[1] *Sukun A, Onal C, Tufanoğlu FH*. **The effect of living at high altitude on carotid intima-media thickness in the elderly: a comparative study**. Acta radiologica (Stockholm, Sweden : 1987) 2021:2841851211022503.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=34082596
ABSTRACT
BACKGROUND: Previous studies have shown that high altitude may have a protective effect on cardiovascular diseases. However, the effects of high altitude on carotid atherosclerosis have been less evidenced. PURPOSE: To compare the effect of altitude on atherosclerosis by using carotid artery ultrasonography (CAU) findings. MATERIAL AND METHODS: A total of 180 patients aged >60 years, who had proper recorded data of ultrasonography and blood tests, and who resided in the same city for at least five years were included. Patients with anemia, hyperlipidemia, diabetes mellitus, hypertension, and those who did not meet the inclusion criteria were excluded. Patients were divided into two groups: high altitude group (HAG) and sea level group (SLG). CAU findings of each patient-including common carotid artery intima-media thickness (CIMT) ≥1 mm and <1 mm, internal carotid artery (ICA) stenosis rate, and plaque types-were recorded and compared between the two groups. Blood test parameters and lipid profiles were additionally recorded. RESULTS: Prevalence of patients with CIMT ≥1 mm was significantly higher in the SLG (SLG: 50%, HAG: 15.6%; P<0.001). Carotid stenosis was found to be significantly different in both groups (HAG: 9.96%±23.27%, SLG: 29.83%±23.30%; P<0.001). RBC, HGB, HDL values, and HDL/LDL ratio were found to be significantly higher in the HAG (P<0.001) whereas LDL, TG, and TC values were significantly higher in the SLG (P<0.001). CONCLUSIONS: People who reside at high altitudes have significantly lower rate of carotid stenosis, lower CIMT values, and less atherogenic lipid profile values, all of which indicate protective effect of high altitude on atherosclerosis.

[2] *Ebell MH*. **Lipid Lowering Is Beneficial for Secondary Prevention but Not Primary Prevention in Patients 75 Years and Older**. American family physician 2021; 103:695-696.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=34060787
ABSTRACT

[3] *Okkonen M, Havulinna AS, Ukkola O et al.* **Risk factors for major adverse cardiovascular events after the first acute coronary syndrome**. Annals of medicine 2021; 53:817-823.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=34080496
ABSTRACT
AIMS: To evaluate risk factors for major adverse cardiac event (MACE) after the first acute coronary syndrome (ACS) and to examine the prevalence of risk factors in post-ACS patients. METHODS: We used Finnish population-based myocardial infarction register, FINAMI, data from years 1993-2011 to identify survivors of first ACS (n = 12686), who were then followed up for recurrent events and all-cause mortality for three years. Finnish FINRISK risk factor surveys were used to determine the prevalence of risk factors (smoking, hyperlipidaemia, diabetes and blood pressure) in post-ACS patients (n = 199). RESULTS: Of the first ACS survivors, 48.4% had MACE within three years of their primary event, 17.0% were fatal. Diabetes (p = 4.4 × 10(-7)), heart failure (HF) during the first ACS attack hospitalization (p = 6.8 × 10(-15)), higher Charlson index (p = 1.56 × 10(-19)) and older age (p = .026) were associated with elevated risk for MACE in the three-year follow-up, and revascularization (p = .0036) was associated with reduced risk. Risk factor analyses showed that 23%

of ACS survivors continued smoking and cholesterol levels were still high (>5mmol/l) in 24% although 86% of the patients were taking lipid lowering medication. CONCLUSION: Diabetes, higher Charlson index and HF are the most important risk factors of MACE after the first ACS. Cardiovascular risk factor levels were still high among survivors of first ACS.

[4] *He Z, Yuan J, Shen F et al.* **Atorvastatin Enhances Inhibitory Effects of Irradiation on Tumor Growth by Reducing MSH2 Expression both in Prostate Cancer Cells and Xenograft Tumor Models**. Anticancer Agents Med Chem 2021.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=34080969
ABSTRACT
BACKGROUND: Prostate cancer (PCa) is the fourth most common tumor in males. OBJECTIVE: To investigate effects of atorvastatin (AS) on PCa cells proliferation and clarify the associated mechanisms. METHODS: PCa cell lines were cultured and treated with irradiation (IR) (4 Gy), AS (6 μg/ml), transfected with Bcl-2 siRNA, and then divided into different groups. Xenograft tumor mouse model was established. Bcl-2 and MSH2 gene transcription and protein expression were evaluated using RT-PCR assay and western blot assay. Plate clone formation assay was employed to examine colony formation. MTT assay was used to detect cell viabilities. Flow cytometry analysis was utilized to verify apoptosis. Co-immunoprecipitation and immuno-fluorescence assay were used to identify interaction between Bcl-2 and MSH2. RESULTS: IR significantly reduced colony formation, enhanced Bcl-2 and reduced MSH2 gene transcription in PCa cells compared to un-treated cells ($p<0.05$). AS significantly strengthened radio-therapeutic effects of IR on colony formation, decreased cell apoptosis and increased Bcl-2 gene transcription/protein expression in PCa cells compared to single IR treatment cells ($p<0.05$). AS combining IR down-regulated MSH2 gene transcription/protein expression in PCa cells compared to single IR treatment cells ($p<0.05$). Bcl-2 interacted with MSH2 both in PCa cells and tumor tissues administrating with AS. AS enhanced reductive effects of IR on tumor size of Xenograft tumor mice. CONCLUSION: Atorvastatin administration enhanced inhibitory effects of IR either on PCa cells or on tumor size of Xenograft tumor mice. The inhibitory effects of atorvastatin were mediated by reducing MSH2 expression and triggering interaction between Bcl-2 and MSH2, both in vitro and in vivo levels.

[5] *Islam SU, Ahmed MB, Ahsan H, Lee YS*. **Recent Molecular Mechanisms and Beneficial Effects of Phytochemicals and Plant-Based Whole Foods in Reducing LDL-C and Preventing Cardiovascular Disease**. Antioxidants (Basel, Switzerland) 2021; 10.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=34063371
ABSTRACT
Abnormal lipid metabolism leads to the development of hyperlipidemia, a common cause of multiple chronic disorders, including cardiovascular disease (CVD), obesity, diabetes, and cerebrovascular disease. Low-density lipoprotein cholesterol (LDL-C) currently remains the primary target for treatment of hyperlipidemia. Despite the advancement of treatment and prevention of hyperlipidemia, medications used to manage hyperlipidemia are limited to allopathic drugs, which present certain limitations and adverse effects. Increasing evidence indicates that utilization of phytochemicals and plant-based whole foods is an alternative and promising strategy to prevent hyperlipidemia and CVD. The current review focuses on phytochemicals and their pharmacological mode of actions for the regulation of LDL-C and prevention of CVD. The important molecular mechanisms illustrated in detail

in this review include elevation of reverse cholesterol transport, inhibition of intestinal cholesterol absorption, acceleration of cholesterol excretion in the liver, and reduction of cholesterol synthesis. Moreover, the beneficial effects of plant-based whole foods, such as fresh fruits, vegetables, dried nuts, flax seeds, whole grains, peas, beans, vegan diets, and dietary fibers in LDL-C reduction and cardiovascular health are summarized. This review concludes that phytochemicals and plant-based whole foods can reduce LDL-C levels and lower the risk for CVD.

[6] *Blais JE, Wei Y, Yap KKW et al.* **Trends in lipid-modifying agent use in 83 countries**. Atherosclerosis 2021; 328:44-51.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=34091069

ABSTRACT

BACKGROUND AND AIMS: Lipid-modifying agents (LMAs) are increasingly used to reduce lipid levels and prevent cardiovascular events but the magnitude of their consumption in different world regions is unknown. We aimed to describe recent global trends in LMA consumption and to explore the relationship between country-level LMA consumption and cholesterol concentrations. METHODS: This cross-sectional and ecological study used monthly pharmaceutical sales data from January 2008 to December 2018 for 83 countries from the IQVIA Multinational Integrated Data Analysis System and total and non-high-density lipoprotein (non-HDL) cholesterol concentrations from the NCD Risk Factor Collaboration. Compound annual growth rate (CAGR) was used to assess changes in LMA consumption over time. RESULTS: From 2008 to 2018, use of LMAs increased from 7468 to 11,197 standard units per 1000 inhabitants per year (CAGR 4.13%). An estimated 173 million people used LMAs in 2018. Statins were the most used class of LMA and their market share increased in 75% of countries between 2008 and 2018. From 2013 to 2018, consumption of low-density lipoprotein lowering therapies increased (statins 3.99%; ezetimibe 4.01%; proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitors 104.47%). Limited evidence supports a clear relationship between country-level changes in LMA consumption and mean total and non-HDL cholesterol concentrations in 2008 versus 2018. CONCLUSIONS: Since 2008, global access to LMAs, especially statins, has improved. In line with international lipid guideline recommendations, recent trends indicate growth in the use of statins, ezetimibe, and PCSK9 inhibitors. Country-level patterns of LMA use and total and non-HDL cholesterol varied considerably.

[7] *Khalil YA, Rabès JP, Boileau C, Varret M.* **APOE gene variants in primary dyslipidemia**. Atherosclerosis 2021; 328:11-22.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=34058468

ABSTRACT

Apolipoprotein E (apoE) is a major apolipoprotein involved in lipoprotein metabolism. It is a polymorphic protein and different isoforms are associated with variations in lipid and lipoprotein levels and thus cardiovascular risk. The isoform apoE4 is associated with an increase in LDL-cholesterol levels and thus a higher cardiovascular risk compared to apoE3. Whereas, apoE2 is associated with a mild decrease in LDL-cholesterol levels. In the presence of other risk factors, apoE2 homozygotes could develop type III hyperlipoproteinemia (familial dysbetalipoproteinemia or FD), an atherogenic disorder characterized by an accumulation of remnants of triglyceride-rich lipoproteins. Several rare APOE gene variants were reported in different types of dyslipidemias including FD, familial combined hyperlipidemia (FCH), lipoprotein glomerulopathy and bona fide autosomal dominant

hypercholesterolemia (ADH). ADH is characterized by elevated LDL-cholesterol levels leading to coronary heart disease, and due to molecular alterations in three main genes: LDLR, APOB and PCSK9. The identification of the APOE-p.Leu167del variant as the causative molecular element in two different ADH families, paved the way to considering APOE as a candidate gene for ADH. Due to non mendelian interacting factors, common genetic and environmental factors and perhaps epigenetics, clinical presentation of lipid disorders associated with APOE variants often strongly overlap. More studies are needed to determine the spectrum of APOE implication in each of the diseases, notably ADH, in order to improve clinical and genetic diagnosis, prognosis and patient management. The purpose of this review is to comment on these APOE variants and on the molecular and clinical overlaps between dyslipidemias.

[8] *Mahboobnia K, Pirro M, Marini E et al.* **PCSK9 and cancer: Rethinking the link**. Biomedicine & pharmacotherapy = Biomedecine & pharmacotherapie 2021; 140:111758.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=34058443

ABSTRACT

BACKGROUND: Cancer is emerging as a major problem globally, as it accounts for the second cause of death despite medical advances. According to epidemiological and basic studies, cholesterol is involved in cancer progression and there are abnormalities in cholesterol metabolism of cancer cells including prostate, breast, and colorectal carcinomas. However, the importance of cholesterol in carcinogenesis and thereby the role of cholesterol homeostasis as a therapeutic target is still a debated area in cancer therapy. Proprotein convertase subtilisin/kexin type-9 (PCSK9), a serine protease, modulates cholesterol metabolism by attachment to the LDL receptor (LDLR) and reducing its recycling by targeting the receptor for lysosomal destruction. Published research has shown that PCSK9 is also involved in degradation of other LDLR family members namely very-low-density-lipoprotein receptor (VLDLR), lipoprotein receptor-related protein 1 (LRP-1), and apolipoprotein E receptor 2 (ApoER2). As a result, this protein represents an interesting therapeutic target for the treatment of hypercholesterolemia. Interestingly, clinical trials on PCSK9-specific monoclonal antibodies have reported promising results with high efficacy in lowering LDL-C and in turn reducing cardiovascular complications. It is important to note that PCSK9 mediates several other pathways apart from its role in lipid homeostasis, including antiviral activity, hepatic regeneration, neuronal apoptosis, and modulation of various signaling pathways. Furthermore, recent literature has illustrated that PCSK9 is closely associated with incidence and progression of several cancers. In a number of studies, PCSK9 siRNA was shown to effectively suppress the proliferation and invasion of the several studied tumor cells. Hence, a novel application of PCSK9 inhibitors/silencers in cancer/metastasis could be considered. However, due to poor data on effectiveness and safety of PCSK9 inhibitors in cancer, the impact of PCSK9 inhibition in these pathological conditions is still unknown. SEARCH METHODS: A vast literature search was conducted to find intended studies from 1956 up to 2020, and inclusion criteria were original peer-reviewed publications. PURPOSE OF REVIEW: To date, PCSK9 has been scantly investigated in cancer. The question that needs to be discussed is "How does PCSK9 act in cancer pathophysiology and what are the risks or benefits associated to its inhibition?". We reviewed the available publications highlighting the contribution of this proprotein convertase in pathways related to cancer, with focus on the potential implications of its long-term pharmacological inhibition in cancer therapy.

[9] *Magro Dos Reis I, Houben T, Gijbels MJJ et al.* **Anti-Inflammatory Effects of Dietary Plant Stanol Supplementation Are Largely Dependent on the Intake of Cholesterol in a Mouse Model of Metabolic Inflammation**. Biomedicines 2021; 9.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=34066407

ABSTRACT
The prevalence of metabolic disorders characterized by chronic inflammation has been on a sharp rise for decades. As such, tools that address metabolic and inflammatory dysregulation are of great importance. Plant stanols are well-known for reducing intestinal cholesterol absorption and may also have direct anti-inflammatory effects. In this study, our aim was to investigate to what extent the benefits of dietary plant stanol supplementation depend on dietary cholesterol intake in an experimental mouse model for cholesterol-induced metabolic inflammation. Here, we used Ldlr(-/-) mice transplanted with Npc1(nih)-derived bone marrow, featuring feature bone marrow-derived immune cells characterized by chronic inflammation induced by lysosomal lipid accumulation. Npc1(nih)- and Npc1(wt)-transplanted mice were placed on either a high fat, high cholesterol (HFC) or on a chow diet low in cholesterol, with or without 2% plant stanols supplementation. At the end of the study, the metabolic and inflammatory status of the mice was analyzed. Plant stanol supplementation to the HFC diet reduced liver cholesterol levels and improved lipid metabolism and liver inflammation, particularly in Npc1(nih)-tp mice. In contrast, plant stanol supplementation to the chow diet did not significantly improve the aforementioned parameters, though similar reductive trends to those in the HFC diet setting were observed regarding liver cholesterol accumulation and liver inflammatory markers. The effects of dietary plant stanol supplementation on dietary cholesterol-induced inflammation are largely dependent on dietary cholesterol intake. Future research should verify whether other models of metabolic inflammation exhibit similar stanol-related effects on inflammation.

[10] *Trakaki A, Marsche G*. **Current Understanding of the Immunomodulatory Activities of High-Density Lipoproteins**. Biomedicines 2021; 9.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=34064071

ABSTRACT
Lipoproteins interact with immune cells, macrophages and endothelial cells - key players of the innate and adaptive immune system. High-density lipoprotein (HDL) particles seem to have evolved as part of the innate immune system since certain HDL subspecies contain combinations of apolipoproteins with immune regulatory functions. HDL is enriched in anti-inflammatory lipids, such as sphingosine-1-phosphate and certain saturated lysophospholipids. HDL reduces inflammation and protects against infection by modulating immune cell function, vasodilation and endothelial barrier function. HDL suppresses immune cell activation at least in part by modulating the cholesterol content in cholesterol/sphingolipid-rich membrane domains (lipid rafts), which play a critical role in the compartmentalization of signaling pathways. Acute infections, inflammation or autoimmune diseases lower HDL cholesterol levels and significantly alter HDL metabolism, composition and function. Such alterations could have a major impact on disease progression and may affect the risk for infections and cardiovascular disease. This review article aims to provide a comprehensive overview of the immune cell modulatory activities of HDL. We focus on newly discovered activities of HDL-associated apolipoproteins, enzymes, lipids, and HDL mimetic peptides.

[11] *Wilms T, Boldrup L, Gu X et al.* **High Levels of Low-Density Lipoproteins Correlate with Improved Survival in Patients with Squamous Cell Carcinoma of the Head and Neck**. Biomedicines 2021; 9.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=34064440
ABSTRACT
Circulating lipoproteins as risk factors or prognostic indicators for various cancers have been investigated previously; however, no clear consensus has been reached. In this study, we aimed at evaluating the impact of serum lipoproteins on the prognosis of patients with squamous cell carcinoma of the head and neck (SCCHN). Levels of total cholesterol, low-density lipoproteins (LDL), high-density lipoproteins (HDL), triglycerides and lipoprotein(a) were measured in serum samples from 106 patients and 28 healthy controls. We found that HDL was the only lipoprotein exhibiting a significant difference in concentration between healthy controls and patients ($p = 0.012$). Kaplan-Meier survival curves indicated that patients with high levels of total cholesterol or LDL had better overall survival than patients with normal levels ($p = 0.028$ and $p = 0.007$, respectively). Looking at patients without lipid medication ($n = 89$) and adjusting for the effects of TNM stage and weight change, multivariate Cox regression models indicated that LDL was an independent prognostic factor for both overall ($p = 0.005$) and disease-free survival ($p = 0.013$). In summary, our study revealed that high LDL level is beneficial for survival outcome in patients with SCCHN. Use of cholesterol-lowering medicines for prevention or management of SCCHN needs to be evaluated carefully.

[12] *Yuvaraj J, Cheng K, Lin A et al.* **The Emerging Role of CT-Based Imaging in Adipose Tissue and Coronary Inflammation**. Cells 2021; 10.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=34068406
ABSTRACT
A large body of evidence arising from recent randomized clinical trials demonstrate the association of vascular inflammatory mediators with coronary artery disease (CAD). Vascular inflammation localized in the coronary arteries leads to an increased risk of CAD-related events, and produces unique biological alterations to local cardiac adipose tissue depots. Coronary computed tomography angiography (CTA) provides a means of mapping inflammatory changes to both epicardial adipose tissue (EAT) and pericoronary adipose tissue (PCAT) as independent markers of coronary risk. Radiodensity or attenuation of PCAT on coronary CTA, notably, provides indirect quantification of coronary inflammation and is emerging as a promising non-invasive imaging implement. An increasing number of observational studies have shown robust associations between PCAT attenuation and major coronary events, including acute coronary syndrome, and 'vulnerable' atherosclerotic plaque phenotypes that are associated with an increased risk of the said events. This review outlines the biological characteristics of both EAT and PCAT and provides an overview of the current literature on PCAT attenuation as a surrogate marker of coronary inflammation.

[13] *Zhang HJ, Wang YY, Chen C et al.* **Cardiovascular and renal burdens of metabolic associated fatty liver disease from serial US national surveys, 1999-2016**. Chinese medical journal 2021.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=34091530
ABSTRACT

BACKGROUND: Non-communicable chronic diseases have become the leading causes of disease burden worldwide. The trends and burden of "metabolic associated fatty liver disease" (MAFLD) are unknown. We aimed to investigate the cardiovascular and renal burdens in adults with MAFLD and non-alcoholic fatty liver disease (NAFLD). METHODS: Nationally representative data were analyzed including data from 19,617 non-pregnant adults aged ≥20 years from the cross-sectional US National Health and Nutrition Examination Survey periods, 1999 to 2002, 2003 to 2006, 2007 to 2010, and 2011 to 2016. MAFLD was defined by the presence of hepatic steatosis plus general overweight/obesity, type 2 diabetes mellitus, or evidence of metabolic dysregulation. RESULTS: The prevalence of MAFLD increased from 28.4% (95% confidence interval 26.3-30.6) in 1999 to 2002 to 35.8% (33.8-37.9) in 2011 to 2016. In 2011 to 2016, among adults with MAFLD, 49.0% (45.8-52.2) had hypertension, 57.8% (55.2-60.4) had dyslipidemia, 26.4% (23.9-28.9) had diabetes mellitus, 88.7% (87.0-80.1) had central obesity, and 18.5% (16.3-20.8) were current smokers. The 10-year cardiovascular risk ranged from 10.5% to 13.1%; 19.7% (17.6-21.9) had chronic kidney diseases (CKDs). Through the four periods, adults with MAFLD showed an increase in obesity; increase in treatment to lower blood pressure (BP), lipids, and hemoglobin A1c; and increase in goal achievements for BP and lipids but not in goal achievement for glycemic control in diabetes mellitus. Patients showed a decreasing 10-year cardiovascular risk over time but no change in the prevalence of CKDs, myocardial infarction, or stroke. Generally, although participants with NAFLD and those with MAFLD had a comparable prevalence of cardiovascular disease and CKD, the prevalence of MAFLD was significantly higher than that of NAFLD. CONCLUSIONS: From 1999 to 2016, cardiovascular and renal risks and diseases have become highly prevalent in adults with MAFLD. The absolute cardiorenal burden may be greater for MAFLD than for NAFLD. These data call for early identification and risk stratification of MAFLD and close collaboration between endocrinologists and hepatologists.

[14] *Roberts R, Fair J*. **Genetics, its role in preventing the pandemic of coronary artery disease**. Clinical cardiology 2021; 44:771-779.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=34080689

ABSTRACT

Epidemiologists have claimed for decades that about 50% of predisposition for coronary artery disease (CAD) is genetic. Advances in technology made possible the discovery of hundreds of genetic risk variants predisposing to CAD. Multiple clinical trials have shown that cardiac events can be prevented by drugs to lower plasma low-density lipoprotein cholesterol (LDL-C). A major barrier to primary prevention is the lack of markers to identify those individuals at risk prior to the development of symptoms of the disease. Conventional risk factors are age-dependent, occurring mostly in the sixth or seventh decade, which is less than desirable for early primary prevention. A polygenic risk score, derived from the number of genetic risk variants predisposing to CAD inherited by an individual, has been evaluated in over 1 million individuals. The risk for CAD is stratified into high, intermediate, and low. Polygenic risk scores derived from retrospective genotyping of several clinical trials evaluating the effect of statin therapy or PCSK9 inhibitors show the genetic risk is reduced 40%-50% by decreasing plasma LDL-C. Prospective randomized placebo-controlled clinical trials document a 40%-50% reduction in cardiac events in individuals at high genetic risk associated with favorable lifestyle changes and increased physical activity. The polygenic risk score is not age-dependent and remains the same throughout life. Thus, the GRS is superior to conventional risk factors in identifying asymptomatic individuals at risk for CAD early in life for primary prevention.

These results indicate clinical embracement of the GRS in primary prevention would be a paradigm shift in the treatment of the number one killer, CAD.

[15] *Aneri M, Fernández G, Gras M et al.* **Degree of lipid control in a Healthcare Management Area in patients at very high cardiovascular risk**. Clinica e investigacion en arteriosclerosis : publicacion oficial de la Sociedad Espanola de Arteriosclerosis 2021.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=34090715

ABSTRACT

INTRODUCTION: The latest cardiovascular risk guides, European and American, establish hard lipid control objectives, that suppose a therapeutic challenge for both, doctor and patient. The objective of this study is determine the degree of adequacy of low-density lipoprotein cholesterol levels (LDLc) presented by patients with very high cardiovascular risk in our healthcare area, with respect to European and American cardiovascular risk guidelines. METHODS: This is an observational and retrospective study of 446 patients discharged between June 2017 and June 2018 with a diagnosis of acute coronary syndrome, ischemic stroke and peripheral arterial disease. We have defined a series of variables among which we want to highlight the levels of LDLc at admission, and its follow-up at discharge, in order to know the degree of lipid control according to current European guidelines, which set the threshold to consider optimal control in patients of very high cardiovascular risk, below 55mg/dl. RESULTS: The revised data indicates a control of the patients in 36.6% according to the 2016 guidelines (LDLc <70mg/dl) and 14.8% according to the current 2019 guidelines (LDLc <55mg/dl), 75.3% of them received lipid lowering treatment. We have also found that the number of absolute events increases exponentially depending on the levels of LDLc, being more evident in patients with acute coronary syndrome. CONCLUSIONS: In this study, we demonstrated that the adequacy of the vascular risk clinical practice guidelines is insufficient in the population with very high vascular risk, in line with other published studies, further studies would be needed to determine the causes. A solution to this problem could be collaboration with the Internal Medicine service that has been launched in our healthcare area in order to derivate patients to the Vascular Consultation whom could be beneficiated by the administration of the PCSK9 inhibitors.

[16] *Maravilla Domínguez MA, Zermeño González ML, Zavaleta Muñiz ER et al.* **Inflammation and atherogenic markers in patients with type 2 diabetes mellitus**. Clinica e investigacion en arteriosclerosis : publicacion oficial de la Sociedad Espanola de Arteriosclerosis 2021.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=34090713

ABSTRACT

Type two diabetes mellitus (T2DM) is characterized by a chronic inflammation status. Altered markers such as lipid concentrations are usually found in this disease. Elevated inflammation markers have been described such as cytokines (interleukin 6, tumour necrosis factor-alpha, and IL-8). However, there is a lack of information about the behaviour of the neutrophil-lymphocyte ratio (NLR), platelet-lymphocyte ratio (PLR), lymphocyte-monocyte ratio (LMR), lipid coefficients, and atherogenic index in T2DM. OBJECTIVE: To describe the atherogenic and inflammation parameters in a group of patients with T2DM. MATERIALS AND METHODS: 42 patients with T2DM were included, all patients were surveyed on clinic history (disease history, comorbidity, smoking, and other relevant variables), measurements of haematological, biochemical, and anthropometric parameters were taken and atherogenic coefficients and inflammation ratios were calculated. RESULTS: Inflammation markers

such as interleukin 6 and 8, necrosis tumour factor, and NLR were elevated. Of the patients, 88% were classified as high risk according to the atherogenic index. Former smokers had lower levels of IL-8 and higher NLR than non-smokers. CONCLUSION: The atherogenic and inflammation markers such as atherogenic index, IL-8, and NLR make it possible to identify a subgroup of patients that are at risk of severe complications and mortality.

[17] *Minhas A, Cubero Salazar I, Kazzi B et al.* **Sex-Specific Plaque Signature: Uniqueness of Atherosclerosis in Women**. Current cardiology reports 2021; 23:84.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=34081222
ABSTRACT
PURPOSE OF REVIEW: Cardiovascular disease is a leading cause of morbidity and mortality in both men and women, although there are notable differences in presentation between men and women. Atherosclerosis remains the predominant driver of coronary heart disease in both sexes; however, sex differences in atherosclerosis should be investigated further to understand clinical manifestations between men and women. RECENT FINDINGS: There are sex differences in the prevalence, progression, and prognostic impact of atherosclerosis. Furthermore, developing evidence demonstrates unique differences in atherosclerotic plaque characteristics between men and women on both noninvasive and invasive imaging modalities. Coronary microvascular dysfunction may be present even if no obstructive lesions are found. Most importantly, non-obstructive coronary artery disease is associated with a heightened risk of future adverse cardiovascular events and should not be ignored. The distinct plaque signature in women should be recognized, and optimal preventive strategies should be performed for both sexes.

[18] *Rached F, Santos RD*. **Beyond Statins and PCSK9 Inhibitors: Updates in Management of Familial and Refractory Hypercholesterolemias**. Current cardiology reports 2021; 23:83.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=34081216
ABSTRACT
PURPOSE OF REVIEW: Elevation in apolipoprotein B-containing lipoproteins in the blood is a cause of atherosclerosis. Statins have changed the preventive cardiology scenario, and more recently monoclonal proprotein convertase subtilisin kexin type 9 (PCSK9) inhibitors were added as robust agents to further reduce pro-atherogenic lipoproteins and therefore prevent cardiovascular events. However, despite this many dyslipidemic individuals persist with inadequate LDL-C levels and still at risk. The purpose of this review was to discuss current status and describe advances in therapies beyond statins and monoclonal PCSK9 inhibitors. RECENT FINDINGS: Ezetimibe and lomitapide have been used for many years to further reduce LDL-C and longer term data reinforce their safety. Bempedoic acid, an inhibitor of adenosine triphosphate-citrate lyase, has been shown to add LDL-C reduction on top of statins and ezetimibe, furthermore it may be an alternative for statin intolerant patients. Inclisiran is a small interfering ribonucleic acid inhibitor that reduces the hepatic production of PCSK9 that induces robust LDL-C lowering, similar to monoclonal antibodies, with the advantage of 2 or 3 injections per year. So far, no safety signs were seen with its use. Evinacumab, a monoclonal antibody that binds angiopoietin-like protein 3 (ANGPTL3), induces robust LDL-C lowering in either homozygous familial hypercholesterolemia or severe hypercholesterolemia patients with good tolerability. Many high-risk individuals persist with elevated LDL-C, newer medications

further lower LDL-C on top of standard lipid-lowering therapies and are well tolerated. Ongoing clinical trials may prove if these novel medications will reduce cardiovascular events with safety.

[19] *Xiang Q, Liu W, Zeng J et al.* **Effect of PCSK9 on Vascular Smooth Muscle Cell Functions: A New Player in Atherosclerosis**. Curr Med Chem 2021.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=34060998
ABSTRACT
Proprotein convertase subtilisin/kexin type 9 (PCSK9) is a secretory serine protease that plays multiple biological functions in the regulation of physiological and pathological processes. PCSK9 inhibitors decrease the circulating LDL-cholesterol level with well-known preventive and therapeutic effects on atherosclerosis (AS), but increasing evidence shows that the direct impact of PCSK9 on the vascular wall also plays an important role in atherosclerotic progression. Compared with other vascular cells, a large proportion of PCSK9 is originated from vascular smooth muscle cells (VSMC). Therefore, defining the effect of VSMC-derived PCSK9 on response changes, such as phenotypic switch, apoptosis, autophagy, inflammation, foam cell formation, and calcification of VSMC, helps us better understand the "pleiotropic" effects of VSMC on the atherosclerotic process. In addition, our understanding of the mechanisms of PCSK9 controlling VSMC functions in vivo is far from enough. This review aims to holistically evaluate and analyze the current state of our knowledge regarding PCSK9 actions affecting on VSMC functions and its mechanism in atherosclerotic lesion development. A mechanistic understanding of PCSK9 effects on VSMC will further underpin the success of a new therapeutic strategy targeting AS.

[20] *Härdtner C, Ehlert CA, Hilgendorf I.* **New insights in statins affecting atheromatous plaque macrophages**. Current opinion in lipidology 2021; 32:258-264.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=34054106
ABSTRACT
PURPOSE OF REVIEW: Macrophages are key protagonists of atherosclerotic plaque development and hence represent targets of therapeutic intervention. Statins are the most potent widely used atheroprotective drugs. Therefore, whether and how statins influence atheromatous plaque macrophages has remained at the center of cardiovascular research for decades. RECENT FINDINGS: Because statins are capable of regulating macrophage functions in cell culture, largely independent of their cholesterol-lowering effect, it was assumed that these pleiotropic effects operate in vivo as well. Recent experimental data, in line with clinical observations, indicate, however, that statins do not interact with macrophages in atherosclerotic plaques, directly, and instead control their functions and assembly indirectly via changes to circulating lipid levels and endothelial activation. SUMMARY: Statin-mediated lipid lowering induces plaque regression which is characterized by a decline in plaque macrophage content. Understanding how statins provoke this protective phenotype may inspire conceptually new therapeutic approaches in cardiovascular medicine.

[21] *Petrelli A, Ravà L, Mascali A et al.* **Estimated insulin sensitivity, cardiovascular risk, and hepatic steatosis after 12 years from the onset of T1D**. Diabetes/metabolism research and reviews 2021:e3479.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=34077603
ABSTRACT

AIM: To test the hypothesis that intensive insulin treatment and optimal glycaemic control are not fully protective against reduction of insulin sensitivity in children with type 1 diabetes. MATERIAL AND METHODS: Cohort study of 78 normal-weight patients with prepubertal onset (T (0)) and follow-up waves at 1 (T (1)), 5 (T (5)), 10 (T (10)), and 12 (T (12)) years; matched for age and sex to 30 controls at T (12) . Estimated insulin sensitivity (eIS) by three formulae; ultrasound evaluation of para and perirenal fat thickness; hepatic steatosis (HS); carotid intima media thickness (cIMT) at T (12) . RESULTS: At T12, the 36 patients (46%) who had constantly or prevalently haemoglobin A1c (HbA1c) < 58 mmol/l during follow-up showed better eIS indexes (p = 0.049 to <0.0001); lipid profile (p = 0.042 to <0.0001), reduced fat mass (p = 0.012) and required lower insulin dose (p = 0.032) than the 42 patients (54%) with HbA1c ≥ 58 at T12. Patients (N = 25) with eIS(EDC) < 8.77 mg kg(-1) min(-1) showed higher cIMT (p < 0.0001). HS was found in 6 patients (~8%). In patients and normal-weight controls, fat mass (p = 0.03), age (p = 0.03), cIMT (p = 0.05) predicted HS; eIS indexes (p from 0.04 to <0.0001) predicted cIMT. Body mass index, perirenal fat, fat mass, and triglycerides to high density lipoprotein cholesterol ratio were associated with eIS indexes (p from 0.03 to <0.0001). CONCLUSIONS: Young T1D patients have reduced insulin sensitivity and higher cIMT. Adiposity, glucose, and lipid control over follow-up are likely to influence both. Enhanced adiposity seems of paramount relevance for the onset of HS in T1D patients alike in healthy youths.

[22] *Tarry-Adkins JL, Grant ID, Ozanne SE et al.* **Efficacy and Side Effect Profile of Different Formulations of Metformin: A Systematic Review and Meta-Analysis**. Diabetes Ther 2021.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=34075573

ABSTRACT

INTRODUCTION: Metformin is among the most frequently prescribed drugs worldwide for a variety of indications. Although metformin has several important advantages, for example being easy to store and administer, it is associated with a high incidence of gastrointestinal side effects. Slower-release formulations of metformin may reduce the incidence of side effects while maintaining efficacy; however, there is a lack of systematic evidence available to guide head-to-head comparisons between different metformin formulations. METHODS: PubMed, Web of Science, OVID EMBASE, MEDLINE, The Cochrane database and Clinicaltrials.gov were systematically searched (from inception to 25 January 2021). Trials that randomized adult participants to extended-release formulation of metformin (met-XR), delayed-release (met-DR) or immediate-release metformin (met-IR) were included. Two reviewers independently assessed articles for eligibility and risk-of-bias, with conflicts resolved by a third reviewer. Outcome measures were change in fasting plasma glucose (FPG), glycated haemoglobin (HbA1c), body weight, BMI, lipid profile and side effects. Meta-analyses were conducted using random-effects models. RESULTS: Fifteen studies (n = 3765) met eligibility criteria. There was no significant difference between the efficacy of met-IR, met-XR or met-DR in changing FPG (p = 0.93). A non-significant reduction in mean body weight was observed in individuals randomized to met-XR vs. met-IR (- 1.03 kg, 95% CI - 2.12 to 0.05, p = 0.06). Individuals randomized to met-XR vs. met-IR had lower low-density lipoprotein (LDL) cholesterol levels (- 5.73 mg/dl, 95% CI - 7.91 to - 3.56, p < 0.00001). Gastrointestinal (GI) side effects were markedly reduced in patients randomised to met-DR vs. met-IR (OR 0.45, 95% CI 0.26-0.80, p = 0.006). CONCLUSION: Our results demonstrate equal efficacy of longer-acting formulations (met-XR, met-DR) versus immediate-release metformin formulations in terms of glycaemic control. There were insufficient studies available to compare the efficacy of different metformin formulations outside of diabetes care. However met-XR

was associated with reduced serum LDL cholesterol concentrations, while met-DR was strongly associated with reduced GI side effects, which could improve drug compliance.

[23] *Kosmas CE, Muñoz Estrella A, Sourlas A, Pantou D*. **Inclisiran in dyslipidemia**. Drugs of today (Barcelona, Spain : 1998) 2021; 57:311-319.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=34061126
ABSTRACT
Cardiovascular disease (CVD) is the leading cause of death worldwide. Hypercholesterolemia has been shown to be one of the most important risk factors for CVD. Statins are currently the standard of care for the management of hypercholesterolemia. However, certain patients on statin therapy fail to achieve the desired low-density lipoprotein cholesterol (LDL-C) goals or are intolerant to statins due to side effects (mostly myalgias). The discovery of proprotein convertase subtilisin/kexin type 9 (PCSK9) and the subsequent development of PCSK9 inhibitors provided another route to lower LDL-C levels by increasing recycling of LDL receptors (LDLR) in the hepatocytes. More recently, inclisiran, a small interfering RNA (siRNA) molecule, which increases the number of LDLR in the hepatocyte membranes by halting the transcription of PCSK9, has emerged as a novel promising agent for the management of hypercholesterolemia. Inclisiran received marketing authorization in the European Union in December 2020 for use in adults with primary hypercholesterolemia or mixed dyslipidemia. This review aims to focus on the role of inclisiran in the management of hypercholesterolemia.

[24] *You A, Li Y, Tomlinson B et al.* **Association Between Renal Dysfunction and Low HDL Cholesterol Among the Elderly in China**. Frontiers in cardiovascular medicine 2021; 8:644208.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=34055931
ABSTRACT
Objective: Chronic kidney disease (CKD) and cardiovascular disease (CVD) have a high morbidity and mortality among the elderly. Low levels of high-density lipoprotein cholesterol (HDL-C), a traditional risk marker for CVD, are common in CKD patients. Little is known about the association of low HDL-C with renal dysfunction in the community dwelling population. Methods: This was a population-based cross-sectional study included 4,753 participants enrolled in a prospective study, the Shanghai Elderly Cardiovascular Health (SHECH) study. Estimated glomerular filtration rate (eGFR), calculated by the Chinese Modification of Diet in Renal Disease (C-MDRD equation), was used to assess renal dysfunction. Associations between renal dysfunction and low HDL-C were evaluated using multiple logistic regression models and restricted cubic splines. Results: Of 4,649 individuals who met inclusion criteria, 620 (13.34%) had low HDL-C at <40 mg/dl. In the fully adjusted model, lower eGFR of <60 ml/min/1.73 m(2) (OR, 2.03; 95% CI, 1.21-3.43) and marginal eGFR of 60 to 90 ml/min/1.73 m(2) (OR, 1.26; 95% CI, 1.01-1.58) were significantly associated with low HDL-C, compared with normal eGFR of ≥90 ml/min/1.73 m(2). Moreover, consistent findings were obtained in subsidiary analyses using the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation. Fully adjusted cubic spline models indicated a significant dose-response relationship between eGFR and low HDL-C (P for non-linearity, 0.356). Conclusion: In this general elderly population, renal dysfunction was independently and significantly associated with low HDL-C, and the prevalence of low HDL-C increased with decreasing eGFR, such that even slight changes in renal function may be associated with altered lipid levels.

[25] *Kashefiolasl S, Wagner M, Brawanski N et al.* **Statins Improve Clinical Outcome After Non-aneurysmal Subarachnoid Hemorrhage: A Translational Insight From a Systematic Review of Experimental Studies**. Frontiers in neurology 2021; 12:620096.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=34054685

ABSTRACT

The efficacy of statin-treatment in aneurysmal subarachnoid hemorrhage (SAH) remains controversial. We aimed to investigate the effects of statin-treatment in non-aneurysmal (na)SAH in accordance with animal research data illustrating the pathophysiology of naSAH. We systematically searched PubMed using PRISMA-guidelines and selected experimental studies assessing the statin-effect on SAH. Detecting the accordance of the applied experimental models with the pathophysiology of naSAH, we analyzed our institutional database of naSAH patients between 1999 and 2018, regarding the effect of statin treatment in these patients and creating a translational concept. Patient characteristics such as statin-treatment (simvastatin 40 mg/d), the occurrence of cerebral vasospasm (CVS), delayed infarction (DI), delayed cerebral ischemia (DCI), and clinical outcome were recorded. In our systematic review of experimental studies, we found 13 studies among 18 titles using blood-injection-animal-models to assess the statin-effect in accordance with the pathophysiology of naSAH. All selected studies differ on study-setting concerning drug-administration, evaluation methods, and neurological tests. Patients from the Back to Bedside project, including 293 naSAH-patients and 51 patients with simvastatin-treatment, were recruited for this analysis. Patients under treatment were affected by a significantly lower risk of CVS ($p < 0.01$; OR 3.7), DI ($p < 0.05$; OR 2.6), and DCI ($p < 0.05$; OR 3). Furthermore, there was a significant association between simvastatin-treatment and favorable-outcome ($p < 0.05$; OR 3). However, dividing patients with statin-treatment in pre-SAH ($n = 31$) and post-SAH ($n = 20$) treatment groups, we only detected a tenuously significant higher chance for a favorable outcome ($p < 0.05$; OR 0.05) in the small group of 20 patients with statin post-SAH treatment. Using a multivariate-analysis, we detected female gender (55%; $p < 0.001$; OR 4.9), Hunt&Hess ≤III at admission ($p < 0.002$; OR 4), no anticoagulant-therapy ($p < 0.0001$; OR 0.16), and statin-treatment ($p < 0.0001$; OR 24.2) as the main factors improving the clinical outcome. In conclusion, we detected a significantly lower risk for CVS, DCI, and DI in naSAH patients under statin treatment. Additionally, a significant association between statin treatment and favorable outcome 6 months after naSAH onset could be confirmed. Nevertheless, unified animal experiments should be considered to create the basis for developing new therapeutic schemes.

[26] *Alanbaei M, Abu-Farha M, Hebbar P et al.* **ANGPTL3 Variants Associate with Lower Levels of Irisin and C-Peptide in a Cohort of Arab Individuals**. Genes 2021; 12.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=34067751

ABSTRACT

ANGPTL3 is an important regulator of lipid metabolism. Its inhibition in people with hypercholesteremia reduces plasma lipid levels dramatically. Genome-wide association studies have associated ANGPTL3 variants with lipid traits. Irisin, an exercise-modulated protein, has been associated with lipid metabolism. Intracellular accumulation of lipids impairs insulin action and contributes to metabolic disorders. In this study, we evaluate the impact of ANGPTL3 variants on levels of irisin and markers associated with lipid metabolism and insulin resistance. ANGPTL3 rs1748197 and rs12130333 variants were genotyped in a cohort of 278 Arab individuals from Kuwait.

Levels of irisin and other metabolic markers were measured by ELISA. Significance of association signals was assessed using Bonferroni-corrected p-values and empirical p-values. The study variants were significantly associated with low levels of c-peptide and irisin. Levels of c-peptide and irisin were mediated by interaction between carrier genotypes (GA + AA) at rs1748197 and measures of IL13 and TG, respectively. While levels of c-peptide and IL13 were directly correlated in individuals with the reference genotype, they were inversely correlated in individuals with the carrier genotype. Irisin correlated positively with TG and was strong in individuals with carrier genotypes. These observations illustrate ANGPTL3 as a potential link connecting lipid metabolism, insulin resistance and cardioprotection.

[27] *Wang J, Han P, Gao M et al.* **Prognostic Value of PCSK9 Levels in Non-ST elevation myocardial infarction Patients Undergoing Percutaneous Coronary Intervention (PCI)**. Hellenic journal of cardiology : HJC = Hellenike kardiologike epitheorese 2021.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=34058371

ABSTRACT

BACKGROUND: The role of proprotein convertase subtilisin/kexin type 9(PCSK9) in predicting major adverse cardiovascular events (MACEs) in Non-ST elevation myocardial infarction (NSTEMI) patients is still an open question and the PCSK9 concentration of clinical usefulness remains unknown in guiding treatment. METHODS AND RESULTS: 272 patients with NSTEMI were included in our prospective observational cohort study. Patients were followed up for 1 year. Their baseline plasma PCSK9 levels were determined by ELISA. Patients were divided into high, medium and low PCSK9 groups. All patients followed up for the occurrence of MACEs and received PCI therapy after admission. The associations of PCSK9 with MACEs were evaluated. The results showed that the incidence of composite MACEs was greater at higher concentrations of PCSK9. PCSK9 level was related to level of lipoproteins, high-sensitivity C-reactive protein(hs-CRP), PDW(platelet volume distribution width), and D-Dimer. There was also a statistically significant correlation between PCSK9 concentrations and GRACE score. The Kaplan-Meier curves showed patients with high PCSK9 level had lower event-free survival rate. Survival analysis indicated high level of PCSK9 predicted MACEs independently. Subgroup analysis demonstrated the prognostic value of high PCSK9 level was greater for patients classified by the GRACE score as high risk. CONCLUSION: In a NSTEMI setting, the concentration of PCSK9 is associated with hypercoagulability and hyper-inflammation. High levels of PCSK9 independently predict future MACEs in NSTEMI patients, particularly those classified by the GRACE score as high risk.

[28] *Park JH, Koo BK, Kim W, Kim WH*. **Histological severity of nonalcoholic fatty liver disease is associated with 10-year risk for atherosclerotic cardiovascular disease**. Hepatology international 2021.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=34081289

ABSTRACT

BACKGROUND AND AIM: Nonalcoholic fatty liver disease (NAFLD) is associated with atherosclerotic cardiovascular disease (ASCVD). However, few studies have investigated the association between the histological severity of NAFLD and ASCVD. Therefore, we investigated whether the histological severity of NAFLD is associated with ASCVD risk. METHODS: We performed cross-sectional analysis of prospectively enrolled, biopsy-proven NAFLD patients. The 10-year

ASCVD risk was assessed using the Korean Risk Prediction Model. The histological spectrum of NAFLD was classified by the nonalcoholic steatohepatitis (NASH) clinical research network histological scoring system. The association between each histological subgroup and ASCVD risk was analyzed using logistic regression analysis. RESULTS: This study included 398 Korean subjects (mean age, 57.9 years; male, 44.2%) with biopsy-proven NAFLD and 102 no-NALFD controls. Subjects with ASCVD risk≥10% showed more severe grades of hepatocellular ballooning and more advanced stages of fibrosis when compared with subjects with ASCVD risk<10% ($p<0.05$ for each). The presence of NASH (odds ratio [OR] 4.07; 95% confidence interval [CI] 1.40-11.88) or advanced fibrosis (OR 8.11; 95% CI 1.83-35.98) was independently associated with a higher risk of ASCVD even after adjustment for age, sex, body mass index, blood pressure, lipids, liver enzymes, systemic inflammation, and insulin resistance. CONCLUSIONS: Patients with NASH or advanced fibrosis are at an increased risk of developing ASCVD compared with no-NAFLD controls or subjects with NAFL, independent of conventional metabolic risk factors for CVD. Histological information on NAFLD may be helpful to promote our understanding of extrahepatic complications, such as ASCVD, resulting from NAFLD progression.

[29] *Haji Aghajani M, Moradi O, Azhdari Tehrani H et al.* **Promising effects of atorvastatin on mortality and need for mechanical ventilation in patients with severe COVID-19; a retrospective cohort study**. Int J Clin Pract 2021:e14434.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=34080261
ABSTRACT
PURPOSE: Considering the anti-inflammatory effect of atorvastatin and the role of medical comorbidities such as hypertension and coronary artery disease on the prognosis of the COVID-19 patients, we aimed to assess the effect of atorvastatin add-on therapy on mortality caused by COVID-19. METHODS: We conducted a retrospective cohort study, including patients who were hospitalised with confirmed diagnosis of severe COVID-19. Baseline characteristics and related clinical data of patients were recorded. Clinical outcomes consist of in-hospital mortality, need for invasive mechanical ventilation and hospital length of stay. COX regression analysis models were used to assess the association of independent factors to outcomes. RESULTS: Atorvastatin was administered for 421 of 991 patients. The mean age was 61.640 ± 17.003 years. Older age, higher prevalence of hypertension and coronary artery disease reported in patients who received atorvastatin. These patients have shorter hospital length of stay (P = .001). Based on COX proportional hazard model, in-hospital use of atorvastatin was associated with decrease in mortality (HR = 0.679, P = .005) and lower need for invasive mechanical ventilation (HR = 0.602, P = .014). CONCLUSIONS: Atorvastatin add-on therapy in patient with severe COVID-19 was associated with lower in-hospital mortality and reduced the risk of need for invasive mechanical ventilation which supports to continue the prescription of the medication.

[30] *Ben Cherifa F, El Ati J, Doggui R et al.* **Prevalence of High HDL Cholesterol and Its Associated Factors Among Tunisian Women of Childbearing Age: A Cross-Sectional Study**. International journal of environmental research and public health 2021; 18.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=34065252
ABSTRACT

The protective role of high high-density lipoprotein cholesterol (HDL-C) against cardiovascular risk has been questioned recently. Due to the increasing trend of cardiovascular diseases (CVD) in Tunisia, this study aimed to determine the prevalence of high HDL-C and its associated factors in Tunisian women of childbearing age. A cross-sectional survey was conducted among a subsample of 1689 women, aged 20 to 49 years, in the Great Tunis region. Data on socio-demographic and lifestyle factors were collected by a questionnaire. Overall adiposity was assessed by body mass index (BMI). All biological variables were assayed in blood samples coated with anticoagulant ethylene diamine tetra acetic acid (EDTA) by enzymatic methods. Stata software (2015) was used for data management and statistical analysis. High HDL-C values were recorded in 26.6% of selected women. After adjustment for all socio-demographic and lifestyle factors, age, hypertension, and smoking were negatively associated with high HDL-C levels, while family history of cancer was positively associated with high HDL-C in women. An additional investigation on the relationship between high HDL-C and cancer risk should be performed due to controversial results.

[31] *Bhuiyan AR, Payton M, Mitra AK et al.* **Progression of Metabolic Syndrome Components along with Depression Symptoms and High Sensitivity C-Reactive Protein: The Bogalusa Heart Study**. International journal of environmental research and public health 2021; 18.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=34065158

ABSTRACT

This study examined the association between depression symptoms and metabolic syndrome (MetS) or its components prospectively. It assessed the mediator role of high-sensitivity C-reactive protein (hs-CRP) and intracellular adhesion molecule-1 (ICAM-1). Self-reported depression symptoms were assessed using the Center for Epidemiologic Studies-Depression scale. MetS was defined as having at least three of the following five criteria: (1) waist circumference >102 centimeters (cm) in men or >88 cm in women; (2) triglycerides ≥ 50 milligrams per deciliter (mg/dL); (3) high-density lipoprotein cholesterol <40 mg/dL in men or <50 mg/dL in women; (4) blood pressure: systolic ≥ 30 and diastolic ≥85 mm of mercury or on antihypertensive medication; and (5) fasting glucose ≥110 mg/dL. The risk ratios (RR) with 95% confidence interval (CI) were estimated using multivariate Poisson regression models. A total of 419 White and 180 Black individuals with a mean age of 36 years were followed for 6.9 years. The findings demonstrated that hs-CRP mediated the influence of depression symptoms on central obesity in White young adults. The adjusted RR for central obesity was 1.08 with 95% CI of 0.88-1.32, and the value for hs-CRP was 1.12 with 95% CI of 1.02-1.23. Although depression did not influence MetS in this study cohort, the complete mediator role of hs-CRP was established for central obesity, a component of MetS in White young adults.

[32] *Gurgel do Amaral M, Reijneveld SA, Almansa J et al.* **Do Uncontrolled Hypertension, Diabetes, Dyslipidemia, and Obesity Mediate the Relationship Between Health Literacy and Chronic Kidney Disease Complications?** International journal of environmental research and public health 2021; 18.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=34069095

ABSTRACT

Health literacy is the ability to deal with information related to one's health. Patients with low health literacy and chronic diseases, such as chronic kidney disease (CKD), have poor disease-management skills, which could lead to complications. We used logistic regressions and structural

equational modeling to assess whether low health literacy is associated with the development of cardiovascular disease and mortality in patients with CKD, and whether this association is mediated by the presence of uncontrolled hypertension, diabetes, dyslipidemia, obesity, or albuminuria. Data from 2742 adult participants with CKD from the Lifelines study were analyzed at baseline and after approximately four years. Low health literacy was associated with cardiovascular disease and mortality in the crude models, with OR and 95%CI of 1.93 (1.46 to 2.55) and 1.59 (1.08 to 2.36), respectively. After adjustment for age and sex, low health literacy was only associated with cardiovascular disease (OR 1.76 (1.31 to 2.23)). This association was mediated by uncontrolled diabetes (27.1%) and obesity (8.0%). Low health literacy is associated with the development of cardiovascular disease after adjustment for age and sex, and this association is mediated by uncontrolled diabetes and obesity.

[33] *Barale C, Melchionda E, Morotti A, Russo I*. **PCSK9 Biology and Its Role in Atherothrombosis**. International journal of molecular sciences 2021; 22.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=34070931

ABSTRACT

It is now about 20 years since the first case of a gain-of-function mutation involving the as-yet-unknown actor in cholesterol homeostasis, proprotein convertase subtilisin/kexin type 9 (PCSK9), was described. It was soon clear that this protein would have been of huge scientific and clinical value as a therapeutic strategy for dyslipidemia and atherosclerosis-associated cardiovascular disease (CVD) management. Indeed, PCSK9 is a serine protease belonging to the proprotein convertase family, mainly produced by the liver, and essential for metabolism of LDL particles by inhibiting LDL receptor (LDLR) recirculation to the cell surface with the consequent upregulation of LDLR-dependent LDL-C levels. Beyond its effects on LDL metabolism, several studies revealed the existence of additional roles of PCSK9 in different stages of atherosclerosis, also for its ability to target other members of the LDLR family. PCSK9 from plasma and vascular cells can contribute to the development of atherosclerotic plaque and thrombosis by promoting platelet activation, leukocyte recruitment and clot formation, also through mechanisms not related to systemic lipid changes. These results further supported the value for the potential cardiovascular benefits of therapies based on PCSK9 inhibition. Actually, the passive immunization with anti-PCSK9 antibodies, evolocumab and alirocumab, is shown to be effective in dramatically reducing the LDL-C levels and attenuating CVD. While monoclonal antibodies sequester circulating PCSK9, inclisiran, a small interfering RNA, is a new drug that inhibits PCSK9 synthesis with the important advantage, compared with PCSK9 mAbs, to preserve its pharmacodynamic effects when administrated every 6 months. Here, we will focus on the major understandings related to PCSK9, from its discovery to its role in lipoprotein metabolism, involvement in atherothrombosis and a brief excursus on approved current therapies used to inhibit its action.

[34] *Garcia-Arguinzonis M, Diaz-Riera E, Peña E et al.* **Alternative C3 Complement System: Lipids and Atherosclerosis**. International journal of molecular sciences 2021; 22.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=34066088

ABSTRACT

Familial hypercholesterolemia (FH) is increasingly associated with inflammation, a phenotype that persists despite treatment with lipid lowering therapies. The alternative C3 complement system (C3),

as a key inflammatory mediator, seems to be involved in the atherosclerotic process; however, the relationship between C3 and lipids during plaque progression remains unknown. The aim of the study was to investigate by a systems biology approach the role of C3 in relation to lipoprotein levels during atherosclerosis (AT) progression and to gain a better understanding on the effects of C3 products on the phenotype and function of human lipid-loaded vascular smooth muscle cells (VSMCs). By mass spectrometry and differential proteomics, we found the extracellular matrix (ECM) of human aortas to be enriched in active components of the C3 complement system, with a significantly different proteomic signature in AT segments. Thus, C3 products were more abundant in AT-ECM than in macroscopically normal segments. Furthermore, circulating C3 levels were significantly elevated in FH patients with subclinical coronary AT, evidenced by computed tomographic angiography. However, no correlation was identified between circulating C3 levels and the increase in plaque burden, indicating a local regulation of the C3 in AT arteries. In cell culture studies of human VSMCs, we evidenced the expression of C3, C3aR (anaphylatoxin receptor) and the integrin α(M)β(2) receptor for C3b/iC3b (RT-PCR and Western blot). C3mRNA was up-regulated in lipid-loaded human VSMCs, and C3 protein significantly increased in cell culture supernatants, indicating that the C3 products in the AT-ECM have a local vessel-wall niche. Interestingly, C3a and iC3b (C3 active fragments) have functional effects on VSMCs, significantly reversing the inhibition of VSMC migration induced by aggregated LDL and stimulating cell spreading, organization of F-actin stress fibers and attachment during the adhesion of lipid-loaded human VSMCs. This study, by using a systems biology approach, identified molecular processes involving the C3 complement system in vascular remodeling and in the progression of advanced human atherosclerotic lesions.

[35] *Georgescu A, Simionescu M*. **Extracellular Vesicles: Versatile Nanomediators, Potential Biomarkers and Therapeutic Agents in Atherosclerosis and COVID-19-Related Thrombosis**. International journal of molecular sciences 2021; 22.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=34073119

ABSTRACT

Cells convey information among one another. One instrument employed to transmit data and constituents to specific (target) cells is extracellular vesicles (EVs). They originate from a variety of cells (endothelial, immune cells, platelets, mesenchymal stromal cells, etc.), and consequently, their surface characteristics and cargo vary according to the paternal cell. The cargo could be DNA, mRNA, microRNA, receptors, metabolites, cytoplasmic proteins, or pathological molecules, as a function of which EVs exert different effects upon endocytosis in recipient cells. Recently, EVs have become important participants in a variety of pathologies, including atherogenesis and coronavirus disease 2019 (COVID-19)-associated thrombosis. Herein, we summarize recent advances and some of our own results on the role of EVs in atherosclerotic cardiovascular diseases, and discuss their potential to function as signaling mediators, biomarkers and therapeutic agents. Since COVID-19 patients have a high rate of thrombotic events, a special section of the review is dedicated to the mechanism of thrombosis and the possible therapeutic potential of EVs in COVID-19-related thrombosis. Yet, EV mechanisms and their role in the transfer of information between cells in normal and pathological conditions remain to be explored.

[36] *Ji E, Lee S*. **Antibody-Based Therapeutics for Atherosclerosis and Cardiovascular Diseases**. International journal of molecular sciences 2021; 22.

PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=34071276

ABSTRACT

Cardiovascular disease is the leading cause of death worldwide, and its prevalence is increasing due to the aging of societies. Atherosclerosis, a type of chronic inflammatory disease that occurs in arteries, is considered to be the main cause of cardiovascular diseases such as ischemic heart disease or stroke. In addition, the inflammatory response caused by atherosclerosis confers a significant effect on chronic inflammatory diseases such as psoriasis and rheumatic arthritis. Here, we review the mechanism of action of the main causes of atherosclerosis such as plasma LDL level and inflammation; furthermore, we review the recent findings on the preclinical and clinical effects of antibodies that reduce the LDL level and those that neutralize the cytokines involved in inflammation. The apolipoprotein B autoantibody and anti-PCSK9 antibody reduced the level of LDL and plaques in animal studies, but failed to significantly reduce carotid inflammation plaques in clinical trials. The monoclonal antibodies against PCSK9 (alirocumab, evolocumab), which are used as a treatment for hyperlipidemia, lowered cholesterol levels and the incidence of cardiovascular diseases. Antibodies that neutralize inflammatory cytokines (TNF-α, IL-1β, IL-6, IL-17, and IL-12/23) have shown promising but contradictory results and thus warrant further research.

[37] *Kim M, Bezprozvanny I*. **Differences in Recycling of Apolipoprotein E3 and E4-LDL Receptor Complexes-A Mechanistic Hypothesis**. International journal of molecular sciences 2021; 22.

PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=34068576

ABSTRACT

Apolipoprotein E (ApoE) is a protein that plays an important role in the transport of fatty acids and cholesterol and in cellular signaling. On the surface of the cells, ApoE lipoparticles bind to low density lipoprotein receptors (LDLR) that mediate the uptake of the lipids and downstream signaling events. There are three alleles of the human ApoE gene. Presence of ApoE4 allele is a major risk factor for developing Alzheimer's disease (AD) and other disorders late in life, but the mechanisms responsible for biological differences between different ApoE isoforms are not well understood. We here propose that the differences between ApoE isoforms can be explained by differences in the pH-dependence of the association between ApoE3 and ApoE4 isoforms and LDL-A repeats of LDLR. As a result, the following endocytosis ApoE3-associated LDLRs are recycled back to the plasma membrane but ApoE4-containing LDLR complexes are trapped in late endosomes and targeted for degradation. The proposed mechanism is predicted to lead to a reduction in steady-state surface levels of LDLRs and impaired cellular signaling in ApoE4-expressing cells. We hope that this proposal will stimulate experimental research in this direction that allows the testing of our hypothesis.

[38] *Paavola T, Bergmann U, Kuusisto S et al.* **Distinct Fatty Acid Compositions of HDL Phospholipids Are Characteristic of Metabolic Syndrome and Premature Coronary Heart Disease-Family Study**. International journal of molecular sciences 2021; 22.

PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=34066314

ABSTRACT

HDL particles can be structurally modified in atherosclerotic disorders associated with low HDL cholesterol level (HDL-C). We studied whether the lipidome of the main phosphatidylcholine (PC), lysophosphatidylcholine (LPC) and sphingomyelin (SM) species of HDL2 and HDL3 subfractions is associated with premature coronary heart disease (CHD) or metabolic syndrome (MetS) in families

where common low HDL-C predisposes to premature CHD. The lipidome was analyzed by LC-MS. Lysophosphatidylcholines were depleted of linoleic acid relative to more saturated and shorter-chained acids containing species in MetS compared with non-affected subjects: the ratio of palmitic to linoleic acid was elevated by more than 30%. A minor PC (16:0/16:1) was elevated (28-40%) in MetS. The contents of oleic acid containing PCs were elevated relative to linoleic acid containing PCs in MetS; the ratio of PC (16:0/18:1) to PC (16:0/18:2) was elevated by 11-16%. Certain PC and SM ratios, e.g., PC (18:0/20:3) to PC (16:0/18:2) and a minor SM 36:2 to an abundant SM 34:1, were higher (11-36%) in MetS and CHD. The fatty acid composition of certain LPCs and PCs displayed a characteristic pattern in MetS, enriched with palmitic, palmitoleic or oleic acids relative to linoleic acid. Certain PC and SM ratios related consistently to CHD and MetS.

[39] *Turpin C, Catan A, Meilhac O et al.* **Erythrocytes: Central Actors in Multiple Scenes of Atherosclerosis**. International journal of molecular sciences 2021; 22.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=34072544
ABSTRACT
The development and progression of atherosclerosis (ATH) involves lipid accumulation, oxidative stress and both vascular and blood cell dysfunction. Erythrocytes, the main circulating cells in the body, exert determinant roles in the gas transport between tissues. Erythrocytes have long been considered as simple bystanders in cardiovascular diseases, including ATH. This review highlights recent knowledge concerning the role of erythrocytes being more than just passive gas carriers, as potent contributors to atherosclerotic plaque progression. Erythrocyte physiology and ATH pathology is first described. Then, a specific chapter delineates the numerous links between erythrocytes and atherogenesis. In particular, we discuss the impact of extravasated erythrocytes in plaque iron homeostasis with potential pathological consequences. Hyperglycaemia is recognised as a significant aggravating contributor to the development of ATH. Then, a special focus is made on glycoxidative modifications of erythrocytes and their role in ATH. This chapter includes recent data proposing glycoxidised erythrocytes as putative contributors to enhanced atherothrombosis in diabetic patients.

[40] *Urschel K, Tauchi M, Achenbach S, Dietel B.* **Investigation of Wall Shear Stress in Cardiovascular Research and in Clinical Practice-From Bench to Bedside**. International journal of molecular sciences 2021; 22.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=34073212
ABSTRACT
In the 1900s, researchers established animal models experimentally to induce atherosclerosis by feeding them with a cholesterol-rich diet. It is now accepted that high circulating cholesterol is one of the main causes of atherosclerosis; however, plaque localization cannot be explained solely by hyperlipidemia. A tremendous amount of studies has demonstrated that hemodynamic forces modify endothelial athero-susceptibility phenotypes. Endothelial cells possess mechanosensors on the apical surface to detect a blood stream-induced force on the vessel wall, known as "wall shear stress (WSS)", and induce cellular and molecular responses. Investigations to elucidate the mechanisms of this process are on-going: on the one hand, hemodynamics in complex vessel systems have been described in detail, owing to the recent progress in imaging and computational techniques. On the other hand, investigations using unique in vitro chamber systems with various flow applications have enhanced the understanding of WSS-induced changes in endothelial cell function and the

involvement of the glycocalyx, the apical surface layer of endothelial cells, in this process. In the clinical setting, attempts have been made to measure WSS and/or glycocalyx degradation non-invasively, for the purpose of their diagnostic utilization. An increasing body of evidence shows that WSS, as well as serum glycocalyx components, can serve as a predicting factor for atherosclerosis development and, most importantly, for the rupture of plaques in patients with high risk of coronary heart disease.

[41] *Sajjadpour Z, Nasli-Esfahani E, Siassi F et al.* **Healthy Dietary Pattern is Related to Blood Lipids in Patients with Type 1 Diabetes Mellitus: A Cross-sectional Study from a Developing Country**. International journal of preventive medicine 2021; 12:7.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=34084304

ABSTRACT

BACKGROUND: The association between dietary patterns and cardiovascular disease (CVD) risk factors has been investigated in very limited studies in patients with type 1 diabetes mellitus (T1DM). The aim of this study was to determine the relationship between the major dietary patterns and CVD risk factors in these patients. METHODS: A cross-sectional study was performed on 169 females of 18--35 years who were diagnosed with T1DM attending Iranian Diabetes Association in Tehran. Anthropometric measures, blood glucose, and lipid levels of all participants were measured. Dietary data was collected using a food frequency questionnaire. Dietary patterns were determined by factor analysis. Using the analysis of covariance (ANCOVA), mean value of the biochemical factors across the tertiles of dietary patterns was compared. RESULTS: Three major dietary patterns were identified: the grain, legume and nut (GLN), the fruits and vegetables (FV), and the high calorie foods, salty snacks, sweet and dessert (HSD). After adjustment for age, body mass index and energy intake, subjects who were in the highest tertile of FV pattern had significantly lower levels of LDL-c (P = 0.01), triglyceride (TG) (P = 0.02), and total cholesterol (P = 0.01). GLN and HSD patterns had no significant relationship with blood glucose and lipids. CONCLUSIONS: This study demonstrates that a dietary pattern rich in vegetables and fruits may be inversely associated with dyslipidemia in patients with T1DM. The results can be used for developing interventions that aim to promote healthy eating for the prevention of CVD in these patients.

[42] *Kong CY, Wang CL, Niu KJ, Qi W*. **Prevalence of metabolic syndrome in patients with rheumatoid arthritis in eastern China-A hospital based study**. International journal of rheumatic diseases 2021.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=34080783

ABSTRACT

OBJECTIVE: The purpose of this hospital clinic based study was to evaluate the potential risk factors associated with the prevalence of MetS in RA population. METHODS: From January 2015 to October 2018, 717 patients with RA and 717 healthy controls who were treated or performed physical examination in Tianjin First Central Hospital were enrolled in this study. The basic disease diagnoses were recorded. A questionnaire was performed on all participants to assess the demographic details of the RA cohort. Moreover, laboratory indicators related to glucose and lipid metabolism in patients with RA were also detected. The potential risk factors for MetS were also analyzed. RESULTS: The prevalence of MetS were 31.2% and 34.2% in case and control groups, respectively (P = .22). There were lower levels of HDL-C, obesity, TG, LDL-C and TC in case group than control group (all

P < .05). The hypertension levels in healthy controls was decreased in compared with patients with RA (P < .05). Nevertheless, in patients with RA, complement 3 (OR: 1.02; 95% CI: 1.01-1.03, P = .007) and less glucocorticoids use (OR: 0.63, 95% CI: 0.39-0.99, P = .046) were associated with MetS. CONCLUSION: The prevalence of MetS was not associated with RA. Complement 3 may be associated with the higher prevalence of MetS in patients with RA. Glucocorticoids treatment may be associated with MetS.

[43] *Sabatine MS, Braunwald E*. **Thrombolysis In Myocardial Infarction (TIMI) Study Group: JACC Focus Seminar 2/8**. Journal of the American College of Cardiology 2021; 77:2822-2845.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=34082913

ABSTRACT

In 1984, the National Heart, Lung, and Blood Institute (NHLBI) decided to study the efficacy and safety of the treatment of acute myocardial infarction with an emerging therapy, coronary thrombolysis, and thus the TIMI (Thrombolysis In Myocardial Infarction) Study Group was born. Following completion of 3 clinical trials of thrombolytic therapy supported by the NHLBI, TIMI became an academic research organization headquartered at Brigham and Women's Hospital and subsequently branched out to study a wide range of patients, including those with stable coronary, cerebrovascular, and peripheral arterial disease; dyslipidemia; heart failure; atrial fibrillation; diabetes; and obesity. TIMI also began to study a wide range of interventions including thrombolytic, antithrombotic, lipid-modifying, anti-inflammatory, heart failure, glucose-lowering, and weight loss agents. TIMI, now in its 37th year, has completed >70 trials. This review describes the origins of the TIMI Study Group, summarizes several of its completed trials and the major lessons learned from them, and discusses ongoing trials and future directions.

[44] *Retnakaran R, Shah BR*. **Patterns of Cardiovascular Risk Factors in the Years Before Pregnancy in Nulliparous Women With and Without Preterm Birth and Small-for-Gestational-Age Delivery**. Journal of the American Heart Association 2021; 10:e021321.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=34075781

ABSTRACT

Background Women with either preterm or small-for-gestational-age (SGA) delivery have an elevated lifetime risk of cardiovascular disease that has been attributed to the accrual of vascular risk factors over time. We sought to determine whether an adverse cardiovascular risk factor profile develops in the years before pregnancies complicated by preterm delivery or SGA. Methods and Results Using administrative databases, we identified all 156 278 nulliparous women in Ontario, Canada, who had singleton pregnancies between January 2011 and December 2018 and ≥2 measurements of the following analytes between January 2008 and the start of pregnancy: glycosylated hemoglobin, glucose, lipids, and alanine aminotransferase. There were 11 078 women with preterm delivery and 19 367 with SGA. The 2 most recent pregravid tests were performed at median 0.6 (interquartile range, 0.3-1.4) and 1.9 (interquartile range, 1.1-3.3) years before pregnancy, respectively. Women with preterm delivery had higher pregravid glycosylated hemoglobin, glucose, low-density lipoprotein cholesterol, triglycerides, and alanine aminotransferase, and lower high-density lipoprotein cholesterol, than those without preterm delivery. In contrast, women with SGA had lower pregravid fasting glucose, random glucose, and triglycerides than those without SGA. In the years before pregnancy, women with preterm delivery had higher annual increases than their peers in glycosylated

hemoglobin (0.7-times higher), triglycerides (7.9-times higher), and alanine aminotransferase (2.2-times higher). During this time, fasting glucose increased in women who developed preterm delivery but decreased in their peers. Conclusions An adverse cardiovascular risk factor profile evolves over time in the years before pregnancy complicated by preterm delivery, but does not necessarily precede SGA.

[45] *Yang Y, Hwang E, Lee SA et al.* **Effect of Rosuvastatin on Coronary Flow Reserve in Hypertensive Patients at Cardiovascular Risk**. J Cardiovasc Imaging 2021.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=34080332

ABSTRACT

BACKGROUND: It has been unclear whether statin therapy directly improves coronary flow reserve (CFR) in hypertensive patients at cardiovascular risk, independent of lifestyle modification and antihypertensive medications. METHODS: In this double-blind, randomized controlled trial, we randomly assigned 95 hypertensive patients at cardiovascular risk to receive either rosuvastatin 10 mg or placebo for 12 months, in addition to antihypertensive therapy and lifestyle modification for hypercholesterolemia. Using Doppler echocardiography, coronary flow velocity in the distal left anterior descending artery was measured and CFR was calculated as the ratio of hyperemic to basal averaged peak diastolic flow velocity. The primary end point was change in CFR from baseline to 12 months follow-up. RESULTS: Low-density lipoprotein-cholesterol was changed from 157 ± 23 to 84 ± 16 mg/dL in the rosuvastatin group ($p < 0.001$) and from 152 ± 19 to 144 ± 22 mg/dL in the control group ($p = 0.041$, but there were no significant differences between the treatment groups in the changes in C-reactive protein, high-density lipoprotein cholesterol, and blood pressures. CFR was changed from 3.03 ± 0.44 to 3.25 ± 0.49 in the rosuvastatin group ($p < 0.001$) and from 3.15 ± 0.54 to 3.17 ± 0.56 in the control group ($p = 0.65$). The primary end point of change in CFR was significantly different between the rosuvastatin group and the control group (0.216 ± 0.279 vs. 0.015 ± 0.217; $p < 0.001$). CONCLUSIONS: Compared with lifestyle modification alone, addition of rosuvastatin significantly improved CFR in hypertensive patients at cardiovascular risk.

[46] *Miao CY, Ye XF, Zhang W et al.* **Association between dyslipidemia and antihypertensive and antidiabetic treatments in a China multicenter study**. Journal of clinical hypertension (Greenwich, Conn.) 2021; 23:1399-1404.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=34092020

ABSTRACT

Dyslipidemia is an emerging disease in China, especially in the presence of hypertension and diabetes mellitus. We investigated the association of dyslipidemia with the use of antihypertensive and antidiabetic agents. The study participants (n = 2423) were hypertensive and diabetic patients enrolled in a China nationwide registry. Serum mean ± (SD, except for serum triglycerides, median [interquatile range]) concentrations were 1.38 (0.97-2.02) mmol/L, 4.85 ± 1.12 mmol/L, 1.30 ± 0.36 mmol/L, and 2.89 ± 0.92 mmol/L for triglycerides and total, high-density lipoprotein (HDL), and low-density lipoprotein (LDL) cholesterol, respectively. The prevalence of dyslipidemia was 18.9%, 13.5%, 16.6%, and 37.7% for hypertriglyceridemia (serum triglycerides ≥2.3 mmol/L), hypercholesterolemia (total cholesterol ≥6.2 mmol/L or LDL cholesterol ≥4.1 mmol/L), low HDL cholesterol (HDL cholesterol <1.0 mmol/L), and any of the three lipid disorders, respectively. Treated (n = 1647), compared with untreated hypertensive patients (n = 303), had a significantly (P ≤ .0006)

lower serum total, LDL, and HDL cholesterol, but similar serum triglycerides (P = .20). Treated (n = 1325), compared with untreated diabetic patients (n = 238), had a significantly (P ≤ .004) lower serum triglycerides, and total and LDL cholesterol, but similar serum HDL cholesterol (P = .81). After adjustment, the odds ratios (OR) were significant for hypercholesterolemia (OR 0.76, 95% confidence interval [CI] 0.58-0.997, P = .048) and low HDL cholesterol (OR 1.56, CI 1.19-2.03, P = .001) in treated versus untreated hypertension, and for low HDL cholesterol (OR 1.50, CI 1.18-1.89, P = .0008) in treated versus untreated diabetes. In conclusion, the prevalence of dyslipidemia differed between treated and untreated hypertension and diabetes.

[47] *Li X, Weber NC, Cohn DM et al.* **Effects of Hyperglycemia and Diabetes Mellitus on Coagulation and Hemostasis**. Journal of clinical medicine 2021; 10.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=34072487
ABSTRACT
In patients with diabetes, metabolic disorders disturb the physiological balance of coagulation and fibrinolysis, leading to a prothrombotic state characterized by platelet hypersensitivity, coagulation disorders and hypofibrinolysis. Hyperglycemia and insulin resistance cause changes in platelet number and activation, as well as qualitative and/or quantitative modifications of coagulatory and fibrinolytic factors, resulting in the formation of fibrinolysis-resistant clots in patients with diabetes. Other coexisting factors like hypoglycemia, obesity and dyslipidemia also contribute to coagulation disorders in patients with diabetes. Management of the prothrombotic state includes antiplatelet and anticoagulation therapies for diabetes patients with either a history of cardiovascular disease or prone to a higher risk of thrombus generation, but current guidelines lack recommendations on the optimal antithrombotic treatment for these patients. Metabolic optimizations like glucose control, lipid-lowering, and weight loss also improve coagulation disorders of diabetes patients. Intriguing, glucose-lowering drugs, especially cardiovascular beneficial agents, such as glucagon-like peptide-1 receptor agonists and sodium glucose co-transporter inhibitors, have been shown to exert direct anticoagulation effects in patients with diabetes. This review focuses on the most recent progress in the development and management of diabetes related prothrombotic state.

[48] *Tarrant SM, Kim RG, McDonogh JM et al.* **Preadmission Statin Prescription and Inpatient Myocardial Infarction in Geriatric Hip Fracture**. Journal of clinical medicine 2021; 10.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=34072776
ABSTRACT
Statins have been shown to reduce myocardial infarction (MI) in cardiac and vascular surgery. MI is common in hip fracture. This study aims to investigate whether statins decrease MI in hip fracture surgery and reduce mortality resulting from MI. Patients aged 65 years and above with a low-energy hip fracture were identified between January 2015 and December 2017. Demographics, comorbidities, predictive scores, medications and outcomes were assessed retrospectively. The primary outcome was inpatient MI. The secondary outcome was inpatient mortality resulting from MI, for which fatal and non-fatal MI were modelled. Regression analysis was conducted with propensity score weighting. Hip fracture occurred in 1166 patients, of which 391 (34%) were actively taking statins. Thirty-one (2.7%) patients were clinically diagnosed with MI. They had a higher inpatient mortality than those who did not sustain an MI (35% vs. 5.3%, $p < 0.0001$). No reduction was seen between statin use and the occurrence of MI (OR = 0.97, 95% CI: 0.45-2.11; p = 0.942) including

Fluvastatin-equivalent dosage (OR = 1.00, 95% CI: 0.96-1.03, p = 0.207). Statins were not associated with having a non-fatal MI (OR 1.47, 95% CI: 0.58-3.71; p = 0.416) or preventing fatal MI (OR = 0.40, 95% CI: 0.08-1.93; p = 0.255). Preadmission statin use and associations with clinically diagnosed inpatient MI or survival after inpatient MI were not able to be established.

[49] *Tomaniak M, Ochijewicz D, Kołtowski Ł et al.* **OCT-Derived Plaque Morphology and FFR-Determined Hemodynamic Relevance in Intermediate Coronary Stenoses**. Journal of clinical medicine 2021; 10.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=34071299

ABSTRACT

BACKGROUND: optical coherence tomography (OCT) might allow identifying lesion features reportedly associated with plaque vulnerability and increased risk of clinical events. Previous studies on correlation between OCT and functional lesion significance indices reported contradictory results, yet integration of complementary information from both modalities is gaining increased interest. The aim of the study was to compare plaque morphology using OCT in hemodynamically relevant vs. non-relevant lesions by fractional flow reserve (FFR). METHODS: consecutive patients with intermediate grade coronary stenoses by angiography were evaluated by both FFR and OCT in this single-center study. Stenoses were labeled hemodynamically relevant in case of the FFR ≤ 0.80. Minimal lumen area (MLA), fibrous cap thickness (FCT), minimal cap thickness over the calcium, angle of the calcium, and necrotic core within the lesions were evaluated. RESULTS: a total of 105 patients (124 vessels) were analyzed. Of them, 65 patients were identified with at least one lesion identified as hemodynamically relevant by FFR (72 vessels, 58.1%). Lesions with FFR ≤0.80 presented with lower mean and minimal lumen area (3.46 ± 1.29 vs. 4.65 ± 2.19, p =0.001 and 1.84 ± 0.97 vs. 2.66 ± 1.40, p = 0.001) compared to patients with FFR > 0.80. No differences were found between groups in the mean and minimal FCT, mean, and maximal necrotic core, calcium angle, as well as the overall rate of calcified and lipid plaques. CONCLUSION: hemodynamic relevance of intermediate grade lesions correlated moderately with the luminal assessment by OCT. No differences were identified in the plaque morphology between relevant and non-relevant coronary stenoses by FFR.

[50] *Wasyluk W, Zwolak A*. **Metabolic Alterations in Sepsis**. Journal of clinical medicine 2021; 10.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=34072402

ABSTRACT

Sepsis is defined as "life-threatening organ dysfunction caused by a dysregulated host response to infection". Contrary to the older definitions, the current one not only focuses on inflammation, but points to systemic disturbances in homeostasis, including metabolism. Sepsis leads to sepsis-induced dysfunction and mitochondrial damage, which is suggested as a major cause of cell metabolism disorders in these patients. The changes affect the metabolism of all macronutrients. The metabolism of all macronutrients is altered. A characteristic change in carbohydrate metabolism is the intensification of glycolysis, which in combination with the failure of entering pyruvate to the tricarboxylic acid cycle increases the formation of lactate. Sepsis also affects lipid metabolism-lipolysis in adipose tissue is upregulated, which leads to an increase in the level of fatty acids and triglycerides in the blood. At the same time, their use is disturbed, which may result in the accumulation of lipids and their toxic metabolites. Changes in the metabolism of ketone bodies and amino acids have also been described. Metabolic disorders in sepsis are an important area of

research, both for their potential role as a target for future therapies (metabolic resuscitation) and for optimizing the current treatment, such as clinical nutrition.

[51] *Amunugama K, Pike DP, Ford DA*. **The lipid biology of sepsis**. Journal of lipid research 2021; 62:100090.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=34087197
ABSTRACT
Sepsis, defined as the dysregulated immune response to an infection leading to organ dysfunction, is one of the leading causes of mortality around the globe. Despite the significant progress in delineating the underlying mechanisms of sepsis pathogenesis, there are currently no effective treatments or specific diagnostic biomarkers in the clinical setting. The perturbation of cell signaling mechanisms, inadequate inflammation resolution, and energy imbalance, all of which are altered during sepsis, are also known to lead to defective lipid metabolism. The use of lipids as biomarkers with high specificity and sensitivity may aid in early diagnosis and guide clinical decision making. In addition, identifying the link between specific lipid signatures and their role in sepsis pathology may lead to novel therapeutics. In this review, we discuss the recent evidence on dysregulated lipid metabolism both in experimental and human sepsis focused on bioactive lipids, fatty acids, and cholesterol as well as the enzymes regulating their levels during sepsis. We highlight not only their potential roles in sepsis pathogenesis but also the possibility of using these respective lipid compounds as diagnostic and prognostic biomarkers of sepsis.

[52] *Meshkov AN, Ershova AI, Kiseleva AV et al.* **The Prevalence of Heterozygous Familial Hypercholesterolemia in Selected Regions of the Russian Federation: The FH-ESSE-RF Study**. Journal of personalized medicine 2021; 11.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=34074024
ABSTRACT
Heterozygous familial hypercholesterolemia (HeFH) is one of the most common genetic conditions but remains substantially underdiagnosed. The aim of our study was to investigate the prevalence of HeFH in the population of 11 different regions of Russia. Individuals were selected from the Epidemiology of Cardiovascular Risk Factors and Diseases in Regions of the Russian Federation Study. All participants who had low-density lipoprotein cholesterol (LDL-C) higher than 4.9 mmol/L, or LDL-C lower than 4.9 mmol/L, but had statin therapy, were additionally examined by FH experts. FH was diagnosed using the Dutch Lipid Clinic Network criteria, incorporating genetic testing. HeFH prevalence was assessed for 18,142 participants. The prevalence of patients with definite or probable HeFH combined was 0.58% (1 in 173). A total of 16.1% of patients with definite or probable HeFH had tendon xanthomas; 36.2% had mutations in one of the three genes; 45.6% of FH patients had coronary artery disease; 63% of HeFH patients received statins; one patient received an additional PCSK9 inhibitor; no patients received ezetimibe. Only 3% of patients reached the LDL-C goal based on 2019 ESC/EAS guidelines. Underdiagnosis and undertreatment of FH in Russia underline the need for the intensification of FH detection with early and aggressive cholesterol-lowering treatment.

[53] *Bharti V, Bhardwaj A, Hood K et al.* **A systematic review and meta-analysis of lipid metabolomic signatures of Major Depressive Disorder**. Journal of psychiatric research 2021; 139:197-205.

PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=34087517
ABSTRACT
The aim of this meta-analysis was to provide a comprehensive synthesis of the evidence examining biomarker signatures in MDD patients including lipids, lipid regulatory proteins (LRP), and polyunsaturated fatty acid (PUFA) as compared to healthy individuals. We performed meta-analyses and meta-regression of the studies comparing lipid, LRP, and PUFA levels between MDD patients and healthy individuals by searching Embase, Ovid Medline, Scopus, PsycINFO, PubMed, and Cochrane databases. Search was performed in these databases up to September 2019 and 29 studies were included. Levels of lipid parameter triglyceride (TG) (SMD 0.55, 95% CI 0.30-0.80, $p < 0.0001$) were higher while total cholesterol (TC) (SMD = -0.46, 95%CI -0.93 to -0.001, $p = 0.04$) and very low-density lipoprotein (VLDL) (SMD = -0.46, 95%CI -0.71 to -0.20, $p = 0.02$) were lower in MDD patients than controls. Subgroup analysis for age showed that the levels of high-density lipoprotein (HDL) were lower in ≥40-year age group (SMD = -0.38, 95%CI -0.70 to -0.06, $p = 0.01$) and levels of TC was lower in MDD patients in studies from Asian countries (SMD = -0.74, 95%CI -1.37 to -0.10, $p = 0.02$). TG levels were found to be high all subgroups in MDD patients than controls. A negative association between TC levels and use of lipid lowering medications and a positive association between smoking and LDL levels was found using meta-regression analysis. This study will be useful for physicians when considering the assessment of lipidand LRP profiles in MDD patients to reduce the cardiovascular morbidity and mortality.

[54] *Chen MH, Yang FC, Liang CS*. **APOE Allele Testing and Alzheimer Disease**. Jama 2021; 325:2210-2211.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=34061149
ABSTRACT

[55] *Choudhury P, Ramanan VK, Boeve BF*. **APOE Allele Testing and Alzheimer Disease-Reply**. Jama 2021; 325:2211.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=34061147
ABSTRACT

[56] *Polonsky TS, McDermott MM*. **Lower Extremity Peripheral Artery Disease Without Chronic Limb-Threatening Ischemia: A Review**. Jama 2021; 325:2188-2198.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=34061140
ABSTRACT
IMPORTANCE: Lower extremity peripheral artery disease (PAD) affects approximately 8.5 million people in the US and approximately 230 million worldwide. OBSERVATIONS: Peripheral artery disease is uncommon before aged 50 years but affects up to 20% of people aged 80 years and older. It can be noninvasively diagnosed with the ankle-brachial index (ABI), a ratio of Doppler-recorded pressures in the dorsalis pedis and/or posterior tibial artery in each leg to brachial artery pressures. An ABI value less than 0.90 is 57% to 79% sensitive and 83% to 99% specific for arterial stenosis of at least 50%. Intermittent claudication, consisting of exertional calf pain that does not begin at rest and that resolves within 10 minutes of rest, is considered the classic symptom of PAD. However, 70% to 90% of people with an ABI value less than 0.90 either report no exertional leg symptoms (ie, asymptomatic) or report leg symptoms with walking that are not consistent with classic claudication.

Over time, people with PAD restrict walking activity or slow walking speed to avoid leg symptoms. Thus, although approximately 75% of people with PAD report no change in leg symptoms over time, those with PAD have significantly greater annual declines in 6-minute walk performance compared with those without it. Approximately 11% of people with PAD develop chronic limb-threatening ischemia, the most severe form of PAD. Compared with people without PAD, those with the disease have approximately twice the rate of all-cause mortality, cardiovascular mortality, and major coronary events at 10-year follow-up. High-dose statins and antiplatelet therapy with or without antithrombotic therapy reduced rates of coronary events and stroke in people with PAD. Supervised treadmill exercise improved 6-minute walk distance by 30 to 35 m, consistent with a clinically meaningful change, whereas effective home-based walking exercise interventions improved 6-minute walk by 42 to 53 m. Effective home-based exercise programs require behavioral methods, including monitoring by a coach. CONCLUSIONS AND RELEVANCE: Peripheral artery disease affects approximately 230 million people worldwide and is associated with increased rates of cardiovascular events, lower extremity events, and functional decline compared with that of people without PAD. People with PAD should be treated with the highest dose of statin tolerated, antithrombotic and/or antiplatelet therapy, and exercise.

[57] *Rubin R*. **Could Statins Do More Than Lower Cholesterol in Patients With COVID-19?** Jama 2021; 325:2424-2425.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=34081086
ABSTRACT

[58] *Verma S, Singh P, Khurana S et al.* **Implications of oxidative stress in chronic kidney disease: a review on current concepts and therapies**. Kidney Res Clin Pract 2021; 40:183-193.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=34078023
ABSTRACT
Moderate levels of endogenous reactive oxygen species (ROS) are important for various cellular activities, but high levels lead to toxicity and are associated with various diseases. Levels of ROS are maintained as a balance between oxidants and antioxidants. Accumulating data suggest that oxidative stress is a major factor in deterioration of renal function. In this review, we highlight the possible mechanism by which oxidative stress can lead to chronic kidney disease (CKD). This review also describes therapies that counter the effect of oxidative stress in CKD patients. Numerous factors such as upregulation of genes involved in oxidative phosphorylation and ROS generation, chronic inflammation, vitamin D deficiency, and a compromised antioxidant defense mechanism system cause progressive detrimental effects on renal function that eventually lead to loss of kidney function. Patients with renal dysfunction are highly susceptible to oxidative stress, as risk factors such as diabetes, renal hypertension, dietary restrictions, hemodialysis, and old age predispose them to increased levels of ROS. Biomolecular adducts (DNA, proteins, and lipids) formed due to reaction with ROS can be used to determine oxidative stress levels. Based on the strong correlation between oxidative stress and CKD, reversal of oxidative stress is being explored as a major therapeutic option. Xanthine oxidase inhibitors, dietary antioxidants, and other agents that scavenge free radicals are gaining interest as treatment modalities in CKD patients.

[59] *Pęczek P, Leśniewski M, Mazurek T et al.* **Antiplatelet Effects of PCSK9 Inhibitors in Primary Hypercholesterolemia**. Life (Basel) 2021; 11.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=34071103

ABSTRACT

Proprotein convertase subtilisin-kexin type 9 (PCSK9) inhibitors are a novel group of hypolipidemic drugs that are recommended particularly for high-risk hypercholesterolemia patients, including those with primary hypercholesterolemia (PH), where lifelong exposure to high low-density lipoprotein (LDL) cholesterol levels results in an elevated risk of atherosclerosis at an early age. The onset and progression of atherosclerosis is significantly influenced by activated platelets. Oxidized LDL influences platelet activation by interacting with their surface receptors and remodeling the composition of their cell membrane. This results in platelet aggregation, endothelial cell activation, promotion of inflammation and oxidative stress, and acceleration of lipid accumulation in atherosclerotic plaques. PCSK9 inhibitors reduce platelet activation by both significantly lowering LDL levels and reducing the LDL receptor-mediated activation of platelets by PCSK9. They also work synergistically with other hypolipidemic and antithrombotic drugs, including statins, ezetimibe, acetylsalicylic acid, clopidogrel, and ticagrelor, which enhances their antiplatelet and LDL-lowering effects. In this review, we summarize the currently available evidence on platelet hyperreactivity in PH, the effects of PCSK9 inhibitors on platelets, and their synergism with other drugs used in PH therapy.

[60] *Kim J, Bae YJ, Shin SJ et al.* **The ratio of triglycerides to high-density lipoprotein cholesterol is associated with the risk of chronic kidney disease in Korean men**. Lipids 2021.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=34089267

ABSTRACT

Dyslipidemia is nephrotoxic and can result in the development of chronic kidney disease (CKD). The ratio of triglycerides (TG) to high-density lipoprotein cholesterol (HDL-C) (TG/HDL-C ratio) is well-correlated with insulin resistance and cardiovascular events. The aim of this study is to examine the association between the TG/HDL-C ratio and CKD in Korean adults. This study was retrospectively designed based on the National Health Insurance Service-National Health Screening cohort. Seventy three thousand and fifty-two participants aged between 40 and 79 years old at baseline (2009-2010) were included in the final analyses. The study population was classified into three tertile groups (T(1) , T(2) , and T(3)) according to the TG/HDL-C ratio by sex. Adjusted hazard ratios (HRs) and 95% confidence intervals (CIs) for CKD were calculated using Cox proportional hazard regression models. The median follow-up duration was 5.9 years. Higher tertile groups of the TG/HDL-C ratio had lower estimated glomerular filtration rates in both sexes. The cumulative incidence of CKD of T(1) , T(2) , and T(3) was 11.89%, 12.90%, and 12.91%, respectively, in men and 10.17%, 10.61%, and 14.87%, respectively, in women (all p values $<$ 0.001). Compared with T(1) of the TG/HDL-C ratio, the HRs (95% CIs) of T(2) and T(3) for CKD were 1.212 (1.118-1.315) and 1.183 (1.087-1.287), respectively, in men and 0.895 (0.806-0.994) and 1.038 (0.937-1.150), respectively, in women after being fully adjusted. Higher TG/HDL-C ratios were positively associated with CKD development in men, while middle levels of TG/HDL ratios reduced the CKD incidence in women.

[61] *Schooneveldt YL, Giles C, Keating MF et al.* **The Impact of Simvastatin on Lipidomic Markers of Cardiovascular Risk in Human Liver Cells Is Secondary to the Modulation of Intracellular Cholesterol**. Metabolites 2021; 11.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=34070445

ABSTRACT

Statins are the first-line lipid-lowering therapy for reducing cardiovascular disease (CVD) risk. A plasma lipid ratio of two phospholipids, PI(36:2) and PC(18:0_20:4), was previously identified to explain 58% of the relative CVD risk reduction associated with pravastatin, independent of a change in low-density lipoprotein-cholesterol. This ratio may be a potential biomarker for the treatment effect of statins; however, the underlying mechanisms linking this ratio to CVD risk remain unclear. In this study, we investigated the effect of altered cholesterol conditions on the lipidome of cultured human liver cells (Hep3B). Hep3B cells were treated with simvastatin (5 µM), cyclodextrin (20 mg/mL) or cholesterol-loaded cyclodextrin (20 mg/mL) for 48 hours and their lipidomes were examined. Induction of a low-cholesterol environment via simvastatin or cyclodextrin was associated with elevated levels of lipids containing arachidonic acid and decreases in phosphatidylinositol species and the PI(36:2)/PC(18:0_20:4) ratio. Conversely, increasing cholesterol levels via cholesterol-loaded cyclodextrin resulted in reciprocal regulation of these lipid parameters. Expression of genes involved in cholesterol and fatty acid synthesis supported the lipidomics data. These findings demonstrate that the PI(36:2)/PC(18:0_20:4) ratio responds to changes in intracellular cholesterol abundance per se, likely through a flux of the n-6 fatty acid pathway and altered phosphatidylinositol synthesis. These findings support this ratio as a potential marker for CVD risk reduction and may be useful in monitoring treatment response.

[62] *Kosowski M, Smolarczyk-Kosowska J, Hachuła M et al.* **The Effects of Statins on Neurotransmission and Their Neuroprotective Role in Neurological and Psychiatric Disorders**. Molecules (Basel, Switzerland) 2021; 26.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=34064670

ABSTRACT

Statins are among the most widely used drug classes in the world. Apart from their basic mechanism of action, which is lowering cholesterol levels, many pleiotropic effects have been described so far, such as anti-inflammatory and antiatherosclerotic effects. A growing number of scientific reports have proven that these drugs have a beneficial effect on the functioning of the nervous system. The first reports proving that lipid-lowering therapy can influence the development of neurological and psychiatric diseases appeared in the 1990s. Despite numerous studies about the mechanisms by which statins may affect the functioning of the central nervous system (CNS), there are still no clear data explaining this effect. Most studies have focused on the metabolic effects of this group of drugs, however authors have also described the pleiotropic effects of statins, pointing to their probable impact on the neurotransmitter system and neuroprotective effects. The aim of this paper was to review the literature describing the impacts of statins on dopamine, serotonin, acetylcholine, and glutamate neurotransmission, as well as their neuroprotective role. This paper focuses on the mechanisms by which statins affect neurotransmission, as well as on their impacts on neurological and psychiatric diseases such as Parkinson's disease (PD), Alzheimer's disease (AD), vascular dementia (VD), stroke, and depression. The pleiotropic effects of statin usage could potentially open

floodgates for research in these treatment domains, catching the attention of researchers and clinicians across the globe.

[63] *Krysiak R, Basiak M, Okopień B*. **Cardiometabolic Risk Factors in Rosuvastatin-Treated Men with Mixed Dyslipidemia and Early-Onset Androgenic Alopecia**. Molecules (Basel, Switzerland) 2021; 26.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=34064815
ABSTRACT
Men with early-onset androgenetic alopecia are characterized by hormonal profiles similar to those observed in women with polycystic ovary syndrome. The purpose of this research was to investigate levels of cardiometabolic risk factors in 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA)-treated men with early-onset androgenic alopecia. We studied two matched rosuvastatin-treated groups of men with mixed dyslipidemia: subjects with early-onset androgenic alopecia (group A) and subjects with normal hair growth (group B). Plasma lipids, glucose homeostasis markers, and levels of sex hormones, uric acid, hsCRP, homocysteine, fibrinogen, and 25-hydroxyvitamin D were measured before entering the study and six months later. Both groups differed in insulin sensitivity and levels of calculated bioavailable testosterone, dehydroepiandrosterone-sulfate, uric acid, hsCRP, fibrinogen, and 25-hydroxyvitamin D. Though observed in both study groups, treatment-induced reductions in total cholesterol, LDL cholesterol, hsCRP, and fibrinogen were more pronounced in group B than group A. Moreover, only in group A did rosuvastatin deteriorate insulin sensitivity, and only in group B did the drug affect uric acid, homocysteine, and 25-hydroxyvitamin D. The impact of rosuvastatin on cardiometabolic risk factors correlated with insulin sensitivity, calculated bioavailable testosterone, and dehydroepiandrosterone-sulfate. The obtained results suggest that men with early-onset androgenic alopecia may benefit to a lesser degree from rosuvastatin treatment than their peers.

[64] *Robson A*. **Three different therapies to target PCSK9**. Nature reviews. Cardiology 2021.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=34089000
ABSTRACT

[65] *Alzahrani AH, Skytte MJ, Samkani A et al.* **Effects of a Self-Prepared Carbohydrate-Reduced High-Protein Diet on Cardiovascular Disease Risk Markers in Patients with Type 2 Diabetes**. Nutrients 2021; 13.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=34067585
ABSTRACT
We previously observed beneficial effects of a carbohydrate-reduced, high-protein (CRHP) diet on cardiovascular risk markers in patients with type 2 diabetes mellitus (T2DM) in a crossover 2 × 6-week trial, when all food was provided to subjects as ready-to-eat meals. Here, we report the results from a 6-month open label extension: 28 patients with T2DM were instructed to self-prepare the CRHP diet with dietetic guidance. At weeks 0, 6, 12, and 36, fasting and postprandial (4-h meal test) blood samples were collected for measurements of total, high-density lipoprotein (HDL) and low-density lipoprotein (LDL) cholesterol, triacylglycerol (TG), apolipoproteins A1 and B, non-esterified fatty acids (NEFA), C-reactive protein (CRP), tumor necrosis factor-α (TNF-α), and interleukin-6. Diurnal blood pressure and heart rate were also assessed. At the end of the study (week 36), concentrations of fasting total and LDL-cholesterol, fasting and postprandial NEFA and TG, and

fasting apolipoprotein-B, CRP and TNF-α concentrations were significantly lower compared with week 0 ($p < 0.05$). A significant decrease in diurnal heart rate was also observed. From week 12 to 36, an increase in HDL-cholesterol and apolipoprotein-A1 concentrations and a further reduction in fasting and postprandial NEFA ($p < 0.05$) were found. These changes were independent of minor fluctuations in body weight. We conclude that the substitution of dietary carbohydrate for protein and fat has beneficial effects on several cardiovascular risk markers in patients with T2DM, which are maintained or augmented over the next 6 months when patients select and prepare the CRHP diet on their own in a dietitian-supported setting.

[66] *Dowis K, Banga S*. **The Potential Health Benefits of the Ketogenic Diet: A Narrative Review**. Nutrients 2021; 13.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=34068325
ABSTRACT
Considering the lack of a comprehensive, multi-faceted overview of the ketogenic diet (KD) in relation to health issues, we compiled the evidence related to the use of the ketogenic diet in relation to its impact on the microbiome, the epigenome, diabetes, weight loss, cardiovascular health, and cancer. The KD diet could potentially increase genetic diversity of the microbiome and increase the ratio of Bacteroidetes to Firmicutes. The epigenome might be positively affected by the KD since it creates a signaling molecule known as β-hydroxybutyrate (BHB). KD has helped patients with diabetes reduce their HbA1c and reduce the need for insulin. There is evidence to suggest that a KD can help with weight loss, visceral adiposity, and appetite control. The evidence also suggests that eating a high-fat diet improves lipid profiles by lowering low-density lipoprotein (LDL), increasing high-density lipoprotein (HDL), and lowering triglycerides (TG). Due to the Warburg effect, the KD is used as an adjuvant treatment to starve cancer cells, making them more vulnerable to chemotherapy and radiation. The potential positive impacts of a KD on each of these areas warrant further analysis, improved studies, and well-designed randomized controlled trials to further illuminate the therapeutic possibilities provided by this dietary intervention.

[67] *Kopylov AT, Malsagova KA, Stepanov AA, Kaysheva AL*. **Diversity of Plant Sterols Metabolism: The Impact on Human Health, Sport, and Accumulation of Contaminating Sterols**. Nutrients 2021; 13.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=34066075
ABSTRACT
The way of plant sterols transformation and their benefits for humans is still a question under the massive continuing revision. In fact, there are no receptors for binding with sterols in mammalians. However, possible biotransformation to steroids that can be catalyzed by gastro-intestinal microflora, microbial cells in prebiotics or cytochromes system were repeatedly reported. Some products of sterols metabolization are capable to imitate resident human steroids and compete with them for the binding with corresponding receptors, thus affecting endocrine balance and entire physiology condition. There are also tremendous reports about the natural origination of mammalian steroid hormones in plants and corresponding receptors for their binding. Some investigations and reports warn about anabolic effect of sterols, however, there are many researchers who are reluctant to believe in and have strong opposing arguments. We encounter plant sterols everywhere: in food, in pharmacy, in cosmetics, but still know little about their diverse properties and, hence, their exact

impact on our life. Most of our knowledge is limited to their cholesterol-lowering influence and protective effect against cardiovascular disease. However, the world of plant sterols is significantly wider if we consider the thousands of publications released over the past 10 years.

[68] *Patel YR, Imran TF, Ellison RC et al.* **Sugar-Sweetened Beverage Consumption and Calcified Atherosclerotic Plaques in the Coronary Arteries: The NHLBI Family Heart Study**. Nutrients 2021; 13.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=34067500
ABSTRACT
BACKGROUND: Sugar-sweetened beverage (SSB) intake is associated with higher risk of weight gain, diabetes, hypertension, cardiovascular disease, and cardiovascular mortality. However, the association of SSB with subclinical atherosclerosis in the general population is unknown. OBJECTIVE: Our primary objective was to investigate the association between SSB intake and prevalence of atherosclerotic plaque in the coronary arteries in The National Heart, Lung, and Blood Institute (NHLBI) Family Heart Study. METHODS: We studied 1991 participants of the NHLBI Family Heart Study without known coronary heart disease. Intake of SSB was assessed through a semi-quantitative food frequency questionnaire. Coronary artery calcium (CAC) was measured by cardiac Computed Tomography (CT) and prevalent CAC was defined as an Agatston score ≥100. We used generalized estimating equations to calculate adjusted prevalence ratios of CAC. A sensitivity analysis was also performed at different ranges of cut points for CAC. RESULTS: Mean age and body mass index (BMI) were 55.0 years and 29.5 kg/m(2), respectively, and 60% were female. In analysis adjusted for age, sex, BMI, smoking, alcohol use, physical activity, energy intake, and field center, higher SSB consumption was not associated with higher prevalence of CAC [prevalence ratio (95% confidence interval) of: 1.0 (reference), 1.36 (0.70-2.63), 1.69 (0.93-3.09), 1.21 (0.69-2.12), 1.05 (0.60-1.84), and 1.58 (0.85-2.94) for SSB consumption of almost never, 1-3/month, 1/week, 2-6/week, 1/day, and ≥2/day, respectively (p for linear trend 0.32)]. In a sensitivity analysis, there was no evidence of association between SSB and prevalent CAC when different CAC cut points of 0, 50, 150, 200, and 300 were used. CONCLUSIONS: These data do not provide evidence for an association between SSB consumption and prevalent CAC in adult men and women.

[69] *Sabouret P, Angoulvant D, Pathak A et al.* **How to fill the GAPS-I in secondary prevention: application of a strategy based on GLP1 analogues, antithrombotic agents, PCSK9 inhibitors, SGLT2 inhibitors and immunomodulators**. Panminerva medica 2021.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=34060278
ABSTRACT
The continuous progress in cardiovascular (CV) risk prevention strategies has led to an impressive reduction in mortality and recurrent ischemic events in patients with coronary artery disease (CAD). However, the control of several CV risk factors remains suboptimal in many CAD patients, with a high rate of recurrent events, underlying the need for more new prevention strategies. The GAPS-I (GLP1 analogues, Antithrombotic agents, PCSK9 inhibitors, SGLT2 inhibitors and Immunomodulators) strategy offers a promising potential in patients with a high-residual CV risk, who are frequently encountered in daily practice, by offering an individualised and structured approach to addressing their individual risk factors. The current review summarises the evidence to date on each of its components, with respect to clinical outcomes and economic feasibility. The current evidence points

to an efficacy of GAPS-I in reducing MACE and mortality, without a compromise on safety, albeit with the need for longer follow-up data. Key Points: - Secondary prevention remains suboptimal in many CAD patients, highlighting the need for innovative prevention strategies. - The present review discusses the current evidence on efficacy of the GAPS-I strategy in reducing MACE and mortality in patients with CAD. - The GAPS-I strategy, if widely adopted, provides a promising potential to assist cardiologists in managing patients at a heightened risk for further CV events.

[70] *Tilija Pun N, Jeong CH*. **Statin as a Potential Chemotherapeutic Agent: Current Updates as a Monotherapy, Combination Therapy, and Treatment for Anti-Cancer Drug Resistance**. Pharmaceuticals (Basel, Switzerland) 2021; 14.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=34065757
ABSTRACT
Cancer is incurable because progressive phenotypic and genotypic changes in cancer cells lead to resistance and recurrence. This indicates the need for the development of new drugs or alternative therapeutic strategies. The impediments associated with new drug discovery have necessitated drug repurposing (i.e., the use of old drugs for new therapeutic indications), which is an economical, safe, and efficacious approach as it is emerged from clinical drug development or may even be marketed with a well-established safety profile and optimal dosing. Statins are inhibitors of HMG-CoA reductase in cholesterol biosynthesis and are used in the treatment of hypercholesterolemia, atherosclerosis, and obesity. As cholesterol is linked to the initiation and progression of cancer, statins have been extensively used in cancer therapy with a concept of drug repurposing. Many studies including in vitro and in vivo have shown that statin has been used as monotherapy to inhibit cancer cell proliferation and induce apoptosis. Moreover, it has been used as a combination therapy to mediate synergistic action to overcome anti-cancer drug resistance as well. In this review, the recent explorations are done in vitro, in vivo, and clinical trials to address the action of statin either single or in combination with anti-cancer drugs to improve the chemotherapy of the cancers were discussed. Here, we discussed the emergence of statin as a lipid-lowering drug; its use to inhibit cancer cell proliferation and induction of apoptosis as a monotherapy; and its use in combination with anti-cancer drugs for its synergistic action to overcome anti-cancer drug resistance. Furthermore, we discuss the clinical trials of statins and the current possibilities and limitations of preclinical and clinical investigations.

[71] *Reig-López J, García-Arieta A, Mangas-Sanjuán V, Merino-Sanjuán M*. **Current Evidence, Challenges, and Opportunities of Physiologically Based Pharmacokinetic Models of Atorvastatin for Decision Making**. Pharmaceutics 2021; 13.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=34068030
ABSTRACT
Atorvastatin (ATS) is the gold-standard treatment worldwide for the management of hypercholesterolemia and prevention of cardiovascular diseases associated with dyslipidemia. Physiologically based pharmacokinetic (PBPK) models have been positioned as a valuable tool for the characterization of complex pharmacokinetic (PK) processes and its extrapolation in special sub-groups of the population, leading to regulatory recognition. Several PBPK models of ATS have been published in the recent years, addressing different aspects of the PK properties of ATS. Therefore, the aims of this review are (i) to summarize the physicochemical and pharmacokinetic characteristics involved in the time-course of ATS, and (ii) to evaluate the major highlights and limitations of the

PBPK models of ATS published so far. The PBPK models incorporate common elements related to the physicochemical aspects of ATS. However, there are important differences in relation to the analyte evaluated, the type and effect of transporters and metabolic enzymes, and the permeability value used. Additionally, this review identifies major processes (lactonization, P-gp contribution, ATS-Ca solubility, simultaneous management of multiple analytes, and experimental evidence in the target population), which would enhance the PBPK model prediction to serve as a valid tool for ATS dose optimization.

[72] *Krysiak R, Basiak M, Szkróbka W, Okopień B*. **The impact of rosuvastatin on hypothalamic-pituitary-testicular axis activity in metformin-treated and metformin-naïve men with low testosterone levels: a pilot study**. Pharmacological reports : PR 2021.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=34086261
ABSTRACT
BACKGROUND: Intense statin therapy was found to impair testosterone production in men. Metformin administered to subjects with hypergonadotropic hypogonadism decreased gonadotropin production. The current study was aimed at investigating whether metformin treatment modulates the impact of high-dose rosuvastatin therapy on hypothalamic-pituitary-testicular axis activity in men. METHODS: The study included 43 very high cardiovascular risk men with late-onset hypogonadism, 20 of whom had been treated with metformin (1.7-3 g daily) for at least 6 months. In all subjects, unsuccessful initial statin treatment was replaced with rosuvastatin (20-40 mg daily). Plasma lipid levels, glucose homeostasis markers, as well as circulating levels of gonadotropins, testosterone, bioavailable testosterone, dehydroepiandrosterone-sulfate, prolactin, estradiol and creatinine were measured at the beginning of the study and 4 months later in 28 individuals in whom rosuvastatin reduced LDL cholesterol levels to below 70 mg/dL. RESULTS: There were no differences between treatment-induced changes in plasma lipids. In both study groups, rosuvastatin reduced total and bioavailable testosterone levels. However, only in metformin-naïve men, rosuvastatin increased LH and FSH levels and slightly impaired insulin sensitivity. The impact on gonadotropin concentrations correlated with treatment-induced decrease in testosterone levels. There were no significant differences between baseline and posttreatment values of dehydroepiandrosterone-sulfate, prolactin, estradiol and the glomerular filtration rate. CONCLUSION: The obtained results suggest that metformin prevents the compensatory increase in gonadotrope function induced by intense statin therapy.

[73] *Dhawan UK, Singhal A, Subramanian M*. **Dead cell and debris clearance in the atherosclerotic plaque: Mechanisms and therapeutic opportunities to promote inflammation resolution**. Pharmacological research : the official journal of the Italian Pharmacological Society 2021; 170:105699.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=34087352
ABSTRACT
Phagocytic clearance of dead cells and debris is critical for inflammation resolution and maintenance of tissue homeostasis. Consequently, defective clearance of dead cells and debris is associated with initiation and exacerbation of several autoimmune disorders and chronic inflammatory diseases such as atherosclerosis. The progressive loss of dead cell clearance capacity within the atherosclerotic plaque leads to accumulation of necrotic cells, chronic non-resolving inflammation, and expansion of

the necrotic core, which triggers atherosclerotic plaque rupture and clinical manifestation of acute thrombotic cardiovascular adverse events. In this review, we describe the fundamental molecular and cellular mechanisms of dead cell clearance and how it goes awry in atherosclerosis. Finally, we highlight novel therapeutic strategies that enhance dead cell and debris clearance within the atherosclerotic plaque to promote inflammation resolution and atherosclerotic plaque stabilization.

[74] *Xu S, Ilyas I, Little PJ et al.* **Endothelial Dysfunction in Atherosclerotic Cardiovascular Diseases and Beyond: From Mechanism to Pharmacotherapies**. Pharmacological reviews 2021; 73:924-967.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=34088867
ABSTRACT
The endothelium, a cellular monolayer lining the blood vessel wall, plays a critical role in maintaining multiorgan health and homeostasis. Endothelial functions in health include dynamic maintenance of vascular tone, angiogenesis, hemostasis, and the provision of an antioxidant, anti-inflammatory, and antithrombotic interface. Dysfunction of the vascular endothelium presents with impaired endothelium-dependent vasodilation, heightened oxidative stress, chronic inflammation, leukocyte adhesion and hyperpermeability, and endothelial cell senescence. Recent studies have implicated altered endothelial cell metabolism and endothelial-to-mesenchymal transition as new features of endothelial dysfunction. Endothelial dysfunction is regarded as a hallmark of many diverse human panvascular diseases, including atherosclerosis, hypertension, and diabetes. Endothelial dysfunction has also been implicated in severe coronavirus disease 2019. Many clinically used pharmacotherapies, ranging from traditional lipid-lowering drugs, antihypertensive drugs, and antidiabetic drugs to proprotein convertase subtilisin/kexin type 9 inhibitors and interleukin 1β monoclonal antibodies, counter endothelial dysfunction as part of their clinical benefits. The regulation of endothelial dysfunction by noncoding RNAs has provided novel insights into these newly described regulators of endothelial dysfunction, thus yielding potential new therapeutic approaches. Altogether, a better understanding of the versatile (dys)functions of endothelial cells will not only deepen our comprehension of human diseases but also accelerate effective therapeutic drug discovery. In this review, we provide a timely overview of the multiple layers of endothelial function, describe the consequences and mechanisms of endothelial dysfunction, and identify pathways to effective targeted therapies. SIGNIFICANCE STATEMENT: The endothelium was initially considered to be a semipermeable biomechanical barrier and gatekeeper of vascular health. In recent decades, a deepened understanding of the biological functions of the endothelium has led to its recognition as a ubiquitous tissue regulating vascular tone, cell behavior, innate immunity, cell-cell interactions, and cell metabolism in the vessel wall. Endothelial dysfunction is the hallmark of cardiovascular, metabolic, and emerging infectious diseases. Pharmacotherapies targeting endothelial dysfunction have potential for treatment of cardiovascular and many other diseases.

[75] *Grgurević D, Grgurević J, Vrca VB et al.* **Incidence of potential drug interactions in co-prescription of statins and macrolide antibiotics in Croatia during the 14 year period**. Pharmazie 2021; 76:272-278.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=34078522
ABSTRACT

The objective of this study was to determine the number of patients on the national level that took macrolide antibiotics along with chronic statin therapy in Croatia in the period from 2002 to 2015, and to analyse prescription patterns. In 2002, statins were used in the treatment of 2.6% of the total number of insured persons in Croatia. By 2015, this number increased to 8.4%. In the period studied, on average 15.3% of the patients on statin therapy were co-prescribed macrolide antibiotics. Erythromycin was combined with different statins on average in 1.4% of cases, clarithromycin in 25.5% and azithromycin in 73.2% of the cases. Relative frequency of combining statins with macrolides was similar for all statins. On average, 11.5% of patients on concomitant statin-macrolide therapy were taking high-dose statins. On average, 90% of these co-prescriptions can lead to potentially clinically significant DDIs (X, D, C). The co-prescription of statins and macrolide antibiotics in the Republic of Croatia is increasing. The greatest number of co-prescriptions with macrolides were with atorvastatin and simvastatin.

[76] *Alhabib KF, Al-Rasadi K, Almigbal TH et al.* **Familial Hypercholesterolemia in the Arabian Gulf Region: Clinical results of the Gulf FH Registry**. PloS one 2021; 16:e0251560.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=34086694
ABSTRACT
BACKGROUND AND AIMS: Familial hypercholesterolemia (FH) is a common autosomal dominant disorder that can result in premature atherosclerotic cardiovascular disease (ASCVD). Limited data are available worldwide about the prevalence and management of FH. Here, we aimed to estimate the prevalence and management of patients with FH in five Arabian Gulf countries (Saudi Arabia, Oman, United Arab Emirates, Kuwait, and Bahrain). METHODS: The multicentre, multinational Gulf FH registry included adults (≥18 years old) recruited from outpatient clinics in 14 tertiary-care centres across five Arabian Gulf countries over the last five years. The Gulf FH registry had four phases: 1-screening, 2- classification based on the Dutch Lipid Clinic Network, 3- genetic testing, and 4- follow-up. RESULTS: Among 34,366 screened patient records, 3713 patients had suspected FH (mean age: 49±15 years; 52% women) and 306 patients had definite or probable FH. Thus, the estimated FH prevalence was 0.9% (1:112). Treatments included high-intensity statin therapy (34%), ezetimibe (10%), and proprotein convertase subtilisin/kexin type 9 inhibitors (0.4%). Targets for low-density lipoprotein cholesterol (LDL-C) and non-high-density lipoprotein cholesterol were achieved by 12% and 30%, respectively, of patients at high ASCVD risk, and by 3% and 6%, respectively, of patients at very high ASCVD risk ($p < 0.001$; for both comparisons). CONCLUSIONS: This snap-shot study was the first to show the high estimated prevalence of FH in the Arabian Gulf region (about 3-fold the estimated prevalence worldwide), and is a "call-to-action" for further confirmation in future population studies. The small proportions of patients that achieved target LDL-C values implied that health care policies need to implement nation-wide screening, raise FH awareness, and improve management strategies for FH.

[77] *Gai MT, Adi D, Chen XC et al.* **Polymorphisms of rs2483205 and rs562556 in the PCSK9 gene are associated with coronary artery disease and cardiovascular risk factors**. Scientific reports 2021; 11:11450.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=34075144
ABSTRACT

PCSK9 plays a crucial role in lipid metabolism. This case-control study explored the associations of novel single nucleotide polymorphisms (SNPs) of the PCSK9 gene with coronary artery disease (CAD) (≥1 coronary artery stenosis≥50%) and its risk factors in the Han population in Xinjiang, China. Four tag SNPs (rs11583680, rs2483205, rs2495477 and rs562556) of the PCSK9 gene were genotyped in 950 CAD patients and 1082 healthy controls. The distributions of genotypes in rs2483205 and rs562556 were significantly different between the groups (all $p<0.05$). The TT genotype of rs2483205, GG genotype of rs562556, and their H4 (T-G) haplotype were associated with CAD [odds ratio (OR) 0.65, confidence interval (CI) 0.45-0.95, $p=0.024$; 0.63, 0.45-0.90, $p=0.011$; 0.50, 0.35-0.70, $p<0.001$, respectively]. Additionally, the model (TT + CT vs. CC) of rs2483205 was associated with increased risk of obesity, and the G allele of rs562556 was associated with lower low-density lipoprotein cholesterol (LDL-C), blood glucose, body mass index (BMI), and mean platelet volume (MPV) (all $p<0.05$). rs2483205, rs562556, and their H4 haplotype of the PCSK9 gene were associated with CAD. Additionally, rs2483205 is associated with obesity, and rs562556 is associated with LDL-C, blood glucose, BMI, and MPV.

[78] *Kaiser K, Nielsen MF, Kallfa E et al.* **Metabolic syndrome in women with previous gestational diabetes**. Scientific reports 2021; 11:11558.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=34078945

ABSTRACT

To evaluate the incidence and timing of the diagnosis of metabolic syndrome in a cohort of Danish women after a pregnancy with gestational diabetes (GDM) to estimate the optimum time for preventative actions in relation to metabolic syndrome (MetS). In this follow-up study, 435 women were included from a consecutive cohort with prior history of GDM. Data on dyslipidemia, hypertension and other cardiovascular disorders (CVD) were extracted from the electronic patient journal. Any antidiabetic, cardiovascular and cholesterol-lowering medicine was ascertained in the national prescription database. Similarly, any blood test taken was evaluated. We defined a patient having MetS if the criteria of the WHO based definition of diabetes or impaired glucose regulation were met. Further, we added as alternative for glucose intolerance, a glycosylated hemoglobin (HbA1c)>44 mmol/mol or the former level≥6.5%. Further, dyslipidemia, lipid lowering medications, BMI>30 kg/m(2) or antihypertensive treatment were used. For MetS outcome, diagnosis or medication for CVD was registered. All women were followed for median 5.7 years (range 0; 9). The incidence of MetS was 28%. Thirteen percent of these qualified already within one year after pregnancy for the diagnosis of MetS. Postpartum MetS was detected after a median of 3 years (range 0; 7 years); further, 36 (8%) had been diagnosed with manifest diabetes after pregnancy. The diagnosis of postpartum MetS was strongly associated with the prevalence of manifest diabetes. Six years after pregnancy the rate of metabolic syndrome was more than tripled (25 vs. 89%, no DM vs manifest DM, RR: 6.7; 95% CI 2.7-17, $p<0.001$). At 40 years the MetS rate nearly tripled if manifest DM was diagnosed (26 vs. 78%, no DM vs. manifest DM, RR: 3.3, 95% CI 1.8-6, $p<0.001$). We found that GDM and later on manifest DM in women increase the risk of metabolic syndrome. There seems to be a window of opportunity before the early thirties where it would be especially beneficial to begin preventive efforts in women with GDM.

[79] *Tang X, Mao L, Chen J et al.* **High-sensitivity CRP may be a marker of HDL dysfunction and remodeling in patients with acute coronary syndrome**. Scientific reports 2021; 11:11444.

PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=34075063

ABSTRACT

In patients with coronary artery disease (CAD), further increasing the level of high-density lipoprotein (HDL) cholesterol (HDL-C) as an add-on to statins cannot reduce cardiovascular risk. And it has been reported that HDL functional metric-cholesterol efflux capacity (CEC) may be a better predictor of CAD risk than HDL-C. CEC measurement is time-consuming and not applicable in clinical settings. Thus, it is meaningful to explore an easily acquired index for evaluating CEC. Thirty-six CAD patients and sixty-one non-CAD controls were enrolled in this cross-sectional study. All CAD patients had acute coronary syndrome (ACS). CEC was measured using a [(3)H] cholesterol loading Raw 264.7 cell model with apolipoprotein B-depleted plasma (a surrogate for HDL). Proton nuclear magnetic resonance (NMR) spectroscopy was used to assess HDL components and subclass distribution. CEC was significantly impaired in CAD patients (11.9 ± 2.3%) compared to controls (13.0 ± 2.2%, $p = 0.022$). In control group, CEC was positively correlated with enzymatically measured HDL-C levels ($r = 0.358$, $p = 0.006$) or with NMR-determined HDL-C levels (NMR-HDL-C, $r = 0.416$, $p = 0.001$). However, in CAD group, there was no significant correlation between CEC and HDL-C ($r = 0.216$, $p = 0.206$) or NMR-HDL-C ($r = 0.065$, $p = 0.708$). Instead, we found that the level of high-sensitivity C-reactive protein (hsCRP) was inversely associated with CEC ($r = -0.351$, $p = 0.036$). Multiple regression analysis showed that the hsCRP level was associated with CEC after adjusting other cardiovascular risk factors and HDL-C, although the association would not reach significance if adjusting for multiple testing. NMR spectroscopy showed that HDL particles shifted to larger ones in patients with high hsCRP levels, and this phenomenon was accompanied by decreased CEC. In patients with CAD, the level of HDL-C cannot reflect HDL function. The impaired correlation between HDL-C and CEC is possibly due to an inflammation-induced HDL subclass remodeling. These hypothesis-generating data suggest that hsCRP levels, a marker of acute inflammation, may associate with HDL dysfunction in ACS subjects. Due to the design limited to be correlative in nature, not permitting causal inference and a larger, strictly designed study is still needed.

[80] *Xargay-Torrent S, Puerto-Carranza E, Marcelo I et al.* **Estimated glomerular filtration rate and cardiometabolic risk factors in a longitudinal cohort of children**. Scientific reports 2021; 11:11702.

PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=34083639

ABSTRACT

Associations between glomerular filtration rate (GFR) and cardiometabolic risk factors have been reported in adult and pediatric patients with renal disease. We aimed to assess the relationship between the estimated GFR (eGFR) and cardiometabolic risk factors in apparently healthy children. A longitudinal study in 401 asymptomatic Caucasian children (mean age 8 years) followed up after 4 years (mean age 12 years). GFR was estimated using the pediatric form of the FAS-equation. Children were classified at baseline according to their obesity status (normal weight and overweight) and according to eGFR levels (lower, average, and higher). The association of eGFR with anthropometric data [body mass index (BMI) and waist], blood pressure [systolic (SBP) and diastolic (DBP)], metabolic parameters [glucose, insulin resistance (HOMA-IR) and serum lipids], and renal ultrasonography measurements were assessed at baseline and follow-up. Baseline eGFR associated with several cardiometabolic risk factors at follow-up including higher waist, SBP, HOMA-IR, and kidney size (all $p < 0.0001$) in both normal weight and overweight children. In multivariate analysis,

baseline eGFR was independently associated with follow-up HOMA-IR and SBP in both normal weight and overweight subjects (model R(2): 0.188-0.444), and with follow-up BMI and waist in overweight subjects (model R(2): 0.367-0.477). Moreover, children with higher filtration rates at baseline showed higher waist, SBP, DBP, HOMA-IR and renal size both at baseline and follow-up. eGFR is related to insulin resistance, blood pressure and adiposity measures in school-age children. eGFR may help to profile the cardiometabolic risk of children.

[81] *Reynolds TM, Pottle A, Quoraishi SH*. **Current Perspectives on the Attainment of Lipid Modification Goals Relating to the Use of Statins and Ezetimibe for the Prevention of Cardiovascular Disease in the United Kingdom**. Vascular health and risk management 2021; 17:227-237.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=34054297
ABSTRACT
Despite widespread evidence of the effectiveness of lipid modification for the reduction of cardiovascular disease (CVD) risk, lipid modification goals are commonly underachieved in the United Kingdom (UK). In order to understand current UK lipid management guidance and the corresponding attainment of recommended lipid lowering goals relating to treatment with statins and ezetimibe, a literature review was conducted using PubMed focusing on publications between January 2017 and February 2020 in order to capture the most up-to-date literature. Identified publications were reviewed against key clinical guidelines for lipid management in relation to CVD risk from the National Institute for Health and Care Excellence (NICE, CG181), the Scottish Intercollegiate Guidelines Network (SIGN, 149) and European Society of Cardiology (ESC)/European Atherosclerosis Society (EAS). Cholesterol lowering goals are central to current lipid lowering therapy guidance, although specific goals vary depending on the guideline and patients' individual risk profile. Current guidance by NICE and SIGN specifies that treatment should achieve a greater than 40% reduction in non-high-density lipoprotein cholesterol (non-HDL-C) at 3 months of treatment, while the ESC/EAS place emphasis on the lowering of low-density lipoprotein (LDL-C) and total cholesterol. Yet, despite widespread availability of guidance and consistent messaging that lipid lowering goals should be ambitious, current evidence suggests a significant proportion of UK patients have sub-optimal reductions in cholesterol/non-HDL-C/LDL-C. The reasons for this are reported to be multifactorial, including a lack of compliance with guidelines, particularly regarding high-intensity statin prescribing, patient adherence, statin intolerance and statin reluctance as well as wider genetic factors. A number of possible strategies to improve current lipid management and attainment of lipid-lowering goals were identified, including improving the patient-healthcare professional partnership, conducting audits of local prescribing versus guidance, implementing plans for the refinement of current services and considering alternative options such as cost-effective single pill combinations for improving adherence.

[82] *Gaško R*. **Comparison of LDL-C calculation by Martin, Sampson and old Friedewald methods in real data and synthetic data set**. Vnitr Lek 2021; 67:9-17.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=34074099
ABSTRACT
OBJECTIVE: LDL-cholesterol (LDL-C) is determined by methods whose accuracy is significantly affected in various clinical or analytical situations. Two computational methods have recently been

described, the Martin equation and the Sampson equation, validity of which we compare with the Friedewald equation. METHODS: LDL-C comparisons determined by the 3 equations were performed on 4 real sets of lipid data, generated in various previous studies, ranging from n = 140 to n = 7 393. We have created an artificial set of data on the extent of 900 members with equally distributed values of TC, HDL-C and TG troughout the commonly found range. Such a data set is independent of the phrase "we performed the calculations on our file". Comparisons were also made on this artificial file. RESULTS: The difference between the LDL-C values determined by the different equations gradually increases with decreasing LDL-C levels, both in the subgroup of low TG values and in the subgroups of medium and higher TG values. This applies to all 4 real files as well as to the artificial file. These differences are more visible the larger the file size. For the artificial set, the overall agreement between the LDL-C categories was lowest when comparing the Friedewald and Martin equations (83.1%), higher between the Sampson and Martin equations (88.9%) and highest when comparing the Friedewald and Sampson equations (90.9%). In all 4 real sets, the trends of overestimation and underestimation between the equations were exactly the same as in the artificial set. CONCLUSION: The results of clinical and epidemiological studies are significantly influenced by the method used to determine LDL-C. When comparing the calculation methods for determining LDL-C, it is possible to preferably use the described artificial set.

[83] *Yang Q, Ma P, Dong Y et al.* **[Prevalence of cardiovascular metabolic risk factors among 12-18 years old adolescents in Yinchuan City from 2017 to 2019]**. Wei sheng yan jiu = Journal of hygiene research 2021; 50:454-459.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=34074368

ABSTRACT

OBJECTIVE: To understand the prevalence of cardiovascular metabolic risk factors among 12-18 years old children and adolescents in Yinchuan City. METHODS: A survey was conducted among 12-18 years old middle school students in Yinchuan from September 2017 to September 2019. A total of 1956 subjects were collected by using convenient sampling method, with an average age of(14. 4±1. 4) years. Boys and girls accounted for 52. 1% and 47. 9%, respectively, The Han and Hui nationalities accounted for 77. 7% and 16. 4%, respectively. Basic data such as age and gender were collected through questionnaire survey, and physical examination was used to measure height, weight, waist circumference and blood pressure. Fasting blood glucose, triglyceride(TG), total cholesterol(TC), high density lipoprotein cholesterol(HDL-C) and low density lipoprotein cholesterol(LDL-C) were measured by laboratory blood pressure biochemistry. RESULTS: The detection rates of obesity, abdominal obesity, hypertension, hyperglycemia, high TG, high LDL-C, low HDL-C, high LDL-C and dyslipidemia among 12-and 18-year-olds in Yinchuan City were 8. 3%, 17. 9%, 12. 4%, 1. 9%, 13. 2%, 2. 4%, 18. 6%, 1. 9% and 30. 1%, respectively. The detection rates of obesity, hyperglycemia, low HDL-C, high TG and dyslipidemia in boys were significantly higher than those in girls. Obesity, abdominal obesity and hypertension in 12-15-year-old group were higher than those in 16-18-year-old group, and the detection rates of high TC, low HDL-C, high LDL-C and dyslipidemia were lower than those in 16-18-year-old group(P& lt; 0. 05). The prevalence of cardiovascular risk factors in different age groups of boys and girls were compared. The detection rates of obesity, abdominal obesity and hypertension in the 12-15 age group were higher than those in the 16-18 age group, while the rates of high TG, low HDL-C, high LDL-C and dyslipidemia were higher in the 12-15 age group, but these differences were only significant in boys. Among girls, the

detection rate of high TC and high LDL-C was higher in the age group of 12 to 15 years old(P& lt; 0. 05). The detection rate of metabolic syndrome in 12-18-year-old adolescents was 7. 9%. The detection rate of metabolic syndrome in boys(10. 1%) was higher than that in girls(5. 5%). The detection rates of metabolic syndrome in 12-15 years old and 16-18 years old were 9. 1% and 4. 9% respectively, and the differences were statistically significant(P& lt; 0. 05). CONCLUSION: The prevalence of cardiovascular metabolic risk factors in 12-18 years old adolescents in Yinchuan City is at a high level, boys are higher than girls, and the prevalence of obesity, abdominal obesity and hypertension are higher in 12-15 years old group. Dyslipidemia varies greatly in different gender and age groups.