Literature update week 40 (2019)

[1] *Hamdi W, Maatallah K*. **Subclinical atherosclerosis: A hidden threat for patients with ankylosing spondylitis**. Anatol J Cardiol 2019; 22:192-193.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=31584441
ABSTRACT

[2] *Hatipsoylu E, Sengul I, Kaya T et al.* **Assessment of subclinical atherosclerotic cardiovascular disease in patients with ankylosing spondylitis**. Anatol J Cardiol 2019; 22:185-191.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=31584431
ABSTRACT
OBJECTIVE: The aim of the present study was to compare patients with ankylosing spondylitis (AS) with healthy controls with respect to subclinical atherosclerotic cardiovascular disease (CVD). METHODS: A total of 44 patients with AS with no history of CVD, diabetes mellitus, hypertension, chronic kidney disease, and lipid-lowering drug use were compared with 40 age- and sex-matched healthy controls with respect to carotid intima-media thickness (CIMT) and pulse wave velocity (PWV), which are surrogate markers of subclinical atherosclerosis. Correlation analysis was also performed to examine the association between surrogate markers and disease activity with inflammation [Ankylosing spondylitis disease activity score with C-reactive protein (ASDAS-CRP)]. RESULTS: In addition to age and sex, both groups were comparable with respect to cigarette smoking, body mass index, and high-density lipoprotein cholesterol (p=0.425, p=0.325, and p=0.103, respectively). The level of total cholesterol was significantly lower in patients with AS (p=0.002). Nonsteroidal anti-inflammatory drug and tumor necrosis factor alpha inhibitor use ratios in patients with AS were 79.5% and 65.9%, respectively. There was no significant difference between both groups regarding PWV and CIMT (p=0.788 and p=0.253, respectively). In patients with AS, there was a significant correlation between ASDAS-CRP and CIMT (r=0.315, p=0.038), but the correlation between ASDAS-CRP and PWV was not significant (r=-0.183, p=0.234). CONCLUSION: The results of the present study could not provide sufficient evidence whether disease activity with inflammation caused subclinical atherosclerotic CVD in patients with AS without overt CVD. The increased atherosclerotic CVD risk is most probably multifactorial in patients with AS, but the extent of the contribution of disease activity with inflammation to increased atherosclerosis is controversial.

[3] *Banerjee P, Chan KC, Tarabocchia M et al.* **Functional Analysis of LDLR (Low-Density Lipoprotein Receptor) Variants in Patient Lymphocytes to Assess the Effect of Evinacumab in Homozygous Familial Hypercholesterolemia Patients With a Spectrum of LDLR Activity**. Arteriosclerosis, thrombosis, and vascular biology 2019:Atvbaha119313051.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=31578082
ABSTRACT
OBJECTIVE: Homozygous familial hypercholesterolemia is a rare disease usually caused by LDLR (low-density lipoprotein receptor) mutations. Homozygous familial hypercholesterolemia is characterized by markedly elevated LDL-C (low-density lipoprotein cholesterol) levels and an extremely high risk of premature atherosclerotic cardiovascular disease. A phase 2, proof-of-concept study (NCT02265952) demonstrated that evinacumab, a fully human monoclonal antibody to ANGPTL3 (angiopoietin-like 3 protein), reduced LDL-C levels in 9 patients with

genotypically confirmed Homozygous familial hypercholesterolemia and was well tolerated. The aim of this study was to analyze the effects of evinacumab on LDLR activity in lymphocytes purified from patients in the proof-of-concept study. Approach and Results: LDLR activity was assessed in patient lymphocytes before and after treatment with evinacumab and versus lymphocytes carrying wild-type LDLR, and also in an LDLR-defective Chinese hamster ovary cell line (CHO-ldlA7) transfected with plasmids encoding the LDLR variants. Overall mean peak reduction in LDL-C with evinacumab was -58+/-18%, occurring between Week 4 and Week 12. Mutations identified in the 9 patients were shown to be pathogenic, with loss of LDLR activity versus wild type. Two of the LDLR variants, p.(Cys681*) and p.(Ala627Profs*38), were class 2 type mutations that are retained in the endoplasmic reticulum. Six variants were class 3 type mutations with impaired LDL-C binding activity: p.(Trp87Gly), occurring in 2 patients, p.(Gln254Pro), p.(Ser177Leu), p.(Gly335Val), and p.(Ser306Leu). Evinacumab had no effect on LDLR activity. CONCLUSIONS: These results suggest that evinacumab is effective for lowering LDL-C in patients with homozygous familial hypercholesterolemia, and the inhibition of ANGPTL3 in humans lowers LDL-C in a mechanism independent of the LDLR.

[4] *Valenti V, Noto D, Giammanco A et al.* **PCSK9-D374Y mediated LDL-R degradation can be functionally inhibited by EGF-A and truncated EGF-A peptides: An in vitro study**. Atherosclerosis 2019.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=31564372
ABSTRACT
BACKGROUND AND AIMS: Proprotein convertase subtilisin/kexin type 9 (PCSK9) binds to low density lipoprotein receptor (LDLR) through the LDLR epidermal growth factor-like repeat A (EGF-A) domain and induces receptor internalization and degradation. PCSK9 has emerged as a novel therapeutic target for hypercholesterolemia. Clinical studies with PCSK9 inhibiting antibodies have demonstrated strong LDL-c lowering effects, but other therapeutic approaches using small molecule inhibitors for targeting PCSK9 functions may offer supplementary therapeutic options. The aim of our study was to evaluate the effect of synthetic EGF-A analogs on mutated (D374Y) PCSK9-D374Y mediated LDLR degradation in vitro. METHODS: Huh7 human hepatoma cells were transiently transfected to overexpress the gain-of-function D374Y PCSK9 mutation, which has been associated with severe hypercholesterolemia in humans. RESULTS: Transient transfection of cells with PCSK9-D374Y expression vector very effectively enhanced degradation of mature LDLR in Huh7. Treatment with both EGF-A and EGF-A truncated peptides inhibited this effect and showed increased LDLR protein in Huh7 cells transfected with PCSK9-D374Y in a clear concentration dependent manner. Huh7 transfected cells treated with increasing concentration of EGF-A analogs also showed an increase internalization of labeled Dil-LDL. CONCLUSIONS: The result of our study shows that EGF-A analogs are able to effectively hamper the enhanced degradation of LDLR in liver cells expressing PCSK9-D374Y.

[5] *Qu KK, Zhang C, Dong LX et al.* **Association of ABCB1 polymorphisms with lipid homeostasis and liver injury response to atorvastatin in Chinese population**. Canadian journal of physiology and pharmacology 2019.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=31574240
ABSTRACT

The present research was to assess the relationship between ABCB1 (G2677T/A, C3435T) polymorphisms and lipid homeostasis, as well as risk of liver injury induced by atorvastatin in inpatients from China. The lipids levels (TC, HDL, TG) as well as metabolic enzyme of hepar (ALT, AST, ALP, GGT) in plasma for 162 patients were measured at baseline and after approximately six months of atorvastatin treatment. Polymorphisms of the ABCB1 gene were determined using the Snapshot technique. The associations between genetic polymorphisms and lipids levels, as well as hepar indexes were evaluated at the end of medical treatment. Based on one-way ANOVA analysis, patients with the 2677GG or 3435TT genotypes showed a remarkable decrease percentage when the level of TC was above 4.00 mmol.L-1, separately (P<0.05). There was a significant decrease percentage in the frequency of patients with 2677GG genotype (LDL-C>2.00 mmol.L-1) (P<0.05). The level of ALT in patients with the 2677 GG or 3435CC genotypes displayed a significantly increase percentage, respectively (P<0.05). The ABCB1 G-C haplotype carriers were associated with an increased risk of AILI. The results provide evidence for clinically individualised utilisation of atorvastatin for lipid homeostasis as well as risk of induced liver injury in Chinese population.

[6] *Pedersen LR, Olsen RH, Anholm C et al.* **Effects of 1 year of exercise training versus combined exercise training and weight loss on body composition, low-grade inflammation and lipids in overweight patients with coronary artery disease: a randomized trial**.
Cardiovascular diabetology 2019; 18:127.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=31575375

ABSTRACT

BACKGROUND: Dyslipidaemia and low-grade inflammation are central in atherogenesis and linked to overweight and physical inactivity. Lifestyle changes are important in secondary prevention of coronary artery disease (CAD). We compared the effects of combined weight loss and interval training with interval training alone on physical fitness, body composition, dyslipidaemia and low-grade inflammation in overweight, sedentary participants with CAD. METHODS: Seventy CAD patients, BMI 28-40 kg/m(2) and age 45-75 years were randomised to (1) 12 weeks' aerobic interval training (AIT) at 90% of peak heart rate three times/week followed by 40 weeks' AIT twice weekly or (2) a low energy diet (LED) (800-1000 kcal/day) for 8-10 weeks followed by 40 weeks' weight maintenance including AIT twice weekly and a high-protein/low-glycaemic load diet. Effects of the intervention were evaluated by physical fitness, body weight and composition. Dyslipidaemia was described using both biochemical analysis of lipid concentrations and lipoprotein particle subclass distribution determined by density profiling. Low-grade inflammation was determined by C-reactive protein, soluble urokinase-type plasminogen activator receptor and tumour necrosis factor alpha. Effects on continuous outcomes were tested by mixed-models analysis. RESULTS: Twenty-six (74%) AIT and 29 (83%) LED + AIT participants completed the study. At baseline subject included 43 (78%) men; subjects averages were: age 63 years (6.2), body weight 95.9 kg (12.2) and VO2peak 20.7 mL O2/kg/min (4.9). Forty-six (84%) had pre-diabetes (i.e. impaired fasting glucose and/or impaired glucose tolerance). LED + AIT reduced body weight by 7.2 kg (- 8.4; - 6.1) and waist circumference by 6.6 cm (- 7.7; - 5.5) compared to 1.7 kg (- 0.7; - 2.6) and 3.3 cm (- 5.1; - 1.5) after AIT (within-group p < 0.001, between-group p < 0.001 and p = 0.018, respectively). Treatments caused similar changes in VO2peak and lowering of total cholesterol, triglycerides,

non-HDL cholesterol and low-grade inflammation. A shift toward larger HDL particles was seen following LED + AIT while AIT elicited no change. CONCLUSIONS: Both interventions were feasible. Both groups obtained improvements in VO2peak, serum-lipids and inflammation with superior weight loss and greater central fat loss following LED + AIT. Combined LED induced weight loss and exercise can be recommended to CAD patients. Trial registration NCT01724567, November 12, 2012, retrospectively registered (enrolment ended in April 2013).

[7] *Douglas G, Mehta V, Zen AAH et al.* **A key role for the novel coronary artery disease gene JCAD in atherosclerosis via shear stress mechanotransduction**. Cardiovascular research 2019.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=31584065
ABSTRACT
INTRODUCTION: Genome Wide Association studies have consistently identified an association between coronary artery disease (CAD) and a locus on chromosome 10 containing a single gene, JCAD (formerly KIAA1462). However, little is known about the mechanism by which JCAD could influence the development of atherosclerosis. METHODS AND RESULTS: Vascular function was quantified in subjects with CAD by flow mediated dilatation [FMD] and vasorelaxation responses in isolated blood vessel segments. The JCAD risk allele identified by GWAS was associated with reduced FMD and reduced endothelial-dependent relaxations. To study the impact of loss of Jcad on atherosclerosis, Jcad-/- mice were crossed to an ApoE-/- background and fed a high fat diet from 6 to16 weeks of age. Loss of Jcad did not affect blood pressure or heart rate. However, Jcad-/-ApoE-/- mice developed significantly less atherosclerosis in the aortic root and the inner curvature of the aortic arch. En-face analysis revealed a striking reduction in pro-inflammatory adhesion molecules at sites of disturbed flow on the endothelial cell layer of Jcad-/- mice. Loss of Jcad lead to a reduced recovery perfusion in response to hind limb ischemia, a model of altered in vivo flow. Knock down of JCAD using siRNA in primary human aortic endothelial cells significantly reduced the response to acute onset of flow, as evidenced by reduced phosphorylation of NF-capital KA, CyrillicB, eNOS and Akt. CONCLUSION: The novel CAD gene JCAD promotes atherosclerotic plaque formation via a role in the endothelial cell shear stress mechanotransduction pathway. TRANSLATIONAL PERSPECTIVE: We reveal that JCAD is a novel coronary artery disease susceptibility gene which determines atherosclerosis progression via a role in the endothelial cell shear stress mechanotransduction pathway. Identifying this new role for JCAD in atherosclerotic plaque progression highlights the importance of new coronary artery disease genes that mediate blood flow mechanotransduction in the pathogenesis of coronary artery disease. These genes are potential novel targets for treatments to reduce atherosclerotic plaque formation, independent of established risk factors and biological mechanisms.

[8] *Sahu SS, Sarkar P, Shrivastava S, Chattopadhyay A*. **Differential Effects of Simvastatin on Membrane Organization and Dynamics in Varying Phases**. Chemistry and physics of lipids 2019:104831.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=31568757
ABSTRACT
Simvastatin belongs to the statin family of cholesterol lowering drugs which act as competitive inhibitors of HMG-CoA reductase, the rate-determining enzyme in cholesterol biosynthesis

pathway. Simvastatin is a semi-synthetic, highly lipophilic statin, and has several side effects. Since HMG-CoA reductase is localized in the endoplasmic reticulum, orally administered simvastatin needs to cross the cellular plasma membrane to be able to act on HMG-CoA reductase. With an overall goal of exploring the interaction of simvastatin with membranes, we examined the effect of simvastatin on the organization and dynamics in membranes of varying phase, in a depth-dependent manner. For this, we employed DPH and TMA-DPH, which represent fluorescent membrane probes localized at two different locations (depths) in the membrane. Analysis of fluorescence anisotropy and lifetime data of these depth-specific probes in membranes of varying phase (gel/fluid/liquid-ordered) showed that the maximum membrane disordering was observed in gel phase, while moderate effects were observed in liquid-ordered phase, with no significant change in membrane order in fluid phase membranes. We conclude that simvastatin induces change in membrane order in a depth-dependent and phase-specific manner. These results provide novel insight in the membrane interaction of simvastatin and could be crucial for understanding its pharmacological effect.

[9] *Ellis KL, Hooper AJ, Pang J et al.* **A genetic risk score predicts coronary artery disease in familial hypercholesterolaemia: enhancing the precision of risk assessment**. Clinical genetics 2019.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=31571196
ABSTRACT
Familial hypercholesterolaemia (FH) is associated with increased risk of coronary artery disease (CAD); however, risk prediction and stratification remain a challenge. Genetic risk scores (GRS) may have utility in identifying FH patients at high CAD risk. The study included 811 patients attending the lipid disorders clinic at Royal Perth Hospital with mutation-positive (n = 251) and mutation-negative (n = 560) FH. Patients were genotyped for a GRS previously associated with CAD. Associations between the GRS, clinical characteristics, and CAD were assessed using regression analyses. The average age of patients was 49.6 years, and 44.1% were male. The GRS was associated with increased odds of a CAD event in mutation-positive [odds ratio (OR) = 3.3; 95% confidence interval (CI) = 1.3-8.2; P = .009] and mutation-negative FH patients (OR = 1.8; 95% CI = 1.0-3.3; P = .039) after adjusting for established predictors of CAD risk. The GRS was associated with greater subclinical atherosclerosis as assessed by coronary artery calcium score (P = .039). A high GRS was associated with CAD defined clinically and angiographically in FH patients. High GRS patients may benefit from more intensive management including lifestyle modification and aggressive lipid-lowering therapy. Further assessment of the utility of the GRS requires investigation in prospective cohorts, including its role in influencing the management of FH patients in the clinic.

[10] *Boffa MB, Koschinsky ML*. **Proprotein convertase subtilisin/kexin type 9 inhibitors and lipoprotein(a)-mediated risk of atherosclerotic cardiovascular disease: more than meets the eye?** Current opinion in lipidology 2019.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=31577611
ABSTRACT
PURPOSE OF REVIEW: Evidence continues to mount for elevated lipoprotein(a) [Lp(a)] as a prevalent, independent, and causal risk factor for atherosclerotic cardiovascular disease.

However, the effects of existing lipid-lowering therapies on Lp(a) are comparatively modest and are not specific to Lp(a). Consequently, evidence that Lp(a)-lowering confers a cardiovascular benefit is lacking. Large-scale cardiovascular outcome trials (CVOTs) of inhibitory mAbs targeting proprotein convertase subtilisin/kexin type 9 inhibitors (PCSK9i) may address this issue. RECENT FINDINGS: Although the ability of PCSK9i to lower Lp(a) by 15-30% is now clear, the mechanisms involved continue to be debated, with in-vitro and in-vivo studies showing effects on Lp(a) clearance (through the LDL receptor or other receptors) and Lp(a)/apolipoprotein(a) biosynthesis in hepatocytes. The FOURIER CVOT showed that patients with higher baseline levels of Lp(a) derived greater benefit from evolocumab and those with the lowest combined achieved Lp(a) and LDL-cholesterol (LDL-C) had the lowest event rate. Meta-analysis of ten phase 3 trials of alirocumab came to qualitatively similar conclusions concerning achieved Lp(a) levels, although an effect independent of LDL-C lowering could not be demonstrated. SUMMARY: Although it is not possible to conclude that PCSK9i specifically lower Lp(a)-attributable risk, patients with elevated Lp(a) could derive incremental benefit from PCSK9i therapy.

[11] *Golledge J, Ward NC, Watts GF*. **Lipid management in people with peripheral artery disease**. Current opinion in lipidology 2019.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=31577608
ABSTRACT
PURPOSE OF REVIEW: To summarize recent data on the role of dyslipidaemia and the benefit from managing this in people with disease of the abdominal aorta and its peripheral branches (peripheral artery disease, PAD). RECENT FINDINGS: Findings from the Further Cardiovascular Outcomes Research with Proprotein convertase subtilisin/kexin type 9 (PCSK9) Inhibition in Subjects with Elevated Risk (FOURIER) trial demonstrate the benefit of intensely lowering low-density lipoprotein-cholesterol (LDL-c) in people with PAD to substantially reduce the incidence of major cardiovascular events (MACE; myocardial infarction, stroke or cardiovascular death) and major adverse limb events (MALE). Despite the evidence of substantial benefits from lowering LDL-c, the uptake of drug therapies to lower LDL-c remains sub-optimal in people with PAD. SUMMARY: Effective methods to educate physicians and patients on best medical management are needed. Further research is needed to examine the benefit of LDL-c lowering and other lipid therapies for PAD-specific problems like abdominal aortic aneurysm progression and walking impairment. Other novel lipid therapies, such as those that lower lipoprotein (a), maybe particularly beneficial to people with PAD given the evidence indicating high concentrations in this population and the high incidence of MACE in these individuals.

[12] *Rana K, Reid J, Rosenwasser JN et al.* **A spotlight on alirocumab in high cardiovascular risk patients with type 2 diabetes and mixed dyslipidemia: a review on the emerging data**. Diabetes, metabolic syndrome and obesity : targets and therapy 2019; 12:1897-1911.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=31571964
ABSTRACT
Diabetes is a significant and independent risk factor for atherosclerotic cardiovascular disease (ASCVD), leading to morbidity and mortality among this population. The prevention of macrovascular complications, such as CVD, peripheral arterial disease, and cerebrovascular

accident, in patients with diabetes is obtained through multifactorial risk reduction, including mixed dyslipidemia management and adequate glycemic control. For patients with diabetes, it is crucial to initiate adequate dyslipidemia therapy to achieve recommended low-density lipoprotein cholesterol (LDL-C) goal of <70 mg/dL or target non-high-density lipoprotein goal of <100 mg/dL. Lipid-lowering therapies (LLTs), such as statins and ezetimibe, are the cornerstone for plasma LDL-C lowering; however, individuals with diabetes are often unable to achieve target lipid goals with these therapies alone and frequently require additional treatments. A new class of LLTs, proprotein convertase subtilisin-kexin type 9 (PCSK9) inhibitors, provides a novel approach to lowering lipids in persons with high CV risk, such as those with diabetes. The clinical data presented in this review indicate the potential benefits of alirocumab in patients with diabetes and its value as a treatment option in patients with diabetic dyslipidemia with no significant safety concerns.

[13] *Wan Z, Fan Y, Liu X et al.* **NLRP3 inflammasome promotes diabetes-induced endothelial inflammation and atherosclerosis**. Diabetes, metabolic syndrome and obesity : targets and therapy 2019; 12:1931-1942.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=31571967
ABSTRACT
Background: NLRP3 inflammasome can be activated by high glucose and links inflammation and metabolic disease. This study aimed to investigate the role of NLRP3 inflammasome in hyperglycemia-induced endothelial inflammation and diabetic atherosclerosis. Methods: NLRP3 levels in peripheral blood mononuclear cell (PBMC) and plasma IL-1beta level were measured in diabetes patients. The activation of NLPR3 was detected in diabetic ApoE-/- mice and human umbilical vein endothelial cells (HUVECs). Results: Compared with healthy controls, NLRP3 expression levels in PBMC and plasma IL-1beta level were significantly higher in diabetes patients but considerably decreased after lifestyle interventions and medicine. Moreover, carotid atherosclerosis was significantly related to plasma IL-1beta level in diabetes patients. In diabetic atherosclerosis mouse model, NLRP3 knockdown suppressed NLRP3 inflammasome activation, inhibited the expression of adhesion molecules ICAM-1 and VCAM-1 in intima, reduced atherosclerosis and stabilized atherosclerotic plaque. In vitro, the expression of NLRP3 inflammasome components and the secretion of IL-1beta were augmented by high glucose in HUVECs. Moreover, either high glucose or IL-1beta promoted the expression of adhesion molecules, which were suppressed by NLRP3 knockdown or IL-1beta receptor antagonist. Conclusion: These findings provide novel insights into pathological mechanisms of diabetic atherosclerosis and have potential therapeutic implications for cardiovascular complications in diabetes.

[14] *Min BK, Oh CJ, Park S et al.* **Therapeutic effect of dichloroacetate against atherosclerosis via hepatic FGF21 induction mediated by acute AMPK activation**. Experimental & molecular medicine 2019; 51:114.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=31570705
ABSTRACT
Dyslipidemia-induced atherosclerosis, which has a risk of high morbidity and mortality, can be alleviated by metabolic activation associated with mitochondrial function. The effect of

dichloroacetate (DCA), a general pyruvate dehydrogenase kinase (PDK) inhibitor, on in vivo energy expenditure in ApoE(-/-) mice fed a western diet (WD) has not yet been investigated. WD-fed ApoE(-/-) mice developed atherosclerotic plaques and hyperlipidemia along with obesity, which were significantly ameliorated by DCA administration. Increased oxygen consumption was associated with heat production in the DCA-treated group, with no change in food intake or physical activity compared with those of the control. These processes were correlated with the increased gene expression of Dio2 and Ucp-1, which represents brown adipose tissue (BAT) activation, in both WD-induced atherosclerosis and high-fat-induced obesity models. In addition, we found that DCA stimulated hepatic fibroblast growth factor 21 (Fgf21) mRNA expression, which might be important for lowering lipid levels and insulin sensitization via BAT activation, in a dose- and time-dependent manner associated with serum FGF21 levels. Interestingly, Fgf21 mRNA expression was mediated in an AMP-activated protein kinase (AMPK)-dependent manner within several minutes after DCA treatment independent of peroxisome proliferator-activated receptor alpha (PPARalpha). Taken together, the results suggest that enhanced glucose oxidation by DCA protects against atherosclerosis by inducing hepatic FGF21 expression and BAT activation, resulting in augmented energy expenditure for heat generation.

[15] *Wang L, Wang Y, Chen A et al.* **Pitavastatin slows tumor progression and alters urine-derived volatile organic compounds through the mevalonate pathway**. FASEB journal : official publication of the Federation of American Societies for Experimental Biology 2019:fj201901388R.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=31585508

ABSTRACT

Bone is a frequent site of metastasis from breast cancer, and a desirable drug could suppress tumor growth as well as metastasis-linked bone loss. Currently, no drug is able to cure breast cancer-associated bone metastasis. In this study, we focused on statins that are known to inhibit cholesterol production and act as antitumor agents. After an initial potency screening of 7 U.S. Food and Drug Administration-approved statins, we examined pitavastatin as a drug candidate for inhibiting tumor and tumor-induced bone loss. In vitro analysis revealed that pitavastatin acted as an inhibitor of tumor progression by altering stress to the endoplasmic reticulum, down-regulating peroxisome proliferator-activated receptor gamma, and reducing Snail and matrix metalloproteinase 9. In bone homeostasis, it blocked osteoclast development by suppressing transcription factors c-Fos and JunB, but stimulated osteoblast mineralization by regulating bone morphogenetic protein 2 and p53. In a mouse model, pitavastatin presented a dual role in tumor inhibition in the mammary fat pad, as well as in bone protection in the osteolytic tibia. In mass spectrometry-based analysis, volatile organic compounds (VOCs) that were linked to lipid metabolism and cholesterol synthesis were elevated in mice from the tumor-grown placebo group. Notably, pitavastatin-treated mice reduced specific VOCs that are linked to lipid metabolites in the mevalonate pathway. Collectively, the results lay a foundation for further investigation of pitavastatin's therapeutic efficacy in tumor-induced bone loss, as well as VOC-based diagnosis of tumor progression and treatment efficacy.-Wang, L., Wang, Y., Chen, A., Teli, M., Kondo, R., Jalali, A., Fan, Y., Liu, S., Zhao, X., Siegel, A., Minami, K., Agarwal,

M., Li, B.-Y., Yokota, H. Pitavastatin slows tumor progression and alters urine-derived volatile organic compounds through the mevalonate pathway.

[16] *Glanz VY, Sobenin IA, Grechko AV et al.* **The role of mitochondria in cardiovascular diseases related to atherosclerosis**. Frontiers in bioscience (Elite edition) 2020; 12:102-112.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=31585872
ABSTRACT
Atherosclerosis is a complex disorder that involves several mechanisms of pathogenesis tightly related to each other: lipid accumulation, inflammation and structural changes in the arterial wall. The main source of lipids accumulating in the arterial wall is low-density lipoprotein (LDL) atherogenically modified by desialylation or oxidation. Oxidized LDL can be produced as a result of enhanced generation of reactive oxygen species by mitochondria during oxidative stress. Mitochondrial dysfunction was found to be involved in every aspect of atherosclerosis, and is currently evaluated as a potential point of therapeutic intervention. In particular, atherosclerosis-associated inflammation and its link to mitochondrial dysfunction appear to be interesting, since mitochondria not only trigger the response to external signals, but also can act as pro-inflammatory agents themselves. In this regard, atherosclerosis is potentially an autoimmune disease. In this review, we summarize recent insights on the role of mitochondrial dysfunction in atherogenesis and discuss the significance of mitochondria for understanding of molecular basis of cardiovascular diseases.

[17] *Liu S, Zheng X, Xu J et al.* **Predictive value of coronary artery calcium score in cardiovascular disease**. Frontiers in bioscience (Elite edition) 2020; 12:113-125.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=31585873
ABSTRACT
We investigated coronary heart disease (CHD) and cardiovascular disease (CVD) event rates in a diverse population with a coronary artery calcium score (CACS) of 0 and the role of CACS in the detection of subclinical noncalcified atherosclerotic plaque. A total of 15,884 participants in five studies were included in this meta-analysis. Hazard ratios (HRs) with 95% confidence intervals (95% CIs) were calculated. The results showed that CHD incidence significantly increased with increased CACS (HR=0.05, 95% CI 0.03-0.06, Z=5.82, P=0.002). The CHD rate was low and further increased with CACS of 101-300. With CACS >300, the CHD rate was highest. Similarly, CVD rate was low with CACS of 0, increased with CACS of 1-100 (HR=0.03, 95% CI 0.01-0.06, Z=1.66, P=0.096), and further increased with CACS of 101-300. With CACS >300, the CVD rate was highest. Clinical evidence indicated that the higher the CACS, the higher the CHD and CVD rates, while the CVD rate does not always decreased compared with CHD rate with the same CACS, especially with CACS of 0.

[18] *Klimis H, Chow CK*. **Clinical consequences of poor adherence to lipid-lowering therapy in patients with cardiovascular disease: can we do better?** Heart Asia 2019; 11:e011200.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=31566625
ABSTRACT

Literature update week 40 (2019)

[19] *Kameyama N, Maruyama C, Shijo Y et al.* **Comparison of Food and Nutrient Intakes between Japanese Dyslipidemic Patients with and without Low-Density Lipoprotein Cholesterol Lowering Drug Therapy: A Cross-Sectional Study**. Journal of atherosclerosis and thrombosis 2019.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=31582622
ABSTRACT
AIM: We aimed to clarify actual food and nutrient intakes in Japanese patients with dyslipidemia. We also compared food and nutrient intakes between patients with and without low-density lipoprotein cholesterol (LDL-C) lowering drug therapy. METHODS: Food and nutrient intakes were assessed employing 3-day weighted dietary records in this cross-sectional study of 104 Japanese outpatients with dyslipidemia, age 30-65 years, not given dietary counseling. Anthropometric and biochemical parameters were measured after an overnight fast. Food and nutrient intakes were compared between patients with versus without LDL-C lowering drug prescriptions. Stepwise multiple regression analysis was performed to identify relationships between the serum LDL-C concentrations and food intakes. RESULTS: Of the 104 patients, 43.3% were prescribed LDL-C lowering drugs, primarily statins. Of the total patients, 83% had lipid intakes over 25% of total energy consumption (%E), exceeding the recommendation for dyslipidemia by the Japan Atherosclerosis Society. Similarly, 77% had saturated fatty acid intakes over 7%E, and 88% had cholesterol intakes over 200 mg per day. Dietary fiber consumption was low (25 g) in 97% of patients. Those taking LDL-C lowering drugs consumed less "meat, poultry and processed meat products" and "cereals", and more "fish", "fruits" and "nuts", than patients not taking these drugs (p0.05). Food intakes correlating with LDL-C concentrations independently of drug therapy differed between patients taking versus not taking these medications. CONCLUSION: Our results support the necessity of diet therapy for patients with dyslipidemia regardless of whether LDL-C lowering drugs are prescribed.The clinical trial registration number: UMIN000022955.

[20] *Watanabe Y, Tatsuno I*. **Prevention of Cardiovascular Events with Omega-3 Polyunsaturated Fatty Acids and the Mechanism Involved**. Journal of atherosclerosis and thrombosis 2019.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=31582621
ABSTRACT
An epidemiological study of Greenlandic Inuit suggested that fish oil, or omega-3 polyunsaturated fatty acids (PUFA), was important in preventing atherosclerotic disease. After this landmark study, many large-scale epidemiological studies and meta-analyses have examined the health benefits of omega-3 PUFA as part of a fatty acid-rich diet to demonstrate its beneficial roles in the prevention of cardiovascular diseases. Recent research has also focused attention on the anti-inflammatory effects of omega-3 PUFA and on specialized pro-resolving mediators. Findings of these studies have led to the development of omega-3 PUFA preparations for the treatment of dyslipidemia, including a highly purified eicosapentaenoic acid (EPA)-ethyl ester product (Epadel((R))) in Japan and an EPA/docosahexaenoic acid (DHA) preparation (Lotriga((R))) in the United States and Europe. Although various large-scale clinical trials on the cardiovascular preventive effect of omega-3 PUFA were conducted and reported, the results were not always consistent. The issues of not targeting subjects with

hypertriglyceridemia and using low dose of omega-3 PUFA have been suggested to contribute to the failure of demonstrating the preventive effect of omega-3 PUFA in these clinical trials. Taking into account the above issues, the REDUCE-IT trial evaluated a highly purified EPA preparation at a high dose of 4 g/day in patients with hypertriglyceridemia and high cardiovascular risk, and demonstrated an extraordinary outcome of 25% relative reduction in cardiovascular events. This article reviews studies on omega-3 fatty acids during the last 50 years, including the progress in elucidating molecular mechanisms and recent large-scale clinical studies.

[21] *Yu DR, Wang T, Huang J et al.* **MicroRNA-9 overexpression suppresses vulnerable atherosclerotic plaque and enhances vascular remodeling through negative regulation of the p38MAPK pathway via OLR1 in acute coronary syndrome**. Journal of cellular biochemistry 2019.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=31571264
ABSTRACT
Acute coronary syndrome (ACS) is characterized by atherosclerotic plaque rupture with a high incidence of recurrent ischemic events. Several microRNAs are found to be aberrantly expressed in atherosclerotic plaques. This study aims to investigate the effects of microRNA-9 (miR-9) on vulnerable atherosclerotic plaque and vascular remodeling in ACS and underlying mechanisms. Microarray-based gene expression profiling was used to identify differentially expressed genes related to ACS and regulatory miRNAs. Oxidized low-density lipoprotein (lectin-like) receptor 1 (OLR1) was identified to be aberrantly activated in ACS and regulated by miR-9. OLR1 was verified as a target gene of miR-9 by bioinformatics prediction and dual luciferase reporter gene assay. The atherosclerotic models were induced in ApoE(-/-) mice, in which the agomir or antagomir of miR-9, or small interfering RNA (siRNA) against OLR1 were separately introduced. Serum lipid levels and expression of vascular remodeling and inflammatory response-related factors were determined, respectively. On the basis of the obtained results, in the atherosclerosis mice treated with the agomir of miR-9 and siRNA against OLR1, the p38-mitogen-activated protein kinase (p38MAPK) pathway was inhibited; levels of triglyceride, total cholesterol, low-density lipoprotein cholesterol, tumor necrosis factor-alpha, interleukin-6, and vascular endothelial growth factor were reduced, but the high-density lipoprotein cholesterol level was increased, along with decreased vulnerable atherosclerotic plaque area and enhanced vascular remodeling. Taken together, these findings suggested an inhibitory role miR-9 acts in the formation of vulnerable atherosclerotic plaques in ACS mice, along with a promoted vascular remodeling, via a negative feedback regulation of OLR1-mediated p38MAPK pathway.

[22] *Sung KC, Huh JH, Ryu S et al.* **Low Levels of Low-Density Lipoprotein Cholesterol and Mortality Outcomes in Non-Statin Users**. Journal of clinical medicine 2019; 8.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=31581520
ABSTRACT
We aimed to test the association between low-density lipoprotein cholesterol (LDL-C) and cardiovascular disease (CVD), cancer, and all-cause mortality in non-statin users. A total of 347,971 subjects in Kangbuk Samsung Health Study (KSHS.57.4% men, mean follow up: 5.64 +/-

3.27 years) were tested. To validate these associations, we analyzed data from another cohort (Korean genome and epidemiology study, KoGES, 182,943 subjects). All subjects treated with any lipid-lowering therapy and who died during the first 3 years of follow up were excluded. Five groups were defined according to baseline LDL-C concentration (<70, 70-99, 100-129, 130-159, >/=160 mg/dL). A total of 2028 deaths occurred during follow-up in KSHS. The lowest LDL-C group (LDL < 70 mg/dL) had a higher risk of all-cause mortality (HR 1.95, 1.55-2.47), CVD mortality (HR 2.02, 1.11-3.64), and cancer mortality (HR 2.06, 1.46-2.90) compared to the reference group (LDL 120-139 mg/dL). In the validation cohort, 2338 deaths occurred during follow-up. The lowest LDL-C group (LDL < 70 mg/dL) had a higher risk of all-cause mortality (HR 1.81, 1.44-2.28) compared to the reference group. Low levels of LDL-C concentration are strongly and independently associated with increased risk of cancer, CVD, and all-cause mortality. These findings suggest that more attention is needed for subjects with no statin-induced decrease in LDL-C concentrations.

[23] *Dankner R, Ben Avraham S, Harats D, Chetrit A*. **ApoE genotype, lipid profile, exercise, and the associations with cardiovascular morbidity and 18-year mortality**. J Gerontol A Biol Sci Med Sci 2019.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=31585002
ABSTRACT
BACKGROUND: Studies of longevity examined apolipoprotein E (ApoE), a gene involved in lipoprotein metabolism, which interacts with susceptibility to age-related diseases, and with mortality. We evaluated the association of ApoE isoforms with cardiovascular disease (CVD) and all-cause mortality. METHODS: A prospective cohort of 949 survivors of the Israel Study of Glucose Intolerance, Obesity, and Hypertension, examined during 1999-2004, mean age 72 years, was followed for mortality until 2017. Participants were interviewed for lifestyle habits and medical history. Anthropometrics and biochemical markers were taken. Logistic regression was used to assess CVD morbidity and Cox proportional-hazard model for mortality. RESULTS: The most common genotype in the cohort was ApoE E3 (76.3%), with the other two almost equally distributed (ApoE E2 11.2% and ApoE E4 12.5%). In men only, ApoE E4 associated with CVD (adjusted OR (aOR)=1.46, 95%CI 0.76, 2.80) and with 18-year mortality (adjusted HR (aHR) =1.47, 95%CI 0.95, 2.26), adjusting for age, ethnicity, physical activity, hypertension, diabetes, LDL-cholesterol, HDL-cholesterol, triglycerides and lipid-lowering medications. Low levels of HDL cholesterol, adjusted for ApoE and the above mentioned variables, associated with higher prevalence of CVD (aOR=1.35, 95%CI 1.00, 1.83) and all-cause mortality (aHR=1.42, 95%CI 1.14, 1.78). ApoE E3 and E2 conferred a lower 18-year mortality risk in the physically active individuals, compared to the sedentary (aHR=0.57, 95%CI 0.44, 0.74, and aHR=0.53, 95%CI 0.78, 1.02, respectively). CONCLUSIONS: In community dwelling older adults, sociodemographic characteristics and physical activity, blood pressure and HDL-cholesterol levels, may outweigh the impact of ApoE polymorphisms on CVD morbidity and all-cause mortality.

[24] *Ho CLB, Breslin M, Chowdhury EK et al.* **Lack of a significant legacy effect of baseline blood pressure 'treatment naivety' on all-cause and cardiovascular mortality in the Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial**. Journal of hypertension 2019.

PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=31584517

ABSTRACT

OBJECTIVES: To investigate legacy effects at 14-year follow-up of all-cause and cardiovascular disease (CVD) mortality in 'treatment-naive' or 'previous treatment' groups based on blood pressure (BP)-lowering treatment status at baseline. METHODS: A post-hoc observational study of the Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial. We excluded participants with a previous history of CVD events. Cox proportional hazard model and 95% confidence interval were used to estimate the effects of treatment naive on mortality outcomes. Moreover, a subgroup analysis by estimated 10-year Framingham risk score was performed. RESULTS: In multivariable models adjusting for baseline and in-trial characteristics (BP values and number of BP medications as time-dependent variables), there was no statistically significant difference in 5 and 14-year all-cause mortality with a hazard ratio of 0.93 (95% confidence interval 0.80-1.09) and hazard ratio 0.95 (0.88-1.03) and in 5 and 14-year CVD mortality hazard ratio 0.94 (0.72-1.23) and hazard ratio 0.93 (0.80-1.08). In subgroup by absolute CVD risk, no heterogeneity of the association between treatment naive and short-term or long-term all-cause or CVD mortality were found. All comparisons are between the treatment-naive and previous treatment groups. CONCLUSION: Physicians are concerned about 'legacy effects' of not treating individuals with a BP of 140 mmHg or over and low absolute risk. When treatment intensification was taken into consideration in the primary prevention population in this study, no adverse legacy effect as a result of baseline BP 'treatment naivety' was evident in 14 years of follow-up. The nonsignificant associations were consistent across the CVD risk subgroups. However, the results may be biased due to unobserved residual confounding and therefore should be interpreted with caution.

[25] *Karmaus PWF, Shi M, Perl S et al.* **Effects of rosuvastatin on the immune system in healthy volunteers with normal serum cholesterol**. JCI insight 2019.

PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=31573980

ABSTRACT

BACKGROUND: Hydroxymethyl-glutaryl-coenzyme A reductase inhibitors ('statins') are prescribed to millions of people. Statins are anti-inflammatory independent of their cholesterol-reducing effects. To date, most reports on the immune effects of statins have assayed a narrow array of variables and have focused on cell lines, rodent models, or patient cohorts. We sought to define the effect of rosuvastatin on the 'immunome' of healthy, normocholesterolemic subjects. METHODS: Prospective study of rosuvastatin (20 mg/day x 28 days) in 18 statin-naive adults with low density lipoprotein-cholesterol <130 mg/dL. A panel of >180 immune/biochemical/endocrinologic variables was measured at baseline, and days 14, 28, and 42 (14 days after drug withdrawal). Drug effect was evaluated using linear mixed effects models. Potential interactions between drug and baseline high-sensitivity C-reactive protein (hsCRP) were evaluated. RESULTS: A wide array of immune measures changed (nominal $p<0.05$) during rosuvastatin treatment, although the changes were modest in magnitude and few met a false discovery rate of 0.05. Among changes noted were a concordant increase in pro-inflammatory cytokines (IFNgamma, IL-1beta, IL-5, IL-6, TNFalpha) and peripheral blood neutrophil frequency, and a decline in activated T regulatory cell frequency. Several drug effects were significantly modified by baseline hsCRP, and some did not resolve after drug

withdrawal. Among other unexpected rosuvastatin effects were changes in erythrocyte indices, glucose-regulatory hormones, CD8+ T cells, and haptoglobin. CONCLUSION: Rosuvastatin induces modest changes in immunologic and metabolic measures in normocholesterolemic subjects, with several effects dependent upon baseline CRP. Future, larger studies are warranted to validate these changes and their physiological significance.

[26] *Mullard A*. **PCSK9-lowering RNAi contender clears first phase III trial**. Nature reviews. Drug discovery 2019; 18:737.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=31570849
ABSTRACT

[27] *Lin Y, Koppenol WP, Knol D et al.* **Serum Concentration of Plant Sterol Oxidation Products (POP) Compared to Cholesterol Oxidation Products (COP) after Intake of Oxidized Plant Sterols: A Randomised, Placebo-Controlled, Double-Blind DoseResponse Pilot Study**. Nutrients 2019; 11.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=31575059
ABSTRACT
Plant sterols (PS) are oxidized to PS oxidation products (POP). This study quantified the change in serum POP compared to cholesterol oxidation products (COP) after the intake of increasing POP doses. This was a double-blind, randomized, placebo-controlled, doseresponse pilot study with healthy individuals in four groups (15 per group). The control group received products with no added PS or POP and treatment groups received daily 20-25 g margarine with added PS (mean 3 g/d) and two cookies (~28 g) for six weeks. Cookies delivered 8.7 (low-dose), 15.2 (medium-dose), or 37.2 (high-dose) mg/d POP. Fasting serum POP and COP were measured at the baseline, days 14, 28, and 42 in all participants and days 7, 21, and 35 in a subset. Sixty individuals completed the study; 52 were included in per protocol analysis. Serum POP increased with increasing POP intake and plateaued at dose >15 mg/d. Stabilized POP concentrations were (mean +/- SD) 38.9 +/- 6.9, 91.0 +/- 27.9, 144.4 +/- 37.9 and 203.0 +/- 63.7 nmol/L, for control, low-, medium-, and high-dose POP groups, respectively. For all groups, the serum COP ranged from 213 to 262 nmol/L and the average POP/COP ratio was <1. Serum POP concentrations increased non-linearly, reaching stabilized concentrations in <7 days, and remained below COP concentrations after the intake of increasing POP doses.

[28] *Aday AW, Goldfine AB, Gregory JM, Beckman JA*. **Impact of Acipimox Therapy on Free Fatty Acid Efflux and Endothelial Function in the Metabolic Syndrome: A Randomized Trial**. Obesity (Silver Spring, Md.) 2019.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=31571412
ABSTRACT
OBJECTIVE: Insulin resistance is associated with increased lipolysis and elevated concentrations of free fatty acids (FFA), which in turn contribute to impaired vascular function. It was hypothesized that lowering FFA with acipimox, a nicotinic acid derivative that impairs FFA efflux, would improve endothelial function, measured by flow-mediated dilation (FMD), in individuals with metabolic syndrome. METHODS: A total of 18 participants with metabolic syndrome and 17 healthy controls were enrolled and treated with acipimox 250 mg orally every

6 hours or placebo for 7 days in a randomized, double-blind, crossover trial. RESULTS: Acipimox reduced FFA concentrations among individuals with metabolic syndrome to near normal levels (P = 0.01), but there was no change among healthy controls (P = 0.17). Acipimox did not improve endothelial-dependent FMD in either group (metabolic syndrome: P = 0.42; healthy controls: P = 0.16), although endothelial-independent nitroglycerin-mediated dilation among those with metabolic syndrome tended to increase (20.3%, P = 0.06). There were no changes in blood lipids or markers of inflammation following therapy. There was minimal correlation between change in FMD and baseline measures of BMI (rho = -0.09) or waist circumference (rho = -0.15). CONCLUSIONS: In groups with normal or elevated baseline FFA, short-term reductions do not improve endothelial function assessed by FMD.

[29] *Lajara R*. **Combination therapy with SGLT-2 inhibitors and GLP-1 receptor agonists as complementary agents that address multi-organ defects in type 2 diabetes**. Postgraduate medicine 2019:1-11.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=31580737
ABSTRACT
Type 2 diabetes (T2D) has a complex pathophysiology composed of multiple underlying defects that lead to impaired glucose homeostasis and the development of macrovascular and microvascular complications. Of the currently available glucose-lowering therapies, sodium-glucose cotransporter-2 inhibitors (SGLT-2is) and glucagon-like peptide-1 receptor agonists (GLP-1RAs) both provide effective glycemic control and have been shown to reduce cardiovascular (CV) events in patients with T2D and a high CV risk or established CV disease. Because these agents have complementary mechanisms of action, they are able to act on multiple defects of T2D when used in combination. This review discusses the rationale for and potential benefits of SGLT-2i plus GLP-1RA combination therapy in patients with T2D. A search of the PubMed database was conducted for studies and reviews describing the combined use of SGLT-2is and GLP-1RAs, with a specific focus on identifying clinical studies of combination therapy in patients with T2D. In clinical studies, glycated hemoglobin (A1c) was significantly reduced over 28-52 weeks with SGLT-2i plus GLP-1RA therapy versus the individual agents or baseline. Several CV risk factors, including body weight, blood pressure, and lipid parameters, were also improved. SGLT-2i plus GLP-1RA therapy was generally well tolerated, with a low risk of hypoglycemia and no unexpected findings. Taken together with results from large CV outcomes trials of SGLT-2is and GLP-1RAs, combination therapy with these agents potentially provides effective durable glycemic control and CV benefits due to their complementary actions on the defects of T2D.

[30] *Nankar SA, Bulani Y, Sharma SS, Pande AH*. **APOE-Derived Peptides Attenuated Diabetes-Induced Oxidative Stress and Inflammation**. Protein and peptide letters 2019.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=31577194
ABSTRACT
Apolipoprotein-derived peptides have emerged as a potential candidate for the treatment of various inflammatory disease conditions. Previously we have shown that peptides derived from human apolipoprotein-E interact with various pro-inflammatory lipids and inhibit their inflammatory functions in cellular assays. In this study, two peptides (E5 and E8, which

corresponds to the 'receptor-binding region' and 'lipid-binding region' of apolipoprotein-E, respectively) were selected to investigate their anti-inflammatory and anti-oxidative effects in streptozotocin-induced diabetic model of inflammation and oxidative stress. 4F peptide, a well-studied apoA1-mimetic peptide that exhibit anti-inflammatory, was also used. Our results suggest that peptides (4F, E5 and E8) are able to reduce oxidative stress as well as lower the level of inflammatory markers in streptozotocin-induced diabetic rats albeit to different extent. E5 peptide was relatively more effective than 4F and E8 peptides in decreasing inflammation and oxidative stress. E5 peptide can be developed as a promising candidate for the treatment of various inflammatory conditions.

[31] *Leckie RL, Lehman DE, Gianaros PJ et al.* **The effects of omega-3 fatty acids on neuropsychological functioning and brain morphology in mid-life adults: a randomized clinical trial**. Psychological medicine 2019:1-10.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=31581959
ABSTRACT
BACKGROUND: The diet of most adults is low in fish and, therefore, provides limited quantities of the long-chain, omega-3 fatty acids (LCn-3FAs), eicosapentaenoic and docosahexaenoic acids (EPA, DHA). Since these compounds serve important roles in the brain, we sought to determine if healthy adults with low-LCn-3FA consumption would exhibit improvements in neuropsychological performance and parallel changes in brain morphology following repletion through fish oil supplementation. METHODS: In a randomized, controlled trial, 271 mid-life adults (30-54 years of age, 118 men, 153 women) consuming 300 mg/day of LCn-3FAs received 18 weeks of supplementation with fish oil capsules (1400 mg/day of EPA and DHA) or matching placebo. All participants completed a neuropsychological test battery examining four cognitive domains: psychomotor speed, executive function, learning/episodic memory, and fluid intelligence. A subset of 122 underwent neuroimaging before and after supplementation to measure whole-brain and subcortical tissue volumes. RESULTS: Capsule adherence was over 95%, participant blinding was verified, and red blood cell EPA and DHA levels increased as expected. Supplementation did not affect performance in any of the four cognitive domains. Exploratory analyses revealed that, compared to placebo, fish oil supplementation improved executive function in participants with low-baseline DHA levels. No changes were observed in any indicator of brain morphology. CONCLUSIONS: In healthy mid-life adults reporting low-dietary intake, supplementation with LCn-3FAs in moderate dose for moderate duration did not affect neuropsychological performance or brain morphology. Whether salutary effects occur in individuals with particularly low-DHA exposure requires further study.

[32] *Ozdemir IH, Copkiran O, Tikiz H, Tikiz C*. **Peripheral polyneuropathy in patients receiving long-term statin therapy**. Turk Kardiyoloji Dernegi arsivi : Turk Kardiyoloji Derneginin yayin organidir 2019; 47:554-563.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=31582682
ABSTRACT
OBJECTIVE: Peripheral neuropathy is an important potential side effect of statin use. This study was an investigation of the incidence of peripheral neuropathy in patients taking atorvastatin or rosuvastatin for hypercholesterolemia and the relationship to the dose and duration of the

treatment. METHODS: In all, 50 patients using a statin treatment and 50 healthy controls matched for age and gender who had never taken a statin were included in the study. Polyneuropathy was assessed with a neurological examination and electroneuromyography (ENMG). RESULTS: While no polyneuropathy was detected in the control group, polyneuropathy was seen in 33 (66%) of the patients in the statin group ($p<0.01$). There was no significant difference between the 2 statin groups in the results of the neurological examination or the ENMG findings regarding the incidence of polyneuropathy ($p=0.288$ and $p=0.720$, respectively). Neuropathy was observed in a neurological examination performed within the first year in 50% of the rosuvastatin users and 18% of those taking atorvastatin. The severity of the polyneuropathy increased with the duration of the treatment in the atorvastatin group ($p=0.030$). CONCLUSION: This study revealed an increased risk of peripheral neuropathy with long-term statin use (>1 year). Electrodiagnostic changes have been detected in motor and sensory nerves in nerve conduction studies of patients on long-term statin treatment. The assessment of neurological symptoms, like tingling, numbness, pain and tremor in the hands and feet, and unsteadiness during walking associated with peripheral neuropathy may be useful in the follow-up of the patients on long-term statin treatment. Early detection of peripheral neuropathy and changing hypercholesterolemia treatment may prevent permanent nerve damage.