[1] Peroxisome Proliferator-Activated Receptor alpha in Lipid Metabolism and Atherosclerosis. Yu XH, Zheng XL, Tang CK. Advances in clinical chemistry 2015; 71:171-203. Atherosclerosis is a chronic inflammatory disease with deposition of excessive cholesterol in the arterial intima. Peroxisome proliferator-activated receptor alpha (PPARalpha) is a nuclear receptor that can activate or inhibit the expression of many target genes by forming a heterodimer complex with the retinoid X receptor. Activation of PPARalpha plays an important role in the metabolism of multiple lipids, including high-density lipoprotein, cholesterol, low-density lipoprotein, triglyceride, phospholipid, bile acids, and fatty acids. Increased PPARalpha activity also mitigates atherosclerosis by blocking macrophage foam cell formation, vascular inflammation, vascular smooth muscle cell proliferation and migration, plaque instability, and thrombogenicity. Clinical use of synthetic PPARalpha agonist fibrate improved dyslipidemia and attenuated atherosclerosis-related disease risk. This review summarizes PPARalpha in lipid and lipoprotein metabolism and atherosclerosis, and also highlights its potential therapeutic benefits.

[2] Treatment of Hypercholesterolemia in 2015. Aronow WS. American journal of therapeutics 2015. Randomized, double-blind, placebo-controlled secondary prevention and primary prevention studies and observational studies have documented that statins reduce cardiovascular events in high-risk patients with hypercholesterolemia. The 2013 American College of Cardiology/American Heart Association guidelines on treatment of hypercholesterolemia support the use of statins in 4 major groups that will be discussed. The Expert Panel of these guidelines could find no data supporting the routine use of nonstatin drugs combined with statins to further reduce cardiovascular events. Since these guidelines were published, a double-blind randomized trial of 18,144 patients with an acute coronary syndrome demonstrated at a 7-year follow-up that the incidence of cardiovascular events was 34.7% in patients randomized to simvastatin plus placebo versus 32.7% in patients randomized to simvastatin plus ezetimibe (hazard ratio = 0.936; P = 0.016). Proprotein convertase subtilisin/kexin type 9 inhibitors further lower serum low-density lipoprotein cholesterol by 50%-70% in patients treated with statins and 4 phase 3 trials including more than 70,000 patients are investigating whether these monoclonal antibodies to proprotein convertase subtilisin/kexin type 9 will lower cardiovascular events.

[3] Therapeutic Potential and Critical Analysis of the PCSK9 Monoclonal Antibodies Evolocumab and Alirocumab. White CM. The Annals of pharmacotherapy 2015. OBJECTIVE: To review the mechanism of action for PCSK9 monoclonal antibodies and critically evaluate the therapeutic potential of evolocumab and alirocumab in the treatment of hypercholesterolemia. DATA SOURCES: Ovid MEDLINE search from 1980 to August 2015 using the terms PCSK9, evolocumab, and alirocumab with forward and backward citation tracking. STUDY SELECTION AND DATA EXTRACTION: English-language trials and studies assessing the mechanism, efficacy, or safety of PCSK9 monoclonal antibodies were included. DATA SYNTHESIS: PCSK9 monoclonal antibodies have a potent ability to reduce low-density lipoprotein (LDL) by almost 50% in controlled trials: -47.49% (95% CI = -69.6% to -25.4%). They have an acceptable safety profile with no significant elevations in Creatine Kinase (CK) (odds ratio [OR] = 0.72; 95% CI = 0.54 to 0.96) or serious adverse events (OR = 1.01; 95% CI = 0.87 to 1.18), and preliminary evidence suggests reductions in myocardial infarction (OR = 0.49; 95% CI = 0.26 to 0.93). Although it is effective in several familial hypercholesterolemia (FH) patient types, it does not work in homozygous patients with dual allele LDL receptor negative polymorphisms or those who are homozygous for autosomal recessive hypercholesterolemia. CONCLUSIONS: Although not preferred over statins because of limited clinical trial evidence of cardiovascular event reductions, dosing convenience, and expense, PCSK9 monoclonal antibodies will have a prominent role to play in the treatment of hypercholesterolemia, especially in patients needing large LDL reductions, including patients with many types of FH.

[4] Statins Trigger Mitochondrial ROS-Induced Apoptosis in Glycolytic Skeletal Muscle. Bouitbir J, Singh F, Charles AL et al. Antioxidants & redox signaling 2015. AIMS: Although statins are the most widely used cholesterol-lowering agents, they are associated with a variety of muscle complaints. The goal of this study was to characterize the effects of statins on the mitochondrial apoptosis pathway induced by mitochondrial oxidative stress in skeletal muscle using human muscle biopsies as well as in vivo and in vitro models. RESULTS: Statins increased mitochondrial H2O2 production, the Bax/Bcl-2 ratio and TUNEL staining in deltoid biopsies of patients with statin-associated myopathy. Furthermore, atorvastatin treatment for two weeks at 10 mg/kg/day in rats increased H2O2 accumulation, and mRNA levels and
immunostaining of the Bax/Bcl-2 ratio, as well as TUNEL staining and caspase 3 cleavage in glycolytic (plantaris) skeletal muscle but not in oxidative (soleus) skeletal muscle, which has a high antioxidative capacity. Atorvastatin also decreased the GSH/GSSG ratio, but only in glycolytic skeletal muscle. Co-treatment with the antioxidant quercetin at 25 mg/kg/d abolished these effects in plantaris. An in vitro study with L6 myoblasts directly demonstrated the link between mitochondrial oxidative stress following atorvastatin exposure and activation of the mitochondrial apoptosis signaling pathway. INNOVATION: Treatment with atorvastatin is associated with mitochondrial oxidative stress, which activates apoptosis and contributes to myopathy. Glycolytic muscles are more sensitive to atorvastatin than oxidative muscles, which may be due to the higher antioxidative capacity in oxidative muscles. CONCLUSION: There is a link between statin-induced mitochondrial oxidative stress and activation of the mitochondrial apoptosis signaling pathway in glycolytic skeletal muscle, which may be associated with statin-associated myopathy.

[5] HMGCR rs17671591 SNP determines Lower Plasma LDL-C after Atorvastatin Therapy in Chilean Individuals. Cuevas A, G CF, T LF et al. Basic & clinical pharmacology & toxicology 2015. Lipid-lowering response to statin therapy shows large interindividual variability. At a genome-wide significance level, single nucleotide polymorphisms (SNPs) in PCSK9 and HMGCR have been implicated in this differential response. However, the influence of these variants is uncertain in the Chilean population. Hence, we aimed to evaluate the contribution of PCSK9 rs7552841 and HMGCR rs17671591 SNPs as genetic determinants of atorvastatin response in Chilean hypercholesterolaemic individuals. One hundred and one hypercholesterolaemic patients received atorvastatin 10 mg/day for 4 weeks. Plasma lipid profile (TC, HDL-C, LDL-C and TG) was determined before and after statin treatment, and SNPs were identified by allelic discrimination using TaqMan(R) SNP Genotyping assays. Adjusted univariate and multivariate analyses models were used for statistical analyses and a p-value <0.05 was considered significant. From baseline (week 0) to the study endpoint (week 4), significant reductions were observed in plasma TC, LDL-C and TG (p<0.001), while HDL-C levels were increased (p<0.001). Multivariate analysis showed no association between lipid levels and atorvastatin therapy for the PCSK9 variant. However, the HMGCR rs17671591 T allele contributed to basal HDL-C concentration variability along with a higher increase in this lipid fraction after statin medication. In addition, this allele determined greater plasma LDL-C reductions after therapy with atorvastatin. Our data suggest that the HMGCR rs17671591 polymorphism can constitute a genetic marker of lower plasma LDL-C and enhanced HDL-C concentration after atorvastatin therapy in the Chilean population. This article is protected by copyright. All rights reserved.

[6] Specific imaging of atherosclerotic plaque lipids with two-wavelength intravascular photoacoustics. Wu M, Jansen K, van der Steen AF, van Soest G. Biomedical optics express 2015; 6:3276-3286. The lipid content in plaques is an important marker for identifying atherosclerotic lesions and disease states. Intravascular photoacoustic (IVPA) imaging can be used to visualize lipids in the artery. In this study, we further investigated lipid detection in the 1.7-microm spectral range. By exploiting the relative difference between the IVPA signal strengths at 1718 and 1734 nm, we could successfully detect and differentiate between the plaque lipids and peri-adventitial fat in human coronary arteries ex vivo. Our study demonstrates that IVPA imaging can positively identify atherosclerotic plaques using only two wavelengths, which could enable rapid data acquisition in vivo.

[7] Next-generation-sequencing-based identification of familial hypercholesterolemia-related mutations in subjects with increased LDL-C levels in a Latvian population. Radovica Spalvina I, Latkovskis G, Silamikelis I et al. BMC medical genetics 2015; 16:86. BACKGROUND: Familial hypercholesterolemia (FH) is one of the commonest monogenic disorders, predominantly inherited as an autosomal dominant trait. When untreated, it results in early coronary heart disease. The vast majority of FH remains undiagnosed in Latvia. The identification and early treatment of affected individuals remain a challenge worldwide. Most cases of FH are caused by mutations in one of four genes, APOB, LDLR, PCSK9, or LDLRAP1. The spectrum of disease-causing variants is very diverse and the variation detection panels usually used in its diagnosis cover only a minority of the disease-causing gene variants. However, DNA-based tests may provide an FH diagnosis for FH patients with no physical symptoms and with no known family history of the disease. Here, we evaluate the use of targeted next-generation sequencing (NGS) to identify cases of FH in a cohort of patients with coronary artery disease (CAD) and individuals with abnormal low-density lipoprotein-cholesterol (LDL-C) levels. METHODS: We used targeted
amplification of the coding regions of LDLR, APOB, PCSK9, and LDLRAP1, followed by NGS, in 42 CAD patients (LDL-C, 4.1-7.2 mmol/L) and 50 individuals from a population-based cohort (LDL-C, 5.1-9.7 mmol/L). RESULTS: In total, 22 synonymous and 31 nonsynonymous variants, eight variants in close proximity (10 bp) to intron-exon boundaries, and 50 other variants were found. We identified four pathogenic mutations (p.(Arg3527Gln) in APOB, and p.(Gly20Arg), p.(Arg350*), and c.1706-10G > A in LDLR) in seven patients (7.6%). Three possible pathogenic variants were also found in four patients. CONCLUSION: NGS-based methods can be used to detect FH in high-risk individuals when they do not meet the defined clinical criteria.

[8] Hyperchloremic Metabolic Acidosis due to Cholestyramine: A Case Report and Literature Review. Kamar FB, McQuillan RF. Case Rep Nephrol 2015; 2015:309791. Cholestyramine is a bile acid sequestrant that has been used in the treatment of hypercholesterolemia, pruritus due to elevated bile acid levels, and diarrhea due to bile acid malabsorption. This medication can rarely cause hyperchloremic nonanion gap metabolic acidosis, a complication featured in this report of an adult male with concomitant acute kidney injury. This case emphasizes the caution that must be taken in prescribing cholestyramine to patients who may also be volume depleted, in renal failure, or taking spironolactone.

[9] Atherogenic Lipoprotein Subfractions Determined by Ion Mobility and First Cardiovascular Events After Random Allocation to High-Intensity Statin or Placebo: The JUPITER Trial. Mora S, Caulfield MP, Wohlgemuth J et al. Circulation 2015. BACKGROUND: Cardiovascular disease (CVD) can occur in individuals with low LDL-cholesterol (LDL-c). We investigated whether detailed measures of LDL subfractions and other lipoproteins can be used to assess CVD risk in a population with both low LDL-c and high C-reactive protein that was randomized to high-intensity statin or placebo. METHODS AND RESULTS: In 11,186 JUPITER participants, we tested whether lipids, apolipoproteins, and ion mobility (IM)-measured particle concentrations at baseline and after random allocation to rosuvastatin 20 mg/d or placebo were associated with first CVD events (n=307) or CVD/all-cause death (n=522). In placebo-allocated participants, baseline LDL-c was not associated with CVD (adjusted HR per SD, 1.03, 95% CI 0.88-1.21). In contrast, associations with CVD events were observed for baseline non-HDL-cholesterol (non-HDL-c: 1.18, 1.01-1.38), apolipoprotein B (apoB: 1.28, 1.11-1.48), and IM-measured non-HDL particles (non-HDL-p: 1.19, 1.05-1.35) and LDL particles (LDL-p: 1.21, 1.07-1.37). Association with CVD events was also observed for several LDL and VLDL subfractions, but not for IM-measured HDL subfractions. In statin-allocated participants, CVD events were associated with on-treatment LDL-c, non-HDL-c, and apoB; these were also associated with CVD/all-cause death, as were several LDL and VLDL subfractions albeit with a pattern of association that differed from the baseline risk. CONCLUSIONS: In JUPITER, baseline LDL-c was not associated with CVD events, in contrast with significant associations for non-HDL-c and atherogenic particles: apoB and IM-measured non-HDL-p, LDL-p, and select subfractions of VLDL-p and LDL-p. During high-intensity statin therapy, on-treatment levels of LDL-c and atherogenic particles were associated with residual risk of CVD/all-cause death. Clinical Trial Registration Information: ClinicalTrials.gov. Identifier: NCT00239681.

[10] Transient azoospermia following rosuvastatin medication for hypercholesterolemia. Tada Y, Hayashi T, Iwaki Y et al. Clinical and experimental obstetrics & gynecology 2015; 42:545-546. The authors report a case of transient azoospermia following hydroxymethylglutaryl-coenzyme A reductase (HMGR) inhibitor rosuvastatin medication for hypercholesterolemia. While a primary infertile couple with oligoasthenospermia was preparing for an in vitro fertilization program, the male partner had been diagnosed with hypercholesterolemia in a medical check-up and prescribed four-week oral administration of rosuvastatin. No motile spermatozoa were found in the ejaculated semen and urine on the day of follicular aspiration. Azoospermia was confirmed by reexamination in weeks 3 and 7. Spermatozoa appeared in the ejaculated semen in two weeks of drug withdrawal. In week 16, the sperm count and motility increased to the level where intracytoplasmic sperm injection was available.

both primary and secondary prevention of CVD. However, the optimal treatment strategy for patients who cannot tolerate statin therapy or those who need additional lipid-lowering therapy is unclear in light of recent evidence that demonstrates a lack of improved cardiovascular outcomes with combination therapy. The purpose of this review is to summarize and interpret evidence that evaluates nonstatin drug classes in reducing cardiovascular outcomes, to provide recommendations for use of nonstatin therapies in clinical practice, and to review emerging nonstatin therapies for management of dyslipidemia. METHODS: Relevant articles were identified through searches of PubMed, International Pharmaceutical Abstracts, and the Cochrane Database of Systematic Reviews by using the terms niacin, omega-3 fatty acids (FAs), clofibrate, fibrate, fenofibrate, fenofibric acid, gemfibrozil, cholestyramine, colestipol, colesvelam, ezetimibe, proprotein convertase subtilisin/kexin 9 (PCSK9), cholesteryl ester transfer protein (CETP), and cardiovascular outcomes. Only English language, human clinical trials, meta-analyses, and systematic reviews were included. Additional references were identified from citations of published articles. FINDINGS: Niacin may reduce cardiovascular events as monotherapy; however, recent trials in combination with statins have failed to show a benefit. Trials with omega-3 FAs have failed to demonstrate significant reductions in cardiovascular outcomes. Fibrates may improve cardiovascular outcomes as monotherapy; however, trials in combination with statins have failed to show a benefit, except in those with elevated triglycerides (>200 mg/dL) or low HDL-C (<40 mg/dL). There is a lack of data that evaluates bile acid sequestrant in combination with statin therapy on reducing cardiovascular events. Ezetimibe-statin combination therapy can reduce cardiovascular outcomes in those with chronic kidney disease and following vascular surgery or acute coronary syndrome. Long-term effects of emerging nonstatin therapies (CETP and PCSK9 inhibitors) are currently being evaluated in ongoing Phase III trials. IMPLICATIONS: Nonstatin therapies have a limited role in reducing cardiovascular events in those maintained on guideline-directed statin therapy. In certain clinical situations, such as patients who are unable to tolerate statin therapy or recommended intensities of statin therapy, those with persistent severe elevations in triglycerides, or patients with high cardiovascular risk, some nonstatin therapies may be useful in reducing cardiovascular events. Future research is needed to evaluate the role of nonstatin therapies in those who are unable to tolerate guideline-directed statin doses.

AIMS/HYPOTHESIS: Statins and niacin (nicotinic acid) reduce circulating LDL-cholesterol (LDL-C) levels by different mechanisms. Yet, both increase the risk of diabetes mellitus. Our objective was to relate blood LDL-C concentrations and a genetic risk score (GRS) for LDL-C to the risk of incident diabetes in individuals not treated with lipid-modifying therapy. METHODS: We evaluated participants of the Framingham Heart Study who attended any of Offspring cohort examination cycles 3-8 and Third Generation cohort examination cycle 1 (N =14,120 person-observations, 6,011 unique individuals; mean age 50 +/-11 years, 56% women), who were not treated with lipid-modifying or antihypertensive medications and who were free from cardiovascular disease at baseline. Incident diabetes was assessed at the next examination. RESULTS: The GRS was significantly associated with LDL-C concentrations (sex- and age-adjusted estimated influence 0.24, p < 0.0001). On follow-up (mean 4.5 +/-1.5 years), 312 individuals (2.2%) developed new-onset diabetes. In multivariable models, a higher LDL-C concentration was associated with lower risk of diabetes (OR per SD increment 0.81, 95% CI 0.70, 0.93, p = 0.004). The GRS was associated with incident diabetes in a similar direction and of comparable magnitude (OR per SD increment 0.85, 95% CI 0.76, 0.96, p = 0.009). CONCLUSIONS/INTERPRETATION: Among individuals not treated with lipid-modifying therapy low LDL-C concentrations were associated with increased diabetes risk. These observations may contribute to our understanding of why lipid-lowering treatment may cause diabetes in some individuals. Additional studies are warranted to elucidate the molecular mechanisms underlying our observations.

The aim of this study was to evaluate the effects of perindopril or barnidipine alone or combined with simvastatin on metabolic parameters and hepatic steatosis degree. One hundred and forty nine mild to moderate hypertensive, normocholesterolemic, overweight or obese outpatients with hepatic steatosis were enrolled. They were treated with perindopril 5mg/day, or barnidipine, 20mg/day, for 6 months; subsequently simvastatin, 20mg/day was added to both
treatments for further 6 months. Blood pressure variation was recorded. Patients also underwent an ultrasound examination, at baseline and after 6, and 12 months. We also assessed: fasting plasma glucose (FPG), fasting plasma insulin (FPI), lipid profile, adiponectin (ADN), tumor necrosis factor-alpha (TauNuF-alpha), interleukin-6 (IL-6), high-sensitivity C reactive protein (Hs-CRP).


INTRODUCTION: Statins alone often do not reduce LDL cholesterol levels sufficiently to given maximum cardiovascular benefit. Thus, additional drugs are required to reduce the levels of LDL cholesterol. Monoclonal antibodies to PCSK9 have recently been shown to decrease LDL cholesterol, but it is not known whether they improve cardiovascular outcomes. Areas covered: We evaluated two clinical trials reporting cardiovascular outcomes with antibodies to PCSK9, the OSLER extension with evolocumab, and the ODYSSEY LONG TERM trial with alirocumab. Expert opinion: In OSLER and ODYSSEY LONG TERM, there were very few cardiovascular outcomes, but the trials do suggest that evolocumab and alirocumab may reduce these outcomes. However, there are also some safety concerns with both of these antibodies. Large clinical outcome trials are underway with both evolocumab and alirocumab, which will probably clarify both the safety concerns and any cardiovascular benefits with these antibodies. In our opinion, these antibodies may be suitable for use in subjects with familial hypercholesterolemia, who are uncontrolled with their present medications, provided intensive safety and cardiovascular monitoring is being undertaken. However, evolocumab and alirocumab should be used with caution in other subjects, until outcome studies in higher numbers of subjects have shown acceptable safety and cardiovascular profiles.

[15] Investigational new drugs for the treatment of acute coronary syndrome. O'Connor CT, Kiernan TJ, Yan BP. Expert opinion on investigational drugs 2015:1-14. INTRODUCTION: Ischemic heart disease is the most common cause of death worldwide. Despite improvements in interventional and pharmacological therapy for acute coronary syndrome (ACS), the risk of recurrent myocardial ischemia and mortality early after ACS remains high. Our improved understanding of the increasing role of inflammation in the pathogenesis of ACS and its relationship to atherosclerotic plaque rupture and thrombosis has led to the development of more potent anti-thrombotic and novel anti-inflammatory therapies for the treatment of ACS. Areas covered: In this review, the authors explore: the developing pharmacotherapy in the field of cardiology for ACS; antiplatelet agents (both further development of classical modalities together with pioneering agents); evolving use of anticoagulation in its treatment, and exploration in the use of novel anti-inflammatories and biological agents. Expert opinion: Data from trials involving the use of immunological and cellular-based treatments show promising results and herald further possible reduction in infarct burden in ACS alongside the possibility of recovery in cardiac function following infarction.

[16] Pleiotropic effects of statins. Kavalipati N, Shah J, Ramakrishan A, Vasnawala H. Indian journal of endocrinology and metabolism 2015; 19:554-562. Statins or 3-hydroxy-methylglutaryl coenzyme A (HMG CoA) reductase inhibitors not only prevents the synthesis of cholesterol biosynthesis but also inhibits the synthesis of essential isoprenoid intermediates such as farnesyl pyrophosphate, geranylgeranyl pyrophosphate, isopentenyl adenosine, dolichols and polyisoprenoid side chains of ubiquinone, heme A, and nuclear lamins. These isoprenoid intermediates are required for activation of various intracellular/signaling proteins- small guanosine triphosphate bound protein Ras and Ras-like proteins like Rho, Rab, Rac, Ral, or Rap which plays an indispensible role in multiple cellular processes. Reduction of circulating isoprenoids intermediates as a result of HMG CoA reductase inhibition by statins prevents activation of these signalling proteins. Hence, the multiple effects of statins such as antiinflammatory effects, antioxidant effects, antiproliferative and immunomodulatory effects, plaque stability, normalization of sympathetic outflow, and prevention of platelet aggregation are due to reduction of circulating isoprenoids and hence inactivation of signalling proteins.
These multiple lipid-independent effects of statins termed as statin pleiotropy would potentially open floodgates for research in multiple treatment domains catching attentions of researchers and clinician across the globe.


[18] Assessment of Carotid Artery Stenosis and the Use of Statins. Whayne TF, Jr. Int J Angiol 2015; 24:173-178. General thinking has previously centered on managing carotid artery stenosis (CAS) by carotid endarterectomy and subsequently, stenting for higher risk patients. However for CAS and other forms of vascular disease, especially when asymptomatic, there is new emphasis on defining underlying mechanisms. Knowledge of these mechanisms can lead to medical treatments that result in possible atherosclerotic plaque stabilization, and even plaque regression, including in the patient with CAS. For now, the key medication class for a medical approach are the statins. Their use is supported by good cardiovascular clinical trial evidence including some directed carotid artery studies, especially with a demonstrated decrease in carotid intima-media thickness. Procedural controversy still exists but the current era in medicine offers significant support for medical management of asymptomatic CAS while techniques to recognize the vulnerable plaque evolve. If CAS converts to a symptomatic status, early referral for endarterectomy or stenting is indicated.


[20] Usual Blood Pressure and Risk of New-Onset Diabetes: Evidence From 4.1 Million Adults and a Meta-Analysis of Prospective Studies. Emdin CA, Anderson SG, Woodward M, Rahimi K. Journal of the American College of Cardiology 2015; 66:1552-1562. BACKGROUND: Reliable quantification of the association between blood pressure (BP) and risk of type 2 diabetes is lacking. OBJECTIVES: This study sought to determine the association between usual BP and risk of diabetes, overall and by participant characteristics. METHODS: A cohort of 4.1 million adults, free of diabetes and cardiovascular disease, was identified using validated linked electronic health records. Analyses were complemented by a meta-analysis of prospective studies that reported relative risks of new-onset diabetes per unit of systolic blood pressure (SBP). RESULTS: Among the overall cohort, 20 mm Hg higher SBP and 10 mm Hg higher diastolic BP were associated with a 58% and a 52% higher risk of new-onset diabetes (hazard ratio: 1.58; 95% confidence interval [CI]: 1.56 to 1.59; and hazard ratio: 1.52; 95% confidence interval: 1.51 to 1.54), respectively. There was no evidence of a nadir to a baseline BP of 110/70 mm Hg. The strength of the association per 20 mm Hg higher SBP declined with age and with increasing body mass index. Estimates were similar even after excluding individuals prescribed antihypertensive or lipid-lowering therapies. Systematic review identified 30 studies with 285,664 participants and 17,388 incident diabetes events. The pooled relative risk of diabetes for a 20 mm Hg higher usual SBP across these studies was 1.77 (1.53 to 2.05). CONCLUSIONS: People with elevated BP are at increased risk of diabetes. The strength of the association declined with increasing body mass index and age. Further research should determine if the observed risk is modifiable.

[21] Lipid lowering agents (LLA) use and systemic and oral inflammation in overweight or obese adult Puerto Ricans: the SOALS Study. Andriankaja OM, Jimenez JJ, Munoz-Torres FJ et al. Journal of clinical periodontology 2015. The effects of lipid-lowering agents (LLA) on reducing systemic and oral inflammation have not been evaluated. OBJECTIVE: To assess the association of LLA use with high-sensitivity C-reactive protein (hs-CRP) and oral inflammation. DESIGN: Cross-sectional analysis using baseline data from 1,300 overweight/obese participants aged 40-65 years, recruited for the ongoing San Juan Overweight Adults Longitudinal Study. Serum hs-CRP was measured by ELISA, gingival/periodontal inflammation was evaluated as bleeding upon probing (BOP), and LLA was self-reported. Separate logistic models were performed for systemic and oral inflammation. RESULTS: 24% participants reported history of dyslipidemia, of which, 50.3% self-reported LLA use. Sixty percent of the participants had elevated hs-CRP (>3 mg/dL) and 50% had high BOP (defined as at or above the median: 21%). After adjusting for age, gender, smoking, HDL-C, physical activity, diabetes, blood pressure medications, and percent body fat composition, LLA users had significantly lower odds of elevated hs-
CRP compared to LLA non-users (OR=0.55; 95% CI: 0.38-0.81). After adjusting for age, gender, smoking status, educational level, and mean plaque index, LLA users had significantly lower odds of high BOP compared to LLA non-users (OR= 0.62; 95% CI: 0.42-0.91). CONCLUSIONS: Lipid-lowering agents may reduce both systemic and oral inflammatory responses. This article is protected by copyright. All rights reserved.

[22] Plasma proprotein convertase subtilisin/kexin type 9 is associated with Lp(a) in type 2 diabetic patients. Nekaies Y, Baudin B, Kelbousi S et al. Journal of diabetes and its complications 2015. AIM: Recent in vitro researches have shown that plasma Lp(a) can be reduced using a proprotein convertase subtilisin/kexin type 9 (PCSK9)-inhibitory monoclonal antibody. In our clinical study we tried to investigate the association between plasma Lp(a) and PCSK9 in Type 2 diabetic patients with elevated plasma Lp(a), and to check whether such an association would be related to LDL-receptor (LDL-R) levels. METHODS: Plasma PCSK9 and LDL-R concentrations were measured by sandwich ELISA methods using recombinant human PCSK9 protein and LDL-R protein as standards in a cohort with type 2 diabetic patients (n=50) compared to an age- and sex-matched control group (n=50). Both clinical and biochemical parameters were determined in all patients. RESULTS: Plasma PCSK9 level was significantly elevated in T2DM patients compared to controls (44.61+/−14.44 and 33.22+/−11.79ng/mL, respectively, P<0.0001). However LDL-R levels did not differ between the two groups. Remarkably, plasma PCSK9 levels were positively correlated with Lp(a) levels in whole population (r=+0.227, P=0.03) as well as in T2DM group (r=+0.398, P=0.0061) but not in control group. Multiple linear regression analysis showed that plasma Lp(a) levels were independently associated to those of PCSK9. CONCLUSION: Lp(a) has been proposed as a contributing factor to the accelerated development of macrovascular complications in T2DM. Its synergic effect with PCSK9 may explain the enhanced atherogenicity in T2DM patients.

[23] Effect of Extended-Release Niacin on Saphenous Vein Graft Atherosclerosis: Insights from the Atherosclerosis Lesion Progression Intervention Using Niacin Extended Release in Saphenous Vein Grafts (ALPINE-SVG) Pilot Trial. Kotsia AP, Rangan BV, Christopoulos G et al. J Invasive Cardiol 2015; 27:E204-210. BACKGROUND: Intermediate saphenous vein graft (SVG) lesions have high rates of progression. The purpose of this study was to examine the impact of extended-release niacin (ER-niacin) vs placebo on intermediate SVG lesions. METHODS: Patients with intermediate (30%-60% diameter stenosis) SVG lesions were randomized to ER-niacin vs placebo for 12 months. Quantitative coronary angiography (QCA), intravascular ultrasonography (IVUS), and optical coherence tomography (OCT) were performed at baseline and at 12 months. The primary endpoint was change in percent atheroma volume (DeltaPAV). Enrollment was planned for 138 patients for 90% power to detect ≥2.5% difference in the primary endpoint of DeltaPAV, but stopped early after publication of two negative outcome trials of ER-niacin, with enrolled patients completing the 12-month trial protocol. RESULTS: Thirty-eight patients were randomized to niacin (n = 19) or placebo (n = 19), yielding power of 47% to detect the primary planned treatment effect of 2.5 +/- 4.0% difference in DeltaPAV. Between baseline and 12-month follow-up, no significant difference was found between study groups in DeltaPAV (-1.31 +/- 6.05% vs 1.05 +/- 17.8%; P=60). By OCT, the ER-niacin vs placebo group had less plaque rupture within the intermediate SVG lesion (0.0% vs 36.0%; P=.01). CONCLUSION: Administration of ER-niacin did not significantly impact intermediate SVG disease, with the notable limitation of compromised statistical power due to early termination of enrollment.

[24] 64Cu-DOTATATE for non-invasive assessment of atherosclerosis in large arteries and its correlation with risk factors: head-to-head comparison with 68Ga-DOTATOC in 60 patients. Malmberg C, Ripo RS, Johnbeck CB et al. Journal of nuclear medicine : official publication, Society of Nuclear Medicine 2015. BACKGROUND: The somatostatin receptor subtype 2 (SSTR2) is expressed on macrophages, an abundant cell type in the atherosclerotic plaque. Visualization of SSTR2, for oncological purposes, is frequently made using the 1,4,7,10-tetraazacyclodecane-1,4,7,10-tetraaceticacid (DOTA)-derived somatostatin analogues DOTA-Tyr3-octreotide (DOTATOC) or DOTA-Tyr3-octreotate (DOTATATE) for positron emission tomography (PET). We aimed to compare the uptake of the PET-tracers 68Ga-DOTATOC and 64Cu-DOTATATE in large arteries, in assessment of atherosclerosis by non-invasive imaging technique, combining PET and CT. Further, the correlation of uptake and cardiovascular risk factors was investigated. METHODS: Sixty consecutive patients with neuroendocrine tumors underwent both 68Ga-DOTATOC and 64Cu-DOTATATE PET/CT-scans, in random order. For each scan, the maximum and mean standardized uptake values (SUV) were calculated in five arterial segments,
respectively. In addition, blood-pool corrected target-to-background ratio (TBR) was calculated. Uptake of the tracers was correlated with cardiovascular risk factors collected from medical records. RESULTS: We found detectable uptake of both tracers in all arterial segments studied. Uptake of 64Cu-DOTATATE was significantly higher than 68Ga-DOTATOC in the vascular regions both when calculated as maximum and mean uptake. There was a significant association between Framingham risk score and the overall maximum uptake of 64Cu-DOTATATE using SUV (r=0.4; P = 0.004) as well as TBR (r=0.3; P = 0.04), while no association was found with 68Ga-DOTATOC. The association of Framingham risk score and maximum SUV of 64Cu-DOTATATE was found driven by BMI, smoking and diabetes (p<0.001, P = 0.032, P = 0.025, respectively). CONCLUSION: In a series of oncologic patients, vascular uptake of 68Ga-DOTATOC and 64Cu-DOTATATE was found, with highest uptake of the latter. Uptake of 64Cu-DOTATATE, but not of 68Ga-DOTATOC, was correlated with cardiovascular risk factors, suggesting a potential role for 64Cu-DOTATATE in assessment of atherosclerosis.

[25] Non-High-Density Lipoprotein Cholesterol in Children with Diabetes: Proposed Treatment Recommendations Based on Glycemic Control, Body Mass Index, Age, Sex, and Generally Accepted Cut Points. Schwab KO, Doerfer J, Hungele A et al. J Pediatr 2015. Percentile-based non-high-density lipoprotein cholesterol levels were analyzed by glycemic control, weight, age, and sex of children with type 1 diabetes (n = 26 358). Ten percent of all children and 25% of overweight adolescent girls require both immediate lipid-lowering medication and lifestyle changes to achieve non-high-density lipoprotein cholesterol levels <120 mg/dL and cardiovascular risk reduction.

[26] Effects of statin therapy on coronary artery plaque volume and high-risk plaque morphology in HIV-infected patients with subclinical atherosclerosis: a randomised, double-blind, placebo-controlled trial. Lo J, Lu MT, Ihenacho EI et al. The lancet HIV 2015; 2:e52-63. BACKGROUND: HIV-infected patients have a high risk of myocardial infarction. We aimed to assess the ability of statin treatment to reduce arterial inflammation and achieve regression of coronary atherosclerosis in this population. METHODS: In a randomised, double-blind, placebo-controlled trial, 40 HIV-infected participants with subclinical coronary atherosclerosis, evidence of arterial inflammation in the aorta by fluorodeoxyglucose (FDG)-PET, and LDL-cholesterol concentration of less than 3.37 mmol/L (130 mg/dL) were randomly assigned (1:1) to 1 year of treatment with atorvastatin or placebo. Randomisation was by the Massachusetts General Hospital (MGH) Clinical Research Pharmacy with a permuted-block algorithm, stratified by sex with a fixed block size of four. Study codes were available only to the MGH Research Pharmacy and not to study investigators or participants. The prespecified primary endpoint was arterial inflammation as assessed by FDG-PET of the aorta. Additional prespecified endpoints were non-calcified and calcified plaque measures and high risk plaque features assessed with coronary CT angiography and biochemical measures. Analysis was done by intention to treat with all available data and without imputation for missing data. The trial is registered with ClinicalTrials.gov, number NCT00965185. FINDINGS: The study was done from Nov 13, 2009, to Jan 13, 2014. 19 patients were assigned to atorvastatin and 21 to placebo. 37 (93%) of 40 participants completed the study, with equivalent discontinuation rates in both groups. Baseline characteristics were similar between groups. After 12 months, change in FDG-PET uptake of the most diseased segment of the aorta was not different between atorvastatin and placebo, but technically adequate results comparing longitudinal changes in identical regions could be assessed in only 21 patients (atorvastatin Delta -0.03, 95% CI -0.17 to 0.12, vs placebo Delta -0.06, -0.25 to 0.13; p=0.77). Change in plaque could be assessed in all 37 people completing the study. Atorvastatin reduced non-calcified coronary plaque volume relative to placebo: median change -19.4% (IQR -39.2 to 9.3) versus 20.4% (-7.1 to 94.4; p=0.009, n=37). The number of high-risk plaques was significantly reduced in the atorvastatin group compared with the placebo group: change in number of low attenuation plaques -0.2 (95% CI -0.6 to 0.2) versus 0.4 (0.0, 0.7; p=0.03; n=37); and change in number of positively remodelled plaques -0.2 (-0.4 to 0.1) versus 0.4 (-0.1 to 0.8; p=0.04; n=37). Direct LDL-cholesterol (-1.00 mmol/L, 95% CI -1.38 to 0.61 vs 0.30 mmol/L, 0.04 to 0.55, p<0.0001) and lipoprotein-associated phospholipase A2 (-52.2 ng/mL, 95% CI -70.4 to -34.0, vs -13.3 ng/mL, -32.8 to 6.2; p=0.005; n=37) decreased significantly with atorvastatin relative to placebo. Statin therapy was well tolerated, with a low incidence of clinical adverse events. INTERPRETATION: No significant effects of statin therapy on arterial inflammation of the aorta were seen as measured by FDG-PET. However, statin therapy reduced non-calcified plaque volume and high-risk coronary plaque features in HIV-infected patients. Further studies should assess whether reduction in high-risk coronary artery disease translates into effective prevention of cardiovascular events in this at-risk population. FUNDING: National Institutes of Health, Harvard Clinical and Translational Science Center, National Center for Research Resources.
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[27] Rosuvastatin ameliorates diabetes-induced reproductive damage via suppression of oxidative stress, inflammatory and apoptotic pathways in male rats. Heeba GH, Hamza AA. Life sciences 2015. AIM: Besides a cholesterol-lowering effect, rosuvastatin (RUV) possesses antioxidant and anti-inflammatory properties. The present study investigates the possible protective effects of RUV in diabetes-induced reproductive damage in rats. MAIN METHODS: Diabetes was induced in male Wistar rats by injecting a single dose of streptozotocin (65mg/kg, i.p.). RUV in low and high doses (5 and 10mg/kg, p.o.) were administrated to diabetic rats for 8 weeks. Reproductive damage was evaluated by estimation of testes and epididymis relative weights and caudal sperm count and motility in the control, untreated and RUV-treated diabetic rats. In addition, testicular malondialdehyde, reduced glutathione and nitric oxide levels, as well as, superoxide dismutase and myeloperoxidase activities were estimated. Finally, expressions of inflammatory [inducible nitric oxide synthase (iNOS) and nuclear factor-kappa B (NF-kappaB)] and apoptotic (caspase-3) markers besides histological examination of testicular tissues were performed. KEY FINDINGS: Results showed that RUV improved sperm count and motility with decrease in testicular nitric oxide and malondialdehyde levels, as well as, myeloperoxidase activity and increase in reduced glutathione level and superoxide dismutase activity in diabetic rats. Further, RUV reduced testicular inflammation and cell death by decreasing the expressions of iNOS, NF-kappaB and caspase-3. SIGNIFICANCE: Treatment with RUV protects against diabetes-induced testicular damage, in a dose dependent manner, through antioxidant, anti-inflammatory and anti-apoptotic mechanisms.

[28] The role of fatty acids in insulin resistance. Sears B, Perry M. Lipids in health and disease 2015; 14:121. Insulin resistance is a multi-faceted disruption of the communication between insulin and the interior of a target cell. The underlying cause of insulin appears to be inflammation that can either be increased or decreased by the fatty acid composition of the diet. However, the molecular basis for insulin resistance can be quite different in various organs. This review deals with various types of inflammatory inputs mediated by fatty acids, which affect the extent of insulin resistance in various organs.

[29] Renal Protective Effect of Probucol in Rats with Contrast-Induced Nephropathy and its Underlying Mechanism. Wang N, Wei RB, Li QP et al. Medical science monitor : international medical journal of experimental and clinical research 2015; 21:2886-2892. BACKGROUND Contrast-induced nephropathy (CIN) refers to acute renal damage that occurs after the use of contrast agents. This study investigated the renal protective effect of probucol in a rat model of contrast-induced nephropathy and the mechanism of its effect. MATERIAL AND METHODS Twenty-eight Wistar rats were randomly divided into the control group, model group, N-acetylcysteine(NAC) group, and probucol group. We used a rat model of iopromide-induced CIN. One day prior to modeling, the rats received gavage. At 24 h after the modeling, blood biochemistry and urine protein were assessed. Malondialdehyde (MDA) and superoxide dismutase (SOD) were measured in renal tissue. Kidney sections were created for histopathological examination. RESULTS The model group of rats showed significantly elevated levels of blood creatinine, urea nitrogen, 24-h urine protein, histopathological scores, and parameters of oxidative stress (P<0.05). Both the NAC and probucol groups demonstrated significantly lower Scr, BUN, and urine protein levels compared to the model group (P<0.05), with no significant difference between these 2 groups. The NAC group and the probucol group had significantly lower MDA and higher SOD than the model group at 24 h after modeling (P<0.05). The 8-OHdG-positive tubule of the probucol group and NAC group were significantly lower than those of the model group (p=0.046, P=0.0008), with significant difference between these 2 groups (P=0.024). CONCLUSIONS Probucol can effectively reduce kidney damage caused by contrast agent. The underlying mechanism may be that probucol accelerates the recovery of renal function and renal pathology by reducing local renal oxidative stress.

[30] Expression of inflammation-related miRNAs in white blood cells from subjects with metabolic syndrome after 8 wk of following a Mediterranean diet-based weight loss program. Marques-Rocha JL, Milagro Fl, Mansego ML et al. Nutrition 2015. OBJECTIVES: The aim of this study was to evaluate the influence of a dietary strategy for weight loss (the RESMENA [reduction of metabolic syndrome in Navarra, Spain] diet) on the expression of inflammation-related microRNAs (miRNAs) and genes in white blood cells (WBC) from individuals with metabolic syndrome (MetS). METHODS: The clinical, anthropometric, and biochemical characteristics of 40 individuals with MetS (20 men and 20 women; age:
and mRNAs (IL-6, TNF-alpha, ICAM-1, IL-18, SERPINE1, VCAM-1, GAPDH) was assessed by quantitative polymerase chain reaction. RESULTS: The RESMENA nutritional intervention improved most anthropometric and biochemical features. The expression of miR-155-3p was decreased in WBC, whereas Let-7b was strongly upregulated as a consequence of the dietary treatment. However, they were not correlated with the expression of the proinflammatory genes in the same cells. The changes in the expression of let-7b, miR-125b, miR-130a, miR-132-3p, and miR-422b were significantly associated with changes in diet quality when assessed by the Healthy Eating Index. Moreover, low consumption of lipids and saturated fat (g/d) were associated with higher expression of let-7b after the nutritional intervention. CONCLUSIONS: The Mediterranean-based nutritional intervention was able to induce changes in the expression of let-7b and miR-155-3p in WBC from patients with MetS after 8 wk. Moreover, the quality of the diet has an important effect on the miRNAs expression changes. These results should be highlighted because these miRNAs have been associated with inflammatory gene regulation and important human diseases.

[31] Type of LDLR mutation and the pharmacogenetics of familial hypercholesterolemia treatment. Santos PC, Pereira AC. Pharmacogenomics 2015. Familial hypercholesterolemia (FH) is an autosomal dominant disease mainly caused by mutations in the low-density lipoprotein receptor (LDLR) gene. FH patients present a wide variability regarding response to drugs and they are usually undertreated. Here, we review studies that evaluated the association between the type of LDLR mutation and the response to lipid-lowering therapy. The main findings were that patients with a null LDLR mutation had: higher baseline LDL-C, higher LDL-C after drug therapy, lower proportion of patients within the LDL-C target value and higher frequencies of CVD. Thus, we conclude that FH patients harboring a null mutation have a trend to an increased risk, even if diagnosis is early established and lipid-lowering treatment instituted. It is suggested that these individuals may benefit from the use of newly approved lipid-lowering agents.

[32] Atorvastatin improves Y-maze learning behaviour in nicotine treated male albino rats. Syam DS, Nair SS, Kavitha S et al. Pharmacology, biochemistry, and behavior 2015. Nicotine is a parasympathomimetic alkaloid present in tobacco which can induce hyperlipidemia and has a direct effect on neural functions. Statins, competitive inhibitors of 3-hydroxy-3-methyl-glutaryl-coenzyme-A reductase, are cholesterol lowering drugs. It has some neuroprotective effects. Hence we analysed the combined effect of nicotine and statin on the learning behaviour of male albino rats. We employed Y-Maze conditional discrimination task. Rats were divided into 4 groups with six rats in each group. (1) Control, (2) Atorvastatin (10mg/kg b.wt), (3) Nicotine (0.6mg/kg b.wt) and (4) Atorvastatin (10mg/kg b.wt)+Nicotine (0.6mg/kg b.wt). After 30 days of treatment rats from each group were selected for behavioural study and they were observed for 30 days. At the end of the experimental period rats were sacrificed, and brain and liver were dissected out for further biochemical analysis. Nicotine treated group showed least performance in learning in comparison with control, atorvastatin and atorvastatin + nicotine treated groups. Co-administration of atorvastatin and nicotine improved learning behaviour compared to nicotine treated group. Reactive oxygen species level was significantly increased in nicotine group compared to control. The level of neurotransmitter serotonin which has a significant role in learning was found to be decreased in nicotine treated group compared to the control group. Activity of Na+ K+ ATPase, Ca2+ ATPase and glutathione content was significantly reduced in nicotine treated group compared to control. The activity of acetylcholine esterase was significantly increased in the nicotine treated group. Expression studies showed significant decrease in N-methyl D- aspartate receptors and increase in mono amine oxidase-A and mono amine oxidase-B in nicotine treated group and was reversed in atorvastatin + nicotine treated group. It can be concluded that co-administration of nicotine with statin ameliorates the neural functional alterations caused by nicotine to a significant level.

effects of statins in dystrophic skeletal muscle. Simvastatin dramatically reduced damage and enhanced muscle function. Simvastatin improved DMD. However, statins have not been considered for DMD, or other muscular dystrophies, principally because statins inhibit these deleterious processes in ischemic diseases affecting skeletal muscle, and therefore have potential to improve DMD. These improvements were accompanied by autophagy activation, a recent therapeutic target for DMD, and less oxidative stress. Together, our findings highlight that simvastatin substantially improves the overall health and function of dystrophic skeletal muscles and may provide an unexpected, novel therapy for DMD and related neuromuscular diseases.

[34] Anti-aging and tissue regeneration ability of policosanol along with lipid-lowering effect in hyperlipidemic zebrafish via enhancement of high-density lipoprotein functionality. Lee EY, Yoo JA, Lim SM, Cho KH. Rejuvenation research 2015. We investigated the tissue regeneration and lipid-lowering effects of policosanol (PCO) by employing a hyperlipidemic zebrafish model. A reconstituted high-density lipoprotein containing policosanol (PCO-rHDL) facilitated greater cell growth and replication with less apoptosis and ROS production in BV-2 microglial cell lines. From in vivo study, injection of rHDL containing apoA-I caused 76+/−4% (p=0.01) greater tissue regeneration activity than the PBS control, whereas PCO-rHDL caused 94+/−7% (p=0.002) increased regeneration. PCO in Et-OH showed lower CETP inhibitory ability than anacetrapib, whereas PCO-rHDL showed higher inhibitory ability than anacetrapib, suggesting a synergistic effect between PCO and rHDL. Following 9 weeks of PCO consumption, the PCO group (0.003% PCO in tetrabit) showed the highest survivability (80%), whereas normal diet (ND) and high cholesterol diet (HCD) control groups showed 67% and 70% survival rates, respectively. Supplementation with HCD resulted in 2-fold elevation of cholesteryl ester transfer protein (CETP) activity along with 3- and 2.5-fold increases in serum total cholesterol (TC) and triglyceride (TG) levels, respectively. Consumption of PCO for 9 weeks resulted in 40+/−5% (p=0.01 vs HCD) and 33+/−4% (p=0.02 vs HCD) reduction of TC and TG levels, respectively. Serum high-density lipoprotein cholesterol (HDL-C) level increased up to 37+/−2 mg/dL (p=0.004), whereas the percentage of HDL-C/TC increased up to 20+/−2% from 5+/−1% compared to the HCD control. Serum glucose level was reduced to 47+/−2% (p=0.002) compared to the HCD control. Fatty liver change and hepatic inflammation levels were remarkably increased upon HCD consumption and was 2-fold higher than that under ND. However, the PCO group showed 58+/−5% (p=0.001) and 50+/−3% (p=0.006) reduction of inflammation enzyme levels and lipid content in hepatic tissue under HCD. In conclusion, policosanol supplementation showed lipid-lowering and HDL-C-elevating effects with ameliorating fatty liver change. These in vivo anti-atherosclerotic and anti-diabetic effects of policosanol are well associated with in vitro anti-apoptotic activities.

[35] Carotid Intima-Media Thickness, Ankle-Arm Index, and Inflammation Profile in Mexican Patients with Early and Late Onset Type 2 Diabetes. Contreras-Rodriguez A, Gomez-Diaz RA, Tanus-Hajj J et al. Revista de investigacion clinica; organo del Hospital de Enfermedades de la Nutricion 2015; 67:240-249. BACKGROUND: Type 2 diabetes is strongly linked to an increased incidence of cardiovascular outcomes. Carotid artery intima-media thickness and ankle-arm index are non-invasive complementary measures as subclinical markers of atherosclerosis. OBJECTIVE: To evaluate the association of carotid intima-media thickness, ankle-arm index, and inflammation profile in Mexican patients with early- and late-onset type 2 diabetes mellitus. MATERIAL AND METHODS: We included 145 subjects at an academic medical center: 77 patients with early-onset (< 40 years of age) and 33 patients with late-onset (≥ 40 years) type 2 diabetes mellitus, and 35 healthy volunteers. Clinical history, anthropometrics, blood chemistry, lipids profile, glycosylated hemoglobin A1c, cytokines, and high-sensitivity C-reactive protein were determined; carotid and lower limb ultrasound were taken. Groups were compared with ANOVA or Kruskal-Wallis, Student’s t or Mann-Whitney U. Spearman or
Pearson correlation and logistic regression analysis were used. RESULTS: There were anthropometric and biochemical differences between the three groups. Concentrations of interleukin-1beta, -4 and -6 were significantly higher in patients with late versus early onset diabetes. There were differences in carotid intima-media thickness and ankle-arm index between early and late onset. Age, body mass index, high-density lipoprotein cholesterol, high-sensitivity C-reactive protein, waist circumference, and glycosylated hemoglobin A1c showed direct correlation with carotid intima-media thickness, while ankle-arm index showed inverse correlation with blood pressure, glycosylated hemoglobin A1c, time with disease, age at onset, triglycerides, and fibrinogen. Multivariate analysis showed an association between carotid intima-media thickness and disease duration; ankle-arm index with disease duration and high-sensitivity C-reactive protein; while only body mass index associated with end diastolic flow velocity. CONCLUSIONS: Our findings suggest that carotid intima-media thickness and ankle-arm index are associated with inflammation markers and could be included in the evaluation of type 2 diabetes mellitus patients, according to disease onset and duration. There are important differences in interleukin concentrations between early- and late-onset type 2 diabetes mellitus. Additionally, measurement of high-sensitivity C-reactive protein is suggested in patients with abnormal ankle-arm index.

[36] Statins activate the canonical hedgehog-signaling and aggravate non-cirrhotic portal hypertension, but inhibit the non-canonical hedgehog signaling and cirrhotic portal hypertension. Uschner FE, Ranabhat G, Choi SS et al. Scientific reports 2015; 5:14573. Liver cirrhosis but also portal vein obstruction cause portal hypertension (PHT) and angiogenesis. This study investigated the differences in angiogenesis in cirrhotic and non-cirrhotic PHT with special emphasis on the canonical (Shh/Gli) and non-canonical (Shh/RhoA) hedgehog pathway. Cirrhotic (bile duct ligation/BDL; CCl4 intoxication) and non-cirrhotic (partial portal vein ligation/PPVL) rats received either atorvastatin (15 mg/kg; 7d) or control chow before sacrifice. Invasive hemodynamic measurement and Matrigel implantation assessed angiogenesis in vivo. Angiogenesis in vitro was analysed using migration and tube formation assay. In liver and vessel samples from animals and humans, transcript expression was analyzed using RT-PCR and protein expression using Western blot. Atorvastatin decreased portal pressure, shunt flow and angiogenesis in cirrhosis, whereas atorvastatin increased these parameters in PPVL rats. Non-canonical Hh was upregulated in experimental and human liver cirrhosis and was blunted by atorvastatin. Moreover, atorvastatin blocked the non-canonical Hh-pathway RhoA dependently in activated hepatic stellate cells (HSCs). Interestingly, hepatic and extrahepatic Hh-pathway was enhanced in PPVL rats, which resulted in increased angiogenesis. In summary, statins caused contrary effects in cirrhotic and non-cirrhotic portal hypertension. Atorvastatin inhibited the non-canonical Hh-pathway and angiogenesis in cirrhosis. In portal vein obstruction, statins enhanced the canonical Hh-pathway and aggravated PHT and angiogenesis.

[37] Antimetastatic effect of fluvastatin on breast and hepatocellular carcinoma cells in relation to SGK1 and NDRG1 genes. Salis O, Okuyucu A, Bedir A et al. Tumour biology : the journal of the International Society for Oncodevelopmental Biology and Medicine 2015. Metastasis occurs due to migration of the cells from primary tumor toward other tissues by gaining invasive properties. Since metastatic invasion shows a strong resistance against conventional cancer treatments, the studies on this issue have been focused. Within this context, inhibition of migration and determination of the relationships at the gene level will contribute to treatment of metastatic cancer cases. We have aimed to demonstrate the impact of TGF-beta1 and fluvastatin on human breast cancer (MCF-7) and human hepatocellular carcinoma (Hep3B) cell cultures via Real-Time Cell Analyzer (RTCA) and to test the expression levels of some genes (NDRG1, SGK1, TWIST1, AMPKA2) and to compare their gene expression levels according to RTCA results. Both of cell series were applied TGF-beta1 and combinations of TGF-beta1/fluvastatin. Primer and probes were synthesized using Universal Probe Library (UPL, Roche) software, and expression levels of genes were tested via qPCR using the device LightCycler 480 II (Roche). Consequently, fluvastatin dose-dependently inhibited migration induced by TGF-beta1 in both groups. This inhibition was accompanied by low level of SGK1 messenger RNA (mRNA) and high levels of NDRG1 and AMPKA2 mRNA. Thus, we conclude that fluvastatin plays an important role in reducing resistance to chemotherapeutics and preventing metastasis.

[38] [Potential role of microRNA-181b on atherosclerosis]. Li X, Cao G. Zhonghua xin xue guan bing za zhi 2015; 43:516-520. OBJECTIVE: To observe the serum expression of miR-181b in atherosclerotic patients and the in vitro effects of miR-
181b on vascular smooth muscle cell growth and migration. METHODS: Fifty patients (mean age: (78.1 +/- 8.9) years old) with carotid ultrasound examination evidenced atherosclerotic plaque were enrolled as the atherosclerosis group and 50 healthy (mean age: (72.5 +/- 10.7) years old) subjects serve as control group. Stem-loop real time RT-PCR was used to detect the serum expression of miR-181b. Importin-alpha3 was predicted to be a direct target of miR-181b by Targetscan and Pictar. Western-blot was employed to detect the in vitro effects of miR-181b on the expression of Importin-alpha3 in endothelial cells. Luciferase reporter assay was employed to testify the prediction. The effects of miR-181b on vascular smooth muscle cell growth, migration abilities were respectively examined by CCK8 assay and Matrigel migration assay. RESULTS: Compared with healthy controls, serum expression of miR-181b was significantly down-regulated in patients with atherosclerosis (31.69 +/- 0.96 vs. 82.28 +/- 5.95, P < 0.05); Importin-alpha3 was predicted and proved to be a direct target of miR-181b by Western-blot and luciferase reporter assay. The proliferation and migration of vascular smooth muscle cell were significantly downregulated by forced expression of miR-181b (1.57 +/- 0.18 vs. 2.66 +/- 0.16, P < 0.05; 8.7 +/- 1.1 vs. 21.4 +/- 2.3, P < 0.05), while these effects could be abolished by inhibition of miR-181b (2.88 +/- 0.09 vs. 2.04 +/- 0.11, P < 0.05; 15.2 +/- 1.5 vs. 8.4 +/- 1.3, P < 0.05). CONCLUSION: The serum miR-181b level was significantly reduced in patients with atherosclerosis. miR-181b may function as an atherosclerosis suppressor by interrupting the NF-kappaB pathway in endothelial cells and inhibiting the proliferation and migration of vascular smooth muscle cells.