of the American College of Nutrition* 2019:1-10.

PM: <http://www.ncbi.nlm.nih.gov/pubmed/?term=31525129>

ABSTRACT

Objective: This study was designed to assess the effects of replacing high-carbohydrate (CHO) foods with raw almonds on insulin sensitivity and cardiometabolic health markers in overweight or obese adults with prediabetes. Method: This randomized crossover study consisted of two 6-week dietary intervention periods, separated by a \geq 4-week washout. Subjects incorporated 1.5 oz of raw almonds twice daily or isocaloric CHO-based foods into their diets, with instructions to maintain body weight. Dietary intakes as well as insulin sensitivity, CHO metabolism indices, lipoprotein lipids and particles, and inflammatory markers were assessed. Results: Thirty-three subjects (17 male, 16 female), mean age 48.3 \pm 2.2 years and body mass index 30.5 \pm 0.7 kg/m², provided evaluable data. Compared to CHO, almonds resulted in significantly ($p < 0.01$) higher intakes of protein, fat (unsaturated fatty acids), fiber, and magnesium and significantly ($p < 0.001$) lower intakes of CHO and sugars. No differences were observed between diet conditions for changes from baseline in the insulin sensitivity index from

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a short intravenous glucose tolerance test or other indices of glucose homeostasis. No significant differences were observed in biomarkers of cardiovascular risk except that the CHO intervention led to a shift toward a higher concentration of cholesterol in small, dense low-density lipoprotein subfraction 3+4 (LDL3 + 4) particles ($p = 0.024$ vs almonds). Conclusions: Intake of 3.0 oz/d raw almonds, vs energy-matched CHO foods, improved the dietary nutrient profile, but did not significantly affect insulin sensitivity and most markers of cardiometabolic health in overweight and obese men and women with prediabetes.

[25] *Cho Y, Lee H, Park HK et al. Differential Diabetogenic Effect of Pitavastatin and Rosuvastatin, in vitro and in vivo. Journal of atherosclerosis and thrombosis* 2019.

PM: <http://www.ncbi.nlm.nih.gov/pubmed/?term=31527323>

ABSTRACT

AIM: Most statins increase the risk of new-onset diabetes. Unlike other statins, pitavastatin is reported to exert neutral effects on serum glucose level, but the precise mechanism is unknown. METHODS: Eight-week-old male C57BL/6J mice ($n=26$) were fed high-fat diet (HFD, 45% fat) with 0.01% placebo, rosuvastatin, or pitavastatin for 12 weeks. Cultured HepG2, C2C12, and 3T3-L1 cells and visceral adipocytes from HFD-fed mice were treated with vehicle or 10 microM statins for 24 h. The effects of pitavastatin and rosuvastatin on intracellular insulin signaling and glucose transporter 4 (GLUT4) translocation were evaluated. RESULTS: After 12 weeks, the fasting blood glucose level was significantly lower in pitavastatin-treated group than in rosuvastatin-treated group (115.2 ± 7.0 versus 137.4 ± 22.3 mg/dL, $p=0.024$). Insulin tolerance significantly improved in pitavastatin-treated group as compared with rosuvastatin-treated group, and no significant difference was observed in glucose tolerance. Although plasma adiponectin and insulin levels were not different between the two statin treatment groups, the insulin-induced protein kinase B phosphorylation was weakly attenuated in pitavastatin-treated adipocytes than in rosuvastatin-treated adipocytes. Furthermore, minor attenuation in insulin-induced GLUT4 translocation to the plasma membrane of adipocytes was observed in pitavastatin-treated group. CONCLUSION: Pitavastatin showed lower diabetogenic effects than rosuvastatin in mice that may be mediated by minor attenuations in insulin signaling in adipocytes.

[26] *Malik M, Zaffar S, Fatimah M et al. Effect Of Three Pakistani Date-Seed Varieties On Lipid Profile Of Diet Induced Hyperlipidemic Rabbits. Journal of Ayub Medical College, Abbottabad : JAMC* 2019; 31:326-330.

PM: <http://www.ncbi.nlm.nih.gov/pubmed/?term=31535499>

ABSTRACT

BACKGROUND: Hyperlipidemia is one of the major risk factors of cardiovascular diseases. In addition to current therapeutic strategies, a lot of work is being done on nutraceutical management of this condition. This study was designed to assess the effect of date seed powder on lipid profile of diet induced hyperlipidemic rabbits. METHODS: Thirty male rabbits were divided into five groups, having six animals in each. One group was given normal rabbit chow throughout the study period of eight weeks. The remaining four groups were fed high fat diet (4% coconut oil and 1% cholesterol powder) for first four weeks in order to induce hyperlipidemia. After first four weeks, 2% date seed powder of three Pakistani varieties namely

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Dhakki, Khudrawi and Desi was added to the diet of three experimental hyperlipidemic groups for the next four weeks. Body weight and blood samples were taken at zero, 4th and 8th week of study. Serum was analyzed for total cholesterol, LDL-cholesterol, HDL-cholesterol and serum triglycerides. LDL/HDL ratio and AIP were calculated. RESULTS: It was observed that date seed powder of the three varieties significantly decreased total cholesterol, serum triglycerides and AIP. There was no significant change in body weight, HDL-cholesterol, and LDL/HDL ratio. LDL cholesterol was decreased significantly only by Khudrawi date seed powder. CONCLUSIONS: It was concluded that date seed powder has marked antihyperlipidemic properties. However, the difference in appearance, taste and price of different dates does not affect their lipid lowering capacity.

[27] *Peluso MEM, Munnia A, Tarocchi M et al. Exocyclic DNA Adducts in a Murine Model of Non-alcoholic Steatohepatitis. Journal of carcinogenesis & mutagenesis* 2013; 2013.

PM: <http://www.ncbi.nlm.nih.gov/pubmed/?term=31528500>

ABSTRACT

Introduction: Non-alcoholic fatty liver disease is the most common hepatic disorder in Western countries. The transition from abnormal accumulation of lipids toward non-alcoholic steatohepatitis (NASH) represents a key step in the development of chronic liver pathologies. Oxidative stress and lipid peroxidation have often been proposed as mechanisms in the progression to steatohepatitis. Methods: We have examined the hepatic levels of exocyclic DNA adducts, indicated from 3-(2-deoxy-beta-D-erythro-pentafuranosyl)pyrimido[1,2-alpha]purin-10(3H)-one deoxyguanosine (M1dG) adduct, a biomarker of oxidative stress and lipid peroxidation, in a murine model of NASH using the (32)P-DNA postlabeling assay. Results: Our findings show that C57BL/6 mice fed with high-fat and cholesterol diet developed signs associated with NASH after eight weeks, whereas there was no evidence of steatosis in control mice. The score for steatohepatitis ranged from grade 2 to 3 for steatosis, inflammation, and fibrosis, showing that the experimental diet was able to induce pathologic alterations of the parenchyma in eight weeks. Higher levels of M1dG adducts were detected in the livers of C57BL/6 mice which developed experimental NASH after eight weeks of high-fat and cholesterol feed, 5.6 M 1dG +/- 0.4 (SE) per 10(6) total nucleotides, as compared to control mice, 1.6 M1dG +/- 0.4 (SE). The statistical analysis showed that the increment of oxidatively damaged DNA in mice with NASH raised on high-fat and cholesterol diet was statistically significant as compared to control mice, P=0.006. Conclusions: Our report suggests a link between NASH and M1dG in experimental animals fed with a diet rich in saturated fats and cholesterol. High-fat and cholesterol may act together in inducing a broader spectrum of oxidatively damaged DNA, including exocyclic DNA adducts, that may contribute to the decline of hepatocyte functions, from disturbance of critical pathways, such as transcription and replication, triggering transient or permanent cell-cycle arrest and cell-death, up to chromosomal instability.

[28] *Hima L, Pratap UP, Karrunanithi S et al. Virgin coconut oil supplementation in diet modulates immunity mediated through survival signaling pathways in rats. Journal of complementary & integrative medicine* 2019.

PM: <http://www.ncbi.nlm.nih.gov/pubmed/?term=31536034>

ABSTRACT

Background Virgin coconut oil (VCO), a cold processed form of coconut oil, is traditionally consumed in Asian countries owing to its nutritional and medicinal properties. The aim of this study was to investigate whether the health benefits of VCO involve alterations in immune responses that are regulated by intracellular signaling molecules in the spleens of rats. Methods Young male Wistar rats were fed with three doses of VCO in diet for 30 days. At the end of the treatment period, spleens were isolated and in vitro effects on immune responses (Concanavalin A [Con A]-induced lymphoproliferation and cytokine production), and direct effects of VCO treatment on intracellular signaling molecules and antioxidant status were examined. Serum was collected to measure glucose, lipid levels, and leptin. Results VCO supplementation in diet enhanced Con A-induced splenocyte proliferation and Th1 cytokine production while it suppressed the proinflammatory cytokine production. VCO increased the expression of mechanistic target of rapamycin (p-mTOR), sirtuin1 (SIRT1), liver kinase B1 (p-LKB1) p-ERK, and p-CREB in spleen. Similarly, VCO increased the activities of antioxidant enzymes while it suppressed lipid peroxidation in the spleen. VCO diet had hypolipidemic effects on the rats: an increase in high density lipoprotein cholesterol (HDL-C) levels while lowering triacylglycerol (TAG) levels. Conclusion The health benefits of VCO may be mediated through enhanced Th1 immunity through the upregulation of survival signaling pathways and inhibition of free radical generation in the spleen besides its capacity to induce hypolipidemia.

[29] *Le R, Abbas M, McIntyre AD, Hegele RA. Severe Combined Dyslipidemia With a Complex Genetic Basis. Journal of investigative medicine high impact case reports* 2019; 7:2324709619877050.

PM: <http://www.ncbi.nlm.nih.gov/pubmed/?term=31538826>

ABSTRACT

Background. Familial dysbetalipoproteinemia (also known as type 3 hyperlipoproteinemia) is typically associated with homozygosity for the apolipoprotein E2 isoform, but also sometimes with dominant rare missense variants in the APOE gene. Patients present with roughly equimolar elevations of cholesterol and triglyceride (TG) due to pathologic accumulation of remnant lipoprotein particles. Clinical features include tuberous xanthomas, palmar xanthomas, and premature vascular disease. Case. A 48-year-old male presented with severe combined dyslipidemia: total cholesterol and TG were 11.5 and 21.4 mmol/L, respectively. He had dyslipidemia since his early 20s, with tuberous xanthomas on his elbows and knees. His body mass index was 42 kg/m². He also had treated hypertension, mild renal impairment, and a history of gout. He had no history of cardiovascular disease, peripheral arterial disease, or pancreatitis. Multiple medications had been advised including rosuvastatin, ezetimibe, fenofibrate, and alirocumab, but his lipid levels were never adequately controlled. Genetic Analysis. Targeted next-generation sequencing identified (1) the APOE E2/E2 homozygous genotype classically described with familial dysbetalipoproteinemia; (2) in addition, one APOE E2 allele contained the rare heterozygous missense variant p.G145D, previously termed apo E-Bethesda; (3) a rare heterozygous APOC2 nonsense variant p.Q92X; and (4) a high polygenic risk score for TG levels (16 out of 28 TG-raising alleles) at the 82nd percentile for age and sex. Conclusion. The multiple genetic "hits" on top of the classical APOE E2/E2 genotype likely explain the more severe dyslipidemia and refractory clinical phenotype.

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[30] Huang R, Zong X, Nadesan P et al. **Lowering circulating apolipoprotein E levels improves aged bone fracture healing.** *JCI insight* 2019; 4.

PM: <http://www.ncbi.nlm.nih.gov/pubmed/?term=31534056>

ABSTRACT

Age is a well-established risk factor for impaired bone fracture healing. Here, we identify a role for apolipoprotein E (ApoE) in age-associated impairment of bone fracture healing and osteoblast differentiation, and we investigate the mechanism by which ApoE alters these processes. We identified that, in both humans and mice, circulating ApoE levels increase with age. We assessed bone healing in WT and ApoE^{-/-} mice after performing tibial fracture surgery: bone deposition was higher within fracture calluses from ApoE^{-/-} mice. In vitro recombinant ApoE (rApoE) treatment of differentiating osteoblasts decreased cellular differentiation and matrix mineralization. Moreover, this rApoE treatment decreased osteoblast glycolytic activity while increasing lipid uptake and fatty acid oxidation. Using parabiosis models, we determined that circulating ApoE plays a strong inhibitory role in bone repair. Using an adeno-associated virus-based siRNA system, we decreased circulating ApoE levels in 24-month-old mice and demonstrated that, as a result, fracture calluses from these aged mice displayed enhanced bone deposition and mechanical strength. Our results demonstrate that circulating ApoE as an aging factor inhibits bone fracture healing by altering osteoblast metabolism, thereby identifying ApoE as a new therapeutic target for improving bone repair in the elderly.

[31] Munoz D, Uzoije P, Reynolds C et al. **Polypill for Cardiovascular Disease Prevention in an Underserved Population.** *The New England journal of medicine* 2019; 381:1114-1123.

PM: <http://www.ncbi.nlm.nih.gov/pubmed/?term=31532959>

ABSTRACT

BACKGROUND: Persons with low socioeconomic status and nonwhite persons in the United States have high rates of cardiovascular disease. The use of combination pills (also called "polypills") containing low doses of medications with proven benefits for the prevention of cardiovascular disease may be beneficial in such persons. However, few data are available regarding the use of polypill therapy in underserved communities in the United States, in which adherence to guideline-based care is generally low. **METHODS:** We conducted a randomized, controlled trial involving adults without cardiovascular disease. Participants were assigned to the polypill group or the usual-care group at a federally qualified community health center in Alabama. Components of the polypill were atorvastatin (at a dose of 10 mg), amlodipine (2.5 mg), losartan (25 mg), and hydrochlorothiazide (12.5 mg). The two primary outcomes were the changes from baseline in systolic blood pressure and low-density lipoprotein (LDL) cholesterol level at 12 months. **RESULTS:** The trial enrolled 303 adults, of whom 96% were black. Three quarters of the participants had an annual income below \$15,000. The mean estimated 10-year cardiovascular risk was 12.7%, the baseline blood pressure was 140/83 mm Hg, and the baseline LDL cholesterol level was 113 mg per deciliter. The monthly cost of the polypill was \$26. At 12 months, adherence to the polypill regimen, as assessed on the basis of pill counts, was 86%. The mean systolic blood pressure decreased by 9 mm Hg in the polypill group, as compared with 2 mm Hg in the usual-care group (difference, -7 mm Hg; 95% confidence interval [CI], -12 to -2; P = 0.003). The mean LDL cholesterol level decreased by 15 mg per

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deciliter in the polypill group, as compared with 4 mg per deciliter in the usual-care group (difference, -11 mg per deciliter; 95% CI, -18 to -5; $P < 0.001$). CONCLUSIONS: A polypill-based strategy led to greater reductions in systolic blood pressure and LDL cholesterol level than were observed with usual care in a socioeconomically vulnerable minority population. (Funded by the American Heart Association Strategically Focused Prevention Research Network and the National Institutes of Health; ClinicalTrials.gov number, NCT02278471.).

[32] *Nandi S, Kaur A, Bansal AK. Dual Drug Nanocrystals loaded Microparticles for Fixed Dose Combination of Simvastatin and Ezetimibe. Pharmaceutical development and technology 2019;1-40.*

PM: <http://www.ncbi.nlm.nih.gov/pubmed/?term=31524550>

ABSTRACT

Dual drug nanocrystals loaded Nano Embedded Microparticles (DNEM) were prepared for fixed dose combination of Simvastatin (SIM) and Ezetimibe (EZE) using NanoCrySP technology. The purpose was to generate nanonized SIM and EZE dispersed in matrix of single crystallization inducing excipient and investigate their in-vitro performance. DNEM were prepared using Mannitol (MAN) as crystallization inducer (APIs/MAN =3:7 w/w) using spray drying. TPGS (0.1%w/v) was used as surfactant for stabilization of nanocrystals. Crystallinity of DNEM was confirmed by solid-state characterization using DSC and PXRD. Particle size analysis was carried out using Zetasizer(R) and Scherrer equation as primary techniques and SEM & TEM as orthogonal techniques. Size of both SIM and EZE in DNEM was close to 600 nm. In-vitro performance was assessed using USP apparatus II in 0.025% SLS containing Sodium Phosphate buffer. Powder dissolution of DNEM increased 1.45 times for SIM and 1.65 times for EZE as compared to their physical mixture in discriminatory medium. MAN did not plasticize SIM or EZE by virtue of its immiscibility with the two drugs. However, MAN helped in inducing crystallization via heterogeneous nucleation. The generated DNEM were stable in terms of assay, polymorphic form and dissolution for 90 days of accelerated storage at 40 degrees C/75% RH.

[33] *Torrecillas S, Terova G, Makol A et al. Dietary phytochemicals and galactomannan oligosaccharides in low fish meal and fish oil-based diets for European sea bass (*Dicentrarchus labrax*) juveniles: Effects on gut health and implications on in vivo gut bacterial translocation. PloS one 2019; 14:e0222063.*

PM: <http://www.ncbi.nlm.nih.gov/pubmed/?term=31532807>

ABSTRACT

European sea bass were fed four low FM/FO (10%/6%) diets containing galactomannan oligosaccharides (GMOS), a mixture of garlic oil and labiate plants oils (PHYTO), or a combination of both functional products (GMOSPHYTO) for 63 days before exposing the fish to an intestinal *Vibrio anguillarum* infection combined with crowding stress. In order to evaluate functional diets efficacy in terms of gut health maintenance, structural, cellular, and immune intestinal status were evaluated by optical and electron microscopy and gene expression analyses. A semi-automated software was adapted to determine variations in goblet cell area and mucosal mucus coverage during the challenge test. Feeding with functional diets did not affect growth performance; however, PHYTO and GMOS dietary inclusion reduced European

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sea bass susceptibility to *V. anguillarum* after 7 days of challenge testing. Rectum (post-ileorectal valve) showed longer ($p = 0.001$) folds than posterior gut (pre-ileorectal valve), whereas posterior gut had thicker submucosa ($p = 0.001$) and higher mucus coverage as a result of an increased cell density than rectum. Functional diets did not affect mucosal fold length or the grade of granulocytes and lymphocytes infiltration in either intestinal segment. However, the posterior gut fold area covered by goblet cells was smaller in fish fed GMOS ($F = 14.53$; $p = 0.001$) and PHYTO ($F = 5.52$; $p = 0.019$) than for the other diets. PHYTO ($F = 3.95$; $p = 0.049$) reduced posterior gut goblet cell size and increased rodlet cell density ($F = 3.604$; $p = 0.068$). Dietary GMOS reduced submucosal thickness ($F = 51.31$; $p = 0.001$) and increased rodlet cell density ($F = 3.604$; $p = 0.068$) in rectum. Structural TEM analyses revealed a normal intestinal morphological pattern, but the use of GMOS increased rectum microvilli length, whereas the use of PHYTO increased ($p \leq 0.10$) Ocln, N-Cad and Cad-17 posterior gut gene expression. After bacterial intestinal inoculation, posterior gut of fish fed PHYTO responded in a more controlled and belated way in terms of goblet cell size and mucus coverage in comparison to other treatments. For rectum, the pattern of response was similar for all dietary treatments, however fish fed GMOS maintained goblet cell size along the challenge test.

[34] *Brandao JAM, Meireles-Brandao LR, Coelho R, Rocha-Goncalves F. Lipoprotein(a) as a key target in combined therapeutic approaches for cardiovascular disease. Revista portuguesa de cardiologia : orgao oficial da Sociedade Portuguesa de Cardiologia = Portuguese journal of cardiology : an official journal of the Portuguese Society of Cardiology* 2019.

PM: <http://www.ncbi.nlm.nih.gov/pubmed/?term=31530423>

ABSTRACT

INTRODUCTION AND OBJECTIVE: Lipoprotein(a) [Lp(a)] is an independent cardiovascular risk factor but is closely associated with other similar risk factors that are manageable with appropriate treatment and guidance. We aimed to study the impact of using combined therapy for managing Lp(a) levels in patients at high cardiovascular risk but without major adverse cardiovascular events, in primary prevention. **METHODS:** We conducted a retrospective observational study in 516 patients randomly selected from a group of 1677 patients who attended cardiovascular risk and metabolism consultations between 1995 and 2015. The disorders observed and therapies used were classified into nosological and pharmacological groups, respectively. Cardiovascular risk was calculated based on the Framingham risk score, the European Society of Cardiology's SCORE and the American College of Cardiology's ASCVD Risk Estimator, and changes in patients' lifestyle were assessed. **RESULTS:** Significant differences ($p < 0.001$) were found in almost all metabolic variables, except fasting insulin and C-peptide. Lp(a) levels were also significantly reduced ($p < 0.001$). Carotid intima-media thickness improved, decreasing from 2.90 mm to 1.40 mm; however, there was no reduction in the number of cases of vascular stenosis. Of patients with hepatic steatosis (85.5%), 40.7% presented hepatomegaly, but liver function was only altered in a few patients (14.5%). Lipid-lowering therapy, especially statins, significantly decreased Lp(a), benefiting from synergy with other treatments. **CONCLUSIONS:** Lp(a) is a key overall indicator of vascular risk and should be considered a therapeutic target. Besides a healthy lifestyle, primary prevention should include combined drug therapies to address all cardiovascular risk factors and to delay the atherosclerotic process.

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