INTRODUCTION: The findings of many new cardiology clinical trials over the last year have been published or presented at major international meetings. This paper aims to describe and place in context a summary of the key clinical trials in cardiology presented between January and December 2016. METHODS: The authors reviewed clinical trials presented at major cardiology conferences during 2016 including the American College of Cardiology (ACC), European Association for Percutaneous Cardiovascular Interventions (EuroPCR), European Society of Cardiology (ESC), European Association for the Study of Diabetes (EASD), Transcatheter Cardiovascular Therapeutics (TCT), and the American Heart Association (AHA). Selection criteria were trials with a broad relevance to the cardiology community and those with potential to change current practice. RESULTS: A total of 57 key cardiology clinical trials were identified for inclusion. Here we describe and place in clinical context the key findings of new data relating to interventional and structural cardiology including delayed stenting following primary angioplasty, contrast-induced nephropathy, management of jailed wires, optimal duration of dual antiplatelet therapy (DAPT), stenting vs bypass for left main disease, new generation stents (BioFreedom, Orsiro, Absorb), transcatheter aortic valve implantation (Edwards Sapien XT, transcatheter embolic protection), and closure devices (Watchman, Amplatzer). New preventative cardiology data include trials of bariatric surgery, empagliflozin, liraglutide, semaglutide, PCSK9 inhibitors (evolocumab and alirocumab), and inclisiran. Antiplatelet therapy trials include platelet function monitoring and ticagrelor vs clopidogrel for peripheral vascular disease. New data are also presented in fields of heart failure (sacubitril/valsartan, aliskiren, spironolactone), atrial fibrillation (rivaroxaban in patients undergoing coronary intervention, edoxaban in DC cardioversion), cardiac devices (implantable cardioverter defibrillator in non-ischemic cardiomyopathy), and electrophysiology (cryoballoon vs radiofrequency ablation). CONCLUSION: This paper presents a summary of key clinical cardiology trials during the past year and should be of practical value to both clinicians and cardiology researchers.

ABSTRACT
BACKGROUND/AIMS: Nicotinic acid (NA), a lipid-lowering drug, serves as a source of NAD+, the cofactor for Sirt1. Leucine (Leu) stimulates the AMPK/Sirt1 axis and amplifies the effects of other AMPK/Sirt1 activating compounds. Therefore, we tested the interactive effects of leucine and low dose NA on AMPK/Sirt1 signaling and downstream effects of lipid metabolism in cell culture, C. elegans and mice. METHODS: LDL-receptor knockout mice were fed an atherogenic Western diet supplemented with leucine (24 g/kg diet) and sub-therapeutic NA combinations (50 mg/kg diet and 250 mg/kg diet) or low therapeutic NA (1000 mg/kg diet) for 8 weeks to evaluate markers of hyperlipidemia and atherosclerosis. RESULTS: NA-Leu increased P-AMPK


and Sirt1 in adipocytes and myotubes. In C. elegans, NA-Leu increased P-AMPK and DAF-16 (FOXO), reduced lipid accumulation and increased median survival under mild oxidative stress conditions. In the mice, NA-Leu reduced total cholesterol, cholesterol esters, plasma triglycerides, atherosclerotic lesion size, lipid area, and aortic macrophage infiltration, similar to the therapeutic NA dose. CONCLUSION: Leu amplifies the effects of NA on lipid metabolism, hyperlipidemia and atherosclerosis in mice, at least in part by activation of the AMPK/Sirt1 axis. This combination may be a potential therapeutic alternative for hyperlipidemia and atherosclerosis.


**ABSTRACT**

Dietary intake data were gathered on 123 rural and 111 urban males, ages 6, 9, and 15 years, living in and near St. Petersburg, Russia. Data were analyzed to estimate intakes of kilocalories, protein, calcium, iron, vitamin A, thiamin, riboflavin, niacin, vitamin C, and percentage of kilocalories from protein, carbohydrate, and fat. Comparisons were made between nutrient intakes of urban and rural subjects; intakes were also compared with the Recommended Dietary Intakes (RDI) of the USSR Research Institute of Nutrition. There were no significant differences between rural and urban boys in energy intake at any age. Urban boys consumed more vitamin C at ages 6 and 9, had higher intakes of protein, calcium, and niacin at age 9, and consumed more protein at age 15. Rural boys had higher intakes of riboflavin and calcium than urban boys at age 6. Urban boys consumed larger proportions of energy as carbohydrate at age 6, protein at age 9, and both protein and fat at age 15 than rural subjects. Rural boys had higher proportions of kilocalories from fat at age 6 and carbohydrate at age 15 than urban boys. Mean nutrient intakes below the RDI were: energy for rural boys at 9 and 15 years; iron for rural subjects at ages 6 and 9 and urban boys at age 6; calcium for rural and urban boys at all ages; vitamin C for rural subjects at ages 6 and 9; vitamin A for rural and urban boys at age 15; and protein for rural boys at age 15. At age 6, rural boys had nutrient intakes superior to those of urban boys; urban nutrient intakes were better than rural at ages 9 and 15. (c) 1994 Wiley-Liss, Inc.


**ABSTRACT**

For many years, it was widely accepted that control of plasma lipids and blood pressure could lower macrovascular risk in patients with type 2 diabetes mellitus (T2DM), whereas the benefits of lowering plasma glucose were largely limited to improvements in microvascular complications. The Empagliflozin Cardiovascular Outcome Event Trial in Type 2 Diabetes Mellitus Patients-Removing Excess Glucose (EMPA-REG OUTCOME) study demonstrated for the first time that a glucose-lowering agent, the sodium glucose cotransporter 2 (SGLT2) inhibitor...
empagliflozin, could reduce major adverse cardiovascular events, cardiovascular mortality, hospitalization for heart failure, and overall mortality when given in addition to standard care in patients with T2DM at high cardiovascular risk. These results were entirely unexpected and have led to much speculation regarding the potential mechanisms underlying cardiovascular benefits. In this review, the results of EMPA-REG OUTCOME are summarized and put into perspective for the endocrinologist who is treating patients with T2DM and cardiovascular disease.


**ABSTRACT**
OBJECTIVE: The reduced adiponectin levels are associated with atherosclerosis. Adiponectin exerts its functions by activating adiponectin receptor (AdipoR). Proprotein convertase subtilisin kexin type 9 (PCSK9) degrades LDLR protein (low-density lipoprotein receptor) to increase serum LDL-cholesterol levels. PCSK9 expression can be regulated by PPARgamma (peroxisome proliferator-activated receptor gamma) or SREBP2 (sterol regulatory element-binding protein 2). The effects of AdipoR agonists on PCSK9 and LDLR expression, serum lipid profiles, and atherosclerosis remain unknown.

APPROACH AND RESULTS: At cellular levels, AdipoR agonists (ADP355 and AdipoRon) induced PCSK9 transcription/expression that solely depended on activation of PPAR-responsive element in the PCSK9 promoter. AdipoR agonists induced PPARgamma expression; thus, the AdipoR agonist-activated PCSK9 expression/production was impaired in PPARgamma deficient hepatocytes. Meanwhile, AdipoR agonists transcriptionally activated LDLR expression by activating SRE in the LDLR promoter. Moreover, AMP-activated protein kinase alpha (AMPKalpha) was involved in AdipoR agonist-activated PCSK9 expression. In wild-type mice, ADP355 increased PCSK9 and LDLR expression and serum PCSK9 levels, which was associated with activation of PPARgamma, AMPKalpha and SREBP2 and reduction of LDL-cholesterol levels. In contrast, ADP355 reduced PCSK9 expression/secretion in apoE-deficient (apoE/-) mice, but it still activated hepatic LDLR, PPARgamma, AMPKalpha, and SREBP2. More importantly, ADP355 inhibited lesions in en face aortas and sinus lesions in aortic root in apoE/- mice with amelioration of lipid profiles.

CONCLUSIONS: Our study demonstrates that AdipoR activation by agonists regulated PCSK9 expression differently in wild-type and apoE/- mice. However, ADP355 activated hepatic LDLR expression and ameliorated lipid metabolism in both types of mice and inhibited atherosclerosis in apoE/- mice.


**ABSTRACT**
BACKGROUND AND AIMS: Familial hypercholesterolemia (FH) is a high cardiovascular risk condition. Less than 20% of patients achieve the LDL targets. Although PCSK9 inhibitors improve control and reduce cardiovascular events, official recommendations for their use are
restrictive. We aim to assess the number of FH patients suitable for PCSK9 inhibition according to the European guidelines. METHODS: A total of 2685 FH patients, with a minimum follow-up of 6 months, included in the Dyslipidemia Registry of the Spanish Arteriosclerosis Society, were sorted according to the intensity of their lipid-lowering therapy (LLT) and LDL cholesterol levels achieved. The number of patients who met the recommendations for PCSK9 inhibition treatment according to the European Atherosclerosis Society (ESC/EAS), Spanish Arteriosclerosis Society and the European Medicines Agency was calculated. RESULTS: In total, 1573 patients were on high-intensity LLT; 607 were on moderate-intensity statins; 82 were on low-intensity LLT, and 423 were neither on statins nor on ezetimibe in the last visit registered. The mean LDL reduction among those on high-intensity LLT was 54%. Ninety-one percent of patients on high-intensity LLT had an LDL below 5.2 mmol/L, 53% below 3.4 mmol/L, and 23% below 2.6 mmol/L. Only 12% of FH patients with cardiovascular disease achieved 1.8 mmol/L. Despite this, only 17% of patients qualified for PCSK9 inhibition according to ESC/EAS guidelines. CONCLUSIONS: For patients with a condition that exposes them to high cardiovascular risk and who have extreme difficulties in achieving LDL targets, wider access to PCSK9 inhibitor therapy is warranted.


ABSTRACT
BACKGROUND AND AIMS: Proprotein convertase subtilisin/kexin 9 (PCSK9) has emerged as a popular target in the development of new cholesterol-lowering drugs and therapeutic interventions for atherosclerosis. PCSK9 could accelerate atherosclerosis through mechanisms beyond the degradation of the hepatic low-density lipoprotein receptor. Several clinical studies suggested that PCSK9 is involved in atherosclerotic inflammation. Accordingly, this study aimed to explore the role of PCSK9 in vascular inflammation that promotes atherosclerotic progression. METHODS: We examined whether PCSK9 silencing via transduction with the lentivirus-mediated PCSK9 shRNA (LV-PCSK9 shRNA) vector affects the formation of vascular lesions in hyperlipidemia-induced atherosclerosis in apolipoprotein E knockout (apoE KO) mice. In vitro, the effects of PCSK9 on oxLDL-induced macrophages inflammation were investigate using LV-PCSK9 and LV-PCSK9 shRNA for PCSK9 overexpression and PCSK9 silencing. RESULTS: Immunohistochemical analysis showed that PCSK9 expression increased within atherosclerotic plaques in apoE KO mice. These in vivo results showed that the LV-PCSK9 shRNA group of mice developed less aortic atherosclerotic plaques compared with the control group. These lesions also had the reduced number of macrophages and decreased expression of vascular inflammation regulators, such as tumor necrosis factor-alpha, interleukin 1 beta, monocyte chemoattractant protein-1, toll-like receptor 4 and nuclear factor kappa B (NF-kappaB). We further showed that PCSK9 overexpression in macrophages in vitro increased the secretion of oxLDL-induced proinflammatory cytokines. PCSK9 overexpression upregulated TLR4 expression and increased p-IkappaBalpha levels, IkBalpha degradation, and NF-kappaB nuclear translocation in macrophages, but PCSK9 knockdown had the opposite effects in oxLDL-treated macrophages. CONCLUSIONS: PCSK9 gene interference could suppress atherosclerosis directly through decreasing vascular inflammation and inhibiting the TLR4/NF-kappaB signaling.
pathway without affecting plasma cholesterol level in high-fat diet-fed apoE KO mice. PCSK9 may be an inflammatory mediator in the pathogenesis of atherosclerosis.


ABSTRACT
AIM: This study was designed to determine any rebleeding after atorvastatin treatment following spontaneous intracerebral hemorrhage (ICH) in a prospective safety trial. PATIENTS: Atorvastatin (80 mg/day) therapy was initiated in 6 patients with primary ICH with admission Glasgow Coma Score (GCS) >5 within 24 hours of ictus and continued for 7 days, with the dose tapered and treatment terminated over the next 5 days. Patients were studied longitudinally by multiparametric magnetic resonance imaging (MRI) at three time points: acute (3 to 5 days), subacute (4 to 6 weeks) and chronic (3 to 4 months). Imaging sequences included T1, T2-weighted imaging (T2WI), diffusion tensor imaging (DTI) and contrast-enhanced MRI measures of cerebral perfusion, blood volume and blood-brain barrier (BBB) permeability. Susceptibility weighted imaging (SWI) was used to identify primary ICH and to check for secondary rebleeding. Final outcome was assessed using Glasgow Outcome Score (GOS) at 3-4 months. RESULTS: Mean admission GCS was 13.2+/4.0 and mean GOS at 3 months was 4.5+/0.6. Hemorrhagic lesions were segmented into core and rim areas. Mean lesion volumes decreased significantly between the acute and chronic study time points (p=0.008). Average ipsilateral hemispheric tissue loss at 3 to 4 months was 11.4+/-4.6 cm3. MRI showed acutely reduced CBF (p=0.004) and CBV (p=0.002) in the rim, followed by steady normalization. Apparent diffusion coefficient of water (ADC) in the rim demonstrated no alterations at any of the time points (p>0.2). The T2 values were significantly elevated in the rim acutely (p=0.02), but later returned to baseline. The ICH core showed sustained low CBF and CBV values concurrent with a small reduction in ADC acutely, but significant ADC elevation at the end suggestive of irreversible injury. CONCLUSION: Despite the presence of a small, probably permanent, cerebral lesion in the ICH core, no patients exhibited post-treatment rebleeding. These data suggest that larger, Phase 2 trials are warranted to establish long term clinical safety of atorvastatin in spontaneous ICH.


ABSTRACT
Sulfite accumulates in tissues of patients affected by sulfite oxidase (SO) deficiency, a neurometabolic disease characterized by seizures and progressive encephalopathy, often resulting in early death. We investigated the effects of sulfite on mitochondrial function, antioxidant system, glial reactivity and neuronal damage in rat striatum, as well as the potential protective effects of bezafibrate on sulfite-induced toxicity. Thirty-day-old rats were
intrastriatally administered with sulfite (2mumol) or NaCl (2mumol; control) and euthanized 30min after injection for evaluation of biochemical parameters and western blotting, or 7days after injection for analysis of glial reactivity and neuronal damage. Treatment with bezafibrate (30 or 100mg/kg/day) was performed by gavage during 7days before (pre-treatment) or after sulfite administration. Sulfite decreased creatine kinase and citrate synthase activities, mitochondrial mass, and PGC-1alpha nuclear content whereas bezafibrate pre-treatment prevented these alterations. Sulfite also diminished cytochrome c oxidase (COX) IV-1 content, glutathione levels and the activities of glutathione peroxidase (GPx), glutathione reductase (GR), glutathione S-transferase (GST) and glucose-6-phosphate dehydrogenase (G6PDH). On the other hand, catalase activity was increased by sulfite. Bezafibrate pre-treatment prevented the reduction of GPx, GR, GST and G6PDH activities. Finally, sulfite induced glial reactivity and neuronal damage, which were prevented by bezafibrate when administered before or after sulfite administration. Our findings provide strong evidence that sulfite induces neurotoxicity that leads to glial reactivity and neuronal damage. Since bezafibrate exerts neuroprotective effects against sulfite toxicity, it may be an attractive agent for the development of novel therapeutic strategies for SO-deficient patients.


ABSTRACT
Lipids are essential for physiological processes such as maintaining membrane integrity, providing a source of energy and acting as signalling molecules to control processes including cell proliferation, metabolism, inflammation and apoptosis. Disruption of lipid homeostasis can promote pathological changes that contribute towards biological ageing and age-related diseases. Several age-related diseases have been associated with altered lipid metabolism and an elevation in highly damaging lipid peroxidation products; the latter has been ascribed, at least in part, to mitochondrial dysfunction and elevated ROS formation. In addition, senescent cells, which are known to contribute significantly to age-related pathologies, are also associated with impaired mitochondrial function and changes in lipid metabolism. Therapeutic targeting of dysfunctional mitochondrial and pathological lipid metabolism is an emerging strategy for alleviating their negative impact during ageing and the progression to age-related diseases. Such therapies could include the use of drugs that prevent mitochondrial uncoupling, inhibit inflammatory lipid synthesis, modulate lipid transport or storage, reduce mitochondrial oxidative stress and eliminate senescent cells from tissues. In this review, we provide an overview of lipid structure and function, with emphasis on mitochondrial lipids and their potential for therapeutic targeting during ageing and age-related disease.


ABSTRACT
BACKGROUND: Alzheimer’s disease (AD) as a neurodegenerative brain disorder is a devastating pathology leading to disastrous cognitive impairments and dementia, and several studies have shown that AD is closely related to the inflammation, so anti-inflammatory treatment may provide therapeutic benefits. In this study, the effect of simvastatin on inflammation was investigated and the underlying mechanisms were explored. METHODS: First, we tested the effect of simvastatin on AD in clinical research. The fasting venous blood was collected in order to evaluate the levels of interleukin-6 (IL-6), interleukine-1 beta (IL-1beta), antichymotrypsin (ACT) and human tumor necrosis factor alpha (TNF-alpha), which were measured with the enzyme-linked immunosorbent assay (ELISA) kits. Amyloid-beta (Abeta), amyloid-beta precursor protein (APP) and beta-site APP-cleaving enzyme 1 (BACE1) were tested by western blotting. Second, we used an APPswe/PS1E9 (APP/PS1) double transgenic mice to evaluate the amelioration ability of simvastatin against the memory impairment in vivo. Spatial learning and memory of mice were investigated by the Morris water maze test (MWM). The mRNA of inflammatory cytokines were measured using real-time PCR. Third, the phospho-proteome profile of SH-SY5Y human neuroblastoma cells treated with simvastatin was used to investigate the possible mechanisms. RESULTS: The results showed that simvastatin ameliorated the memory deficits both in clinical AD patients and animal model of AD. Simvastatin could reduce the mRNA expression of inflammatory cytokines and mediators, suppress the apoptosis of neural stem cells and improve the survival rate of neurons. Moreover, long non-coding RNA (lnc RNA) n336694 and miR-106b was overexpressed in APP/PS1 mice brain tissues, the relationship between lnc RNA n336694 and miR-106b was explored using the method of Target Scan bioinformatics predictions, the results revealed that miR-106b might be a potential target of lnc RNA n336694. Furthermore, miR-106b mediated apoptosis in SH-SY5Y cell and simvastatin could suppressed this process. CONCLUSION: Our results suggested that simvastatin could be of benefit in preventing the progression of AD and expected to be potentially used as a lead drug for further anti-AD treatment.


ABSTRACT
BACKGROUND: Dyslipidaemia is a major contributor to the increased risk of cardiovascular disease (CVD) associated with type 2 diabetes (T2D). This study aimed to characterize the extent of lipid-lowering therapy use and its impact on lipid and glycaemic outcomes in people with T2D uncontrolled on oral agents who were enrolled in insulin glargine 100 units/mL (Gla-100) randomized controlled trials (RCTs). METHODS: A post hoc patient-level pooled analysis of eleven RCTs (>24 weeks' duration) comparing Gla-100 (+/-oral antidiabetes drugs [OADs]) with OADs alone in people with T2D was performed. Baseline and Week 24 or study endpoint lipid status (low-density lipoprotein cholesterol [LDL-C], high-density lipoprotein cholesterol [HDL-C], non-high-density lipoprotein cholesterol [non-HDL-C] and triglycerides) and indices of glycaemic control (glycosylated haemoglobin, fasting plasma glucose [FPG]) were examined in patient groups according to treatment received and CVD status. Lipid-lowering therapy was
provided at the discretion of physicians at baseline and throughout the studies. RESULTS: Of the 4768 participants included in the analysis, 41% (n = 1940) received lipid-lowering therapy. Only 51% of participants with CVD (1885/3672) were treated with lipid-lowering therapy; these participants had significantly lower levels of LDL-C, HDL-C and non-HDL-C, and higher levels of triglycerides versus patients not treated with lipid-lowering therapy at baseline and study endpoint (P < 0.001 for all). Antihyperglycaemia therapy resulted in decreases in glycosylated haemoglobin (-1.4 to -1.6%) and FPG (-68.9 to -75.3 mg/dl) at Week 24. Furthermore, slight improvements in non-HDL-C (-3.9 to -9.1 mg/dl) and triglyceride levels (-25.8 to -51.2 mg/dl) were observed. Similar changes were seen irrespective of lipid-lowering therapy or CVD status. CONCLUSIONS: In a T2D cohort included in Gla-100 clinical studies, many participants with T2D and CVD did not receive lipid-lowering therapy, and for most categories of lipid the levels were outside the optimal range. Even in patients treated with antihyperglycaemic therapy but not lipid-lowering therapy, there were modest improvements in non-HDL-C and triglyceride levels in all participants with T2D and CVD. There is a need for increased implementation of guideline recommendations such as American College of Cardiology/American Heart Association for the management of dyslipidaemia in patients with T2D.


ABSTRACT

BACKGROUND: Type 2 diabetes mellitus (T2DM) is often associated with mixed dyslipidaemia, where non-high-density lipoprotein cholesterol (non-HDL-C) levels may more closely align with cardiovascular risk than low-density lipoprotein cholesterol (LDL-C). We describe the design and rationale of the ODYSSEY DM-DYSLIPIDEMIA study that assesses the efficacy and safety of alirocumab, a proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitor, versus lipid-lowering usual care in individuals with T2DM and mixed dyslipidaemia at high cardiovascular risk with non-HDL-C inadequately controlled despite maximally tolerated statin therapy. For the first time, atherogenic cholesterol-lowering with a PCSK9 inhibitor will be assessed with non-HDL-C as the primary endpoint with usual care as the comparator. METHODS: DM-DYSLIPIDEMIA is a Phase 3b/4, randomised, open-label, parallel group, multinational study that planned to enrol 420 individuals. Main inclusion criteria were T2DM and mixed dyslipidaemia (non-HDL-C >/=100 mg/dl [>/=2.59 mmol/l], and triglycerides >/=150 and <500 mg/dl [>/=1.70 and <5.65 mmol/l]) with documented atherosclerotic cardiovascular disease or >/=1 additional cardiovascular risk factor. Participants were randomised (2:1) to alirocumab 75 mg every 2 weeks (Q2W) or lipid-lowering usual care on top of maximally tolerated statin (or no statin if intolerant). If randomised to usual care, investigators were able to add their pre-specified choice of one of the following to the patient's current statin regimen: ezetimibe, fenofibrate, omega-3 fatty acids or nicotinic acid, in accordance with local standard-of-care. Alirocumab-treated individuals with non-HDL-C >/=100 mg/dl at week 8 will undergo a blinded dose increase to 150 mg Q2W at week 12. The primary efficacy endpoint is non-HDL-C change from baseline to week 24 with alirocumab versus usual care; other lipid levels (including LDL-C),
glycaemia-related measures, safety and tolerability will also be assessed. Alirocumab will be compared to fenofibrate in a secondary analysis. RESULTS: Recruitment completed with 413 individuals randomised in 14 countries worldwide. Results of this trial are expected in the second quarter of 2017. CONCLUSIONS: ODYSSEY DM-DYSLIPEIDEMIA will provide information on the efficacy and safety of alirocumab versus lipid-lowering usual care in individuals with T2DM and mixed dyslipidaemia at high cardiovascular risk using non-HDL-C as the primary efficacy endpoint. Trial registration NCT02642159 (registered December 24, 2015).


ABSTRACT
INTRODUCTION: Hypercholesterolemia is a causal risk factor for cardiovascular diseases, which is recommended to be treated at least in high-risk patients. Yet, currently there is a lack of epidemiological data on the number of high-risk patients in Germany who do not respond adequately to high-dose statin monotherapy or statin therapy in combination with other lipid-lowering agents. METHODS: Of a total of over 2.6 million patient records from general practitioners in the IMS Disease Analyzer database, all high-risk cardiovascular patients with hypercholesterolemia who did not reach target low-density lipoprotein-cholesterol (LDL-C) levels despite at least 12 months of maximum lipid-lowering therapy and optimal medication supply (medication possession rate >/=80%) were selected over a defined period. RESULTS: On the basis of the practice data, a total of 602 133 patients with a high cardiovascular risk who were treated with statin monotherapy or statin combination therapy with optimal lipid-lowering agents. A total of 79 848 high-risk patients did not reach the target LDL-C level of 70 mg/dl or less despite consistent lipid-lowering therapy; of them, 12 808 had a documented LDL-C level of at least 130 mg/dl. CONCLUSION: The prevalence of high-risk cardiovascular patients with therapy-resistant hypercholesterolemia is substantial in Germany.


ABSTRACT
BACKGROUND: Atherosclerosis is a chronically inflammatory disease and one of the leading causes of deaths worldwide. Endothelial cell apoptosis plays a crucial role in its development. Several microRNAs (miRNAs) are reportedly involved in atherosclerotic plaque formation, including miRNA-210 (miR-210). However, the underlying mechanism of its role in endothelial cell apoptosis during atherosclerosis is still largely unknown. METHODS: A mouse model with atherosclerosis induced by a high-fat diet (HFD) was built in ApoE (-/-) mice. The levels of endothelial cell apoptosis were determined via flow cytometry. The expressions of miR-210 and PDK1 in purified CD31+ endothelial cells from mouse aorta were measured via RT-qPCR and
western blot. Binding between miR-210 and the 3'-untranslated region (UTR) of PDK1 mRNA was predicted using bioinformatics analyses and confirmed with a dual luciferase reporter assay. The effects of miR-210 were further analyzed in an in vitro model using human aortic endothelial cells (HAECs) treated with oxidized low-density lipoprotein (ox-LDL). RESULTS: We found that the HFD mice developed atherosclerosis in 12 weeks and had a significantly higher percentage of endothelial cell apoptosis. The upregulated level of miR-210 in the HFD mice and HAECs inversely correlated with the level of PDK1. Inhibiting miR-210 expression significantly reduced HAEC apoptosis, as evidenced by the results of the MTT and flow cytometry experiments. Further analysis identified PDK1 as the target of miR-210 and showed that PDK1 overexpression reversed the pro-apoptotic effect of miR-210 through mediation of the P13K/Akt/mTOR pathways. CONCLUSION: Our study suggests a novel role for miR-210 in the progression of atherosclerosis through the regulation of endothelial apoptosis. This indicates that miR-210 might have potential in treatment of atherosclerosis.


ABSTRACT

INTRODUCTION: Metabolism and plasma concentration of lipids and lipid-derived compounds play an important role in kidney physiology and pathological processes. The component of membrane phospholipids - arachidonic acid (AA) and its active derivatives - eicosanoids are involved in the development of hypertension, diabetes, inflammation and may contribute to progression of chronic kidney disease (CKD). The purpose of the study was to determine, whether the type of renal replacement therapy has an effect on eicosanoids metabolism.

MATERIALS AND METHODS: The study included 145 patients with CKD: on conservative treatment (n=68), on peritoneal dialysis (PD) (n=23) and undergoing chronic haemodialysis (HD) (n=54). The concentrations of TXB2, 20-HETE, 8-epi-PGF2alpha in platelet poor plasma (PPP) were determined using the ELISA method and 5-HETE, 12-HETE, 15-HETE were measured using the RP-HPLC. RESULTS: The concentrations of TXB2 in HD group, both before (2.28+/-.72ng/mL) and after (1.49+/-.63ng/mL) haemodialysis treatment differed significantly from PD group (57.76+/-.613ng/mL). Haemodialysis session led to the significant decrease in TXB2 plasma concentration (p=0.046). 20-HETE concentrations in HD group (113.55+/-.107.54pg/mL and 199.54+/-.142.98pg/mL before and after haemodialysis, respectively) were significantly higher than in CKD 3-5 group (8.96+/-.12.66pg/mL) and PD group (47.78+/-.34.07pg/mL). The highest concentration of 12-HETE was obtained in PD patients (3.58+/-.399ng/mL) and differed significantly from HD group after haemodialysis (0.97+/-.0.28ng/mL) and CKD3-5 group (1.06+/-.0.52ng/mL). The concentrations of 5-HETE, 15-HETE and 8-epi-PGF2alpha-III did not differ significantly among examined groups. CONCLUSIONS: The concentrations of active AA metabolites depend on the mode of renal replacement therapy and are associated with intensity of oxidative stress. They might be considered as potential indicators of kidney damage.

ABSTRACT
Selection of patients with atherosclerotic carotid stenosis for revascularization is mainly based on the degree of luminal narrowing of the carotid artery. However, identification of other features of plaque apart from the degree of stenosis could enable better selection for intervention if they are also associated with the occurrence of stroke. Before these risk factors can possibly play a role in treatment decisions, their prognostic value needs to be proven. The purpose of this narrative review is to summarize current knowledge regarding the risk factors for stroke in patients with carotid stenosis, how they can be determined, and to what extent they predict stroke, based on recent literature. References for this review were identified by searches of PubMed between 1995 and October, 2016 and references from relevant articles. For each topic in this review different relevant search terms were used. The main search terms were 'carotid stenosis', 'atherosclerosis', 'stroke risk', and 'vulnerable plaque'. Language was restricted to English. The final reference list was generated on the basis of relevance to the topics covered in this review.


ABSTRACT
BACKGROUND: A Phase 2, dose-ranging study of bococizumab, a monoclonal anti-proprotein convertase subtilisin/kexin type 9 antibody, was conducted in Japanese subjects to assess its efficacy, safety, and tolerability in this population.

Methods and Results: Two different hypercholesterolemic study populations were enrolled concurrently: Japanese subjects with uncontrolled low-density lipoprotein cholesterol (LDL-C) despite atorvastatin treatment (LDL-C >/=100 mg/dL; n=121), and Japanese subjects naïve to lipid-lowering agents and with LDL-C >/=130 mg/dL (n=97). Subjects within each study population were randomized to bococizumab 50, 100, or 150 mg, or placebo, q14D for 16 weeks; an open-label ezetimibe 10 mg daily arm was also included for the atorvastatin-treated population. Significant, dose-dependent reductions in fasting LDL-C levels were observed in all bococizumab arms of both study populations at Weeks 12 and 16 (adjusted mean percent changes from baseline: 54.1-76.7% for atorvastatin-treated subjects and 47.7-66.8% for treatment-naive subjects; P<0.001 vs. placebo for all). Bococizumab also caused dose-dependent changes in other lipid parameters in both study populations at Weeks 12 and 16. No serious adverse events (AEs) related to bococizumab treatment occurred and all treatment-emergent AEs were mild or moderate in severity. No dose-dependent relationship between bococizumab treatment and development of anti-drug antibodies was observed. CONCLUSIONS: Bococizumab was well tolerated and significantly
reduced fasting LDL-C in atorvastatin-treated and treatment-naive hypercholesterolemic Japanese subjects. (Clinicaltrials.gov identifier: NCT02055976.).


ABSTRACT
BACKGROUND AND AIMS: Elevated levels of circulating omega-3 polyunsaturated fatty acids like alpha linolenic acid (ALA) may be beneficial for cardiovascular health. Circulating ALA concentrations are elevated dramatically by a cholesterol supplemented diet which increases ALA bioavailability through enhanced micelle formation in the intestines. Conversely, it is possible that drugs which inhibit cholesterol metabolism in the intestine may also inhibit fatty acid absorption. The purpose of this study is to determine if a cholesterol absorption inhibitor, ezetimibe, will decrease circulating levels of ALA. METHODS AND RESULTS: Cardiac patients (n = 34) between 44 and 80 years old, requiring statin therapy to regulate blood cholesterol levels, were randomly assigned to one of four groups for a 6 week trial: 1) placebo; 2) ezetimibe therapy; 3) a supplement of flaxseed oil (containing 1.0 g ALA in 2.0 g of flaxseed oil); or 4) ezetimibe and flaxseed oil supplementation. Ingestion of flaxseed oil resulted in a significant increase in circulating ALA levels (6 ug/dl) in patients who were not given ezetimibe. However, in the presence of ezetimibe, circulating ALA levels did not increase significantly even in the presence of flax oil supplementation (a decrease of 4 ug/dl). There were no significant differences amongst the groups in terms of circulating total cholesterol, LDL, HDL, triglyceride levels in the blood. CONCLUSION: Ezetimibe therapy inhibited the absorption of omega-3 fatty acids. Patients receiving ezetimibe therapy may not receive the expected cardiovascular benefits from dietary supplementation with omega-3 fatty acids. CLINICAL TRIAL REGISTRATION: NCT00955227.


ABSTRACT
BACKGROUND: Cardiovascular disease has taken epidemic proportions during past decades. Cardiovascular risk factors contribute to progression of coronary lesions, worsening the patient’s prognosis. This study was planned to analyze the association of dietary factors with severity of coronary artery disease (CAD) in Indian patients. METHODS: Three hundred patients with known coronary disease above the age of 25 years were included in this study. Blood samples were collected for biochemical markers. Patients were stratified according to severity of CAD [number of vessel involved-single (SVD), double (DVD), triple (TVD)]. RESULTS: Mean age of the patient was 60.9 +/- 12.4 years. Subjects with TVD, DVD, SVD in the study were 52.3%, 25.3% and 22.3% respectively. Patients with TVD had higher body mass index, triglycerides, HOMA-Insulin Resistance, hsCRP and lower high density cholesterol. Diabetes mellitus, hypertension and dyslipidemia were more common in TVD patients. Among macronutrients, patients with TVD had higher intake of carbohydrate and lower intake of protein and dietary...
fibers. There was no association of total fat intake with CAD, however, intake of palmitic acid was higher among patients with TVD. Intake of vitamins namely niacin, riboflavin, thiamine, B6, and vitamin-C decreased with increase in severity. With increase in severity of CAD, mineral intake (potassium, calcium, magnesium, phosphorus, sulfur, iron, chromium, copper, manganese, and zinc) decreased. CONCLUSIONS: Dietary factors are associated with severity of coronary artery disease. Low intake of protein, fiber, vitamins, minerals and high intake of carbohydrate and fat was associated with higher probability of having severe CAD.


ABSTRACT
Familial hypercholesterolemia (FH) is the most common inherited form of dyslipidemia and a major cause of premature cardiovascular disease. Management of FH mainly relies on the efficiency of treatments that reduce plasma low-density lipoprotein (LDL) cholesterol (LDL-C) concentrations. MicroRNAs (miRs) have been suggested as emerging regulators of plasma LDL-C concentrations. Notably, there is evidence showing that miRs can regulate the post-transcriptional expression of genes involved in the pathogenesis of FH, including LDLR, APOB, PCSK9, and LDLRAP1. In addition, many miRs are located in genomic loci associated with abnormal levels of circulating lipids and lipoproteins in human plasma. The strong regulatory effects of miRs on the expression of FH-associated genes support the notion that manipulation of miRs might serve as a potential novel therapeutic approach. The present review describes miRs-targeting FH-associated genes that could be used as potential therapeutic targets in patients with FH or other severe dyslipidemias.


ABSTRACT
PURPOSE: The progressive nature of type 2 diabetes mellitus (T2DM) calls for step-wise intensification of therapy for maintaining normal glycemic levels and lowering cardiovascular (CV) risk. Because obesity is a prominent risk factor and comorbidity of T2DM, it further elevates the CV risk in T2DM. Therefore, it is vital to manage weight, obesity, and glycemic parameters for effective T2DM management. Few oral antidiabetic drugs (sulfonylureas and thiazolidinediones) and insulin are not suitable for obese patients with T2DM because these drugs cause weight gain. The present review discusses the place of glucagon-like peptide-1 receptor agonists (GLP-1RAs) in the treatment of obese patients with T2DM and the significance of these drugs in the prevention of future CV risk in patients with T2DM. METHODS: A literature search of PubMed and EMBASE was conducted by using the search terms T2DM, GLP-1RAs, obesity, and cardiovascular complication. Randomized controlled trials measuring the effect of GLP-1RAs versus that of placebo on CV outcomes were included in the review. FINDINGS: GLP-1RAs have emerged as a therapeutic alternative; these drugs exert their actions by providing glycemic control, improving insulin resistance and o-cell function, and reducing weight. The risk of hypoglycemia with GLP-1RAs is minimal; however, GLP-1RAs are associated
with gastrointestinal adverse events and raise concerns regarding pancreatitis. Combining GLP-1RAs with insulin analogues results in higher efficacy, a lowered insulin dose, and reduced insulin-related hypoglycemia and weight gain. Longer acting GLP-1RAs are also associated with improvement in medication adherence. Improvement in CV risk factors such as blood pressure and lipid profile further increases their usability for improving CV outcomes. IMPLICATIONS: Overall, the properties of GLP-1RAs make them suitable for combination with oral antidiabetic drugs in the early stages of T2DM and with insulins in the later stages for optimizing comprehensive management of the disease.


**ABSTRACT**

PURPOSE OF REVIEW: The purpose of the study is to review the use of statins and the role of both non-statin lipid-lowering agents and diabetes-specific medications in the treatment of diabetic dyslipidemia. RECENT FINDINGS: Statins have a primary role in the treatment of dyslipidemia in people with type 2 diabetes, defined as triglyceride levels >200 mg/dl and HDL cholesterol levels <40 mg/dL. A number of clinical trials suggest that treatment with a fibrate may reduce cardiovascular events. However, the results of these trials are inconsistent, probably because many of their participants did not have dyslipidemia. The choice of medications used to treat diabetes can have major implications regarding management of dyslipidemia; metformin, GLP-1 agonists, and pioglitazone all have favorable lipid effects. These agents, as well as the new SGLT2 inhibitors, may reduce cardiovascular events. Management of dyslipidemia in people with type 2 diabetes should start with statin therapy and optimal glycemic control with agents that have favorable lipid and cardiovascular effects. We believe that there is a role for adding fenofibrate to moderate-intensity statins in selected patients with true dyslipidemia. We propose an algorithm for selecting add-on medications for diabetes (after metformin) based on lipid status.


**ABSTRACT**

PURPOSE OF REVIEW: This study aimed to present the current information on the genetic background of dyslipidemias and provide insights into the complex pathophysiological role of several plasma lipids/lipoproteins in the pathogenesis of atherosclerotic cardiovascular disease. Furthermore, we aim to summarize established therapies and describe the scientific rationale for the development of novel therapeutic strategies. RECENT FINDINGS: Evidence from genetic studies suggests that besides lowering low-density lipoprotein cholesterol, pharmacological reduction of triglyceride-rich lipoproteins, or lipoprotein(a) will reduce risk for coronary heart disease. Dyslipidemia, in particular hypercholesterolemia, is a common clinical condition and represents an important determinant of atherosclerotic vascular disease. Treatment decisions are currently guided by the causative lipid phenotype and the presence of other risk factors suggesting a very high cardiovascular risk. Therefore, the identification of lipid disorders and
the optimal combination of therapeutic strategies provide an outstanding opportunity for reducing the onset and burden of cardiovascular disease.


ABSTRACT
BACKGROUND: Peripheral neuropathy affects about 50% of the diabetic population. The manifestations range from pain, numbness, paresthesia and ulceration in the extremities and it is the major cause of non-traumatic amputations. Currently there is no effective treatment for peripheral neuropathy. With the prevalence of obesity and type 2 diabetes and associated complications reaching epidemic levels there is a critical need for finding a treatment to preserve nerve function. INTRODUCTION: This article will review the potential for fish oil as a treatment for diabetic peripheral neuropathy. METHODS: A through search of the PubMed database was performed and relevant articles on the topic were included in this review. RESULTS: Many studies support a role for fish oil in cardiovascular health. However, less information is available regarding the effect of fish oil on diabetes complications including neuropathy. Pre-clinical studies from my laboratory using diabetic rodent models have demonstrated that fish oil can slow progression and reverse diabetic neuropathy as determined by examining multiple endpoints. Mechanistically fish oil has been shown to have anti-inflammatory properties. Lowering the omega-6/omega-3 fatty acid ratio has been shown to be anti-thrombotic. Moreover, metabolites of eicosapentaenoic and docosahexaenoic acids, the main polyunsaturated fatty acids found in fish oil, commonly referred to as resolvins and neuroprotectin have been shown to be neuroprotective and can stimulate neuron outgrowth in vitro. CONCLUSIONS: Additional studies are required but existing data suggests that dietary enrichment with omega-3 fatty acids contained in fish oil may be beneficial treatment for diabetic neuropathy.


ABSTRACT
Association of hypercholesterolemia and atherosclerotic cardiovascular disease (ASCVD) is well established. Reducing low-density lipoprotein-cholesterol (LDL-C) and raising high-density lipoprotein-cholesterol (HDL-C) have been the therapeutic targets to reduce the risk of ASCVD. Cholesterol-lowering medications have been used to provide both primary and secondary prevention of ASCVD for many years by reducing the absorption and reabsorption, promoting excretion, or decreasing the synthesis of cholesterol. Within the past five years, several new classes of cholesterol-lowering drugs have been tested and approved for patients with hypercholesterolemia that are not well controlled by conventional therapy (ezetimibe, bile-acid sequestrants, and statins). These drugs include proprotein convertase subtilisin/kexin type 9 (PCSK9) antibodies, apolipoprotein A-100 (Apo B-100) antisense, and microsomal triglyceride transfer protein (MTP) inhibitor. Clinical trials revealed that adding PCSK9 antibodies to the preexisting statin therapy can further reduce LDL-C by 60%. ApoB antisense and MTP inhibitor
are currently approved for patients with homozygous familial hypercholesterolemia. Several HDL-raising drugs have also been tested, but the results are not promising. Studies suggest that specifically raising reverse cholesterol transport rather than HDL-C level could be a novel therapeutic approach to reduce cardiovascular risk.


ABSTRACT
Fibroblast growth factor 21 (FGF21) is an atypical member of the FGF family. Acting in an endocrine fashion, it increases glucose uptake, modulates lipid metabolism, and sensitizes insulin response in metabolically active organs, including the liver and adipose tissue. Emerging evidence shows a strong correlation between circulating FGF21 levels and the incidence and severity of atherosclerosis. Animal studies have demonstrated a beneficial role of FGF21 in protecting against aberrant lipid profile, while recent development in FGF21 mimetics has provided further insight into the lipid-lowering effects of FGF21 signaling. The present review summarizes the physiological roles of FGF21, and discusses major breakthroughs and limitations of FGF21 mimetic-based therapeutic strategies for treating atherosclerosis.


ABSTRACT
A panel of European experts on lipids and cardiovascular disease discussed clinical approaches to managing cardiovascular risk in clinical practice, including residual cardiovascular risk associated with lipid abnormalities, such as atherogenic dyslipidaemia (AD). A simplified definition of AD was proposed to enhance understanding of this condition, its prevalence, and its impact on cardiovascular risk. Atherogenic dyslipidaemia can be defined by high fasting triglyceride levels (>\=2.3 mmol/L) and low high-density lipoprotein cholesterol (HDL-c) levels (<\=1.0 and <\=1.3 mmol/L in men and women, respectively) in statin-treated patients at high cardiovascular risk. The use of a single marker for the diagnosis and treatment of AD, such as non-HDL-c, was advocated. Interventions including lifestyle optimization and low-density lipoprotein (LDL)-lowering therapy with statins (+/-ezetimibe) are implemented by all experts. Treatment of residual AD can be performed with the addition of fenofibrate, since it can improve the complete lipoprotein profile and reduce the risk of cardiovascular events in patients with AD. Specific clinical scenarios in which fenofibrate may be prescribed are discussed, and include patients with very high triglycerides (>\=5.6 mmol/L), patients who are intolerant or resistant to statins, and patients with AD and at high cardiovascular risk. The fenofibrate-statin combination was considered by the experts to benefit from a favourable benefit-risk profile. Cardiovascular experts adopt a multifaceted approach to the prevention of atherosclerotic cardiovascular disease, with lifestyle optimization, LDL-lowering therapy, and
treatment of AD with fenofibrate routinely used to help reduce a patient's overall cardiovascular risk.


ABSTRACT
INTRODUCTION: Large-scale epidemiological studies on Greenlandic, Canadian and Alaskan Eskimos have examined the health benefits of omega-3 fatty acids consumed as part of the diet, and found statistically significant relative reduction in cardiovascular risk in people consuming omega-3 fatty acids. Areas covered: This article reviews studies on omega-3 fatty acids during the last 50 years, and identifies issues relevant to future studies on cardiovascular (CV) risk. Expert commentary: Although a meta-analysis of large-scale prospective cohort studies and randomized studies reported that fish and fish oil consumption reduced coronary heart disease-related mortality and sudden cardiac death, omega-3 fatty acids have not yet been shown to be effective in secondary prevention trials on patients with multiple cardiovascular disease (CVD) risk factors. The ongoing long-term CV interventional outcome studies investigate high-dose, prescription-strength omega-3 fatty acids. The results are expected to clarify the potential role of omega-3 fatty acids in reducing CV risk. The anti-inflammatory properties of omega-3 fatty acids are also important. Future clinical trials should also focus on the role of these anti-inflammatory mediators in human arteriosclerotic diseases as well as inflammatory diseases.


ABSTRACT
Cardiovascular diseases (CVDs) are one of the major causes of mortality and disability in Western countries. Prevention is known to be the cornerstone to lessen the incidence of CVDs and also to reduce the economic burden of both the citizen and the healthcare system. "Interventional medicine" certainly puts lifestyle modification as the first therapeutic step, including a healthy diet and physical activity. Secondly, a large body of research individuated a number of food and plant bioactives, which are potentially efficacious in preventing and reducing some highly prevalent CV risk factors, such as hypercholesterolemia, hypertension, vascular inflammation and vascular compliance. Some lipid- and blood pressure-lowering bioactives were studied for their impact on human vascular health, particularly as regards endothelial function and arterial stiffness. Several nutraceuticals showed additive or synergistic properties in combination, sometimes (but not always) allowing a reduction of the administered dose of extracts and determining a "multi-factorial" final effect on many cardiovascular risk factors. Thus, this review focuses on available evidence regarding the effects of berberine, plant sterols, green tea extract, soy, curcumin, cocoa, pycnogenol, lycopene, olive oil, soluble fibers, garlic, resveratrol, beetroot, mineral salts and vitamins on the lipid profile, blood pressure, inflammatory and endothelial markers, and vascular compliance. Future clinical...
research studies will have to focus more on middle term modification of the instrumental markers of vascular aging than on short-term effects on indirect laboratory risk markers.


ABSTRACT
Macrovascular complications of diabetes include cardiovascular events, whereas common microvascular complications include neuropathy, retinopathy, and diabetic kidney disease. Control of hypertension and dyslipidemia is an important step in minimizing the risk of complications. Blood pressure (BP) levels should be maintained at less than 140 mm Hg systolic and less than 90 mm Hg diastolic. In older adults, medical therapy to reduce BP to less than 130/70 mm Hg is not recommended. In these patients, a systolic BP level less than 130 mm Hg has not been shown to improve atherosclerotic cardiovascular disease (ASCVD) outcomes, and a diastolic BP less than 70 mm Hg is associated with a higher mortality risk. Patients with diabetes and a history of ASCVD should be treated with high-dose statins. A combination of ezetimibe and a moderate-dose statin is an option for patients who cannot tolerate high-dose therapy. Screening for kidney disease should be performed using estimated glomerular filtration rate and urine albumin measurement. Clinicians should be familiar with the limitations of both methods. Whether patients with diabetes are at increased risk of concomitant depression is not well understood, although a link has been shown in large, observational studies.


ABSTRACT
Preeclampsia has been linked to high morbidity and mortality during pregnancy. However, no efficient pharmacological options for the prevention of this condition are currently available. Preeclampsia is thought to share several pathophysiologic mechanisms with cardiovascular disease, which has led to investigations for the potential role of statins (HMG CoA reductase inhibitors) in its prevention and early management. Pravastatin seems to have a safer pharmacokinetic profile compared to other statins, however, the existing preclinical evidence for its effectiveness in preeclampsia treatment has been mostly restricted to animal models. This review aims to summarize the current data and delineate the potential future role of statins in the prevention and management of preeclampsia.


ABSTRACT
INTRODUCTION: A number of natural compounds have individually demonstrated to improve glucose and lipid levels in humans. AIM: To evaluate the short-term glucose and lipid-lowering activity in subjects with impaired fasting glucose. METHODS: To assess the effects of a combination of nutraceuticals based on Lagerstroemia speciosa, Berberis aristata, Curcuma longa, Alpha-lipoic acid, Chrome picolinate and Folic acid, we performed a double-blind, parallel group, placebo-controlled, randomized clinical trial in 40 adults affected by impaired fasting glucose (FPG = 100-125 mg/dL) in primary prevention of cardiovascular disease. After a period of 2 weeks of dietary habits correction only, patients continued the diet and began a period of 8 weeks of treatment with nutraceutical or placebo. Data related to lipid pattern, insulin resistance, liver function and hsCRP were obtained at the baseline and at the end of the study. RESULTS: No side effects were detected in both groups of subjects. After the nutraceutical treatment, and compared to the placebo-treated group, the enrolled patients experienced a significant improvement in TG (-34.7%), HDL-C (+13.7), FPI (-13.4%), and HOMA-Index (-25%) versus the baseline values. No significant changes were observed in the other investigated parameters in both groups (Body Mass Index, LDL-C, hsCRP). CONCLUSIONS: The tested combination of nutraceuticals showed clinical efficacy in the improvement of TG, HDL-C, FPI and HOMA-Index, with an optimal tolerability profile. Further confirmation is needed to verify these observations on the middle and long term with a larger number of subjects.


ABSTRACT

BACKGROUND: Psoriasis is a T helper 1 cell-mediated chronic inflammation. Statins have been found to have anti-inflammatory and immunomodulatory effects targeting T helper 1 cells and thus, are being investigated as treatments for psoriasis. AIMS: To investigate the efficacy and safety of atorvastatin as adjunctive treatment for mild to moderate chronic plaque psoriasis; and the impact of atorvastatin on quality of life. The study also aimed to correlate the beneficial effects of atorvastatin with its lipid-lowering effects. METHODS: Twenty-eight (19-65 year old) mild-moderate chronic plaque psoriasis patients were randomly assigned to two groups (treatment group: atorvastatin 40 mg OD; control group: placebo OD) and followed up for 6 months. All were allowed to use betamethasone valerate 0.1% ointment twice a day for a maximum of 3 weeks continuous application with 1-week rest periods in between. Primary outcome measures were the mean percentage reduction in Psoriasis Area and Severity Index (PASI) scores and percentage of patients achieving PASI-50. RESULTS: Fourteen patients (treatment: 6, control: 8) completed the trial. Mean reductions in PASI scores between the treatment (2.15 +/- 2.17) and control (1.69 +/- 2.36) groups were not statistically significant (P = 0.636). Intention-to-treat analysis of PASI-50 showed increased risk of treatment failure with atorvastatin as adjunct but estimates were not significant. Changes in Dermatology Life Quality Index (DLQI) scores (P = 0.214) and high-sensitivity C-reactive protein (P = 0.884) were likewise not statistically significant. Reductions in PASI scores were not linearly correlated with reductions in total cholesterol (P = 0.924), triglycerides (P = 0.274), low-density lipoprotein-cholesterol (P = 0.636), high-density lipoprotein-cholesterol (P = 0.584), or high-sensitivity C-
reactive protein levels (P = 0.906). Adverse effects in the treatment group were transient elevated transaminases (n = 1) and mild myalgia (n = 1). LIMITATIONS: A 50% dropout rate was experienced. This remarkably high dropout rate decreases the robustness of the study results. CONCLUSIONS: Although atorvastatin exhibited earlier percentage reduction in PASI scores, it was not able to produce an additional benefit compared to psoriatic patients applying steroid alone.


ABSTRACT
An Expert Panel convened by the National Lipid Association was charged with updating the recommendations on the use of proprotein convertase subtilisin/kexin type 9 (PCSK9) antibody therapy that were provided by the 2015 National Lipid Association Recommendations for the Patient-Centered Management of Dyslipidemia: Part 2. Recent studies have demonstrated the efficacy of these agents in reducing low-density lipoprotein cholesterol and non-high-density lipoprotein cholesterol and have confirmed their excellent safety profile. A cardiovascular outcomes study has shown that these agents reduce incident atherosclerotic cardiovascular disease (ASCVD) events in patients with stable ASCVD and concomitant risk factors. The current update provides the Expert Panel's evidence-based recommendations on the clinical utility of PCSK9 inhibitors in patients with stable ASCVD, progressive ASCVD, familial hypercholesterolemia phenotype/low-density lipoprotein cholesterol >/=190 mg/dL, and very-high-risk patients with statin intolerance.


ABSTRACT
OBJECTIVE: NONcNZO10 (NZ10) mice are predisposed to obesity and develop type 2 diabetes (T2D) and hepatic steatosis even when maintained on a control diet (CD) of 6% fat. Studies were designed to determine whether this extreme susceptibility phenotype could be alleviated by diet and if so the molecular targets of diet. METHODS: NZ10 and SWR/J (SWR) control mice were fed a CD or a test diet of high protein and fish oil (HPO) for 19 weeks and then analyzed for steatosis, blood chemistry, hepatic gene and micro-RNA expression. RESULTS: HPO diet prevented steatosis, significantly increased serum adiponectin and reduced serum cholesterol and triglycerides only in NZ10 mice. The HPO diet repressed hepatic expression of fatty acid metabolic regulators including PPAR-gamma, sterol regulatory element-binding protein-c1, peroxisome proliferator-activated receptor gamma co-activator-1, fatty acid synthase, fatty acid binding protein-4, and apolipoprotein A4 genes only in NZ10 mice. Also repressed by a HPO diet were adiponectinR2 receptor, leptin-R, PPAR-alpha, pyruvate dehydrogenase kinase isoforms 2 and 4, AKT2 and GSK3beta. Micro-RNA (miR) arrays identified miRs that were diet and/or genetics regulated. QRTPCR confirmed increased expression of miR-205 and suppression
of a series of miRs including miRs-411, 155, 335 and 21 in the NZ10-HPO group, each of which are implicated in the progression of diabetes and/or steatosis. Evidence is presented that miR-205 co-regulates with PPARgamma and may regulate fibrosis and EMT during the progression of steatosis in the livers of NZ10-CD mice. The dietary responses of miR-205 are tissue-specific with opposite effects in adipose and liver. CONCLUSION: The results confirm that a HPO diet overrides the genetic susceptibility of NZ10 mice and this correlates with the suppression of key genes and perhaps micro-RNAs involved in hyperglycemia, dyslipidemia and inflammation including master PPAR regulators, adiponectin and leptin receptors.


ABSTRACT
Objective: To review the potential role and specific impact of statin drugs in women with PCOS. The evidence for this use of statins in PCOS is limited and still under further investigation.
Materials and methods: A search was conducted using PubMed, DynaMed and PubMedHealth databases through October 16, 2016 using the terms polycystic ovary syndrome, PCOS, hydroxymethylglutaryl-CoA reductase inhibitors, hydroxymethylglutaryl-CoA, statin, atorvastatin, fluvastatin, lovastatin, pitavastatin, pravastatin, rosuvastatin and simvastatin. English-language trials evaluating statins in PCOS were obtained and incorporated if they provided relevant data for providers. Results: We summarize twelve trials involving statins in PCOS. The trials were predominantly 12 weeks to 3 months in length (8 of the 12 trials) and low to moderate dose of statin drugs were used. The majority (10 of 12) of the trials show that statins reduce testosterone levels or other androgen hormones (DHEA-S and androstenedione), half of the trials evaluating LH/FSH ratio show an improvement, and all had positive effects on lipid profiles. Conclusion: Statins show promising improvements in serum levels of androgens and LH/FSH ratios translating to improved cardiovascular risk factors above and beyond simply lowering LDL levels. More investigation is needed to determine if statins can clinically impact women with PCOS long term, particularly those who are young and are not yet candidates for traditional preventative treatment with a statin medication.


ABSTRACT
Circulating lipid concentrations are among the strongest modifiable risk factors for coronary artery disease (CAD). Most genetic studies have focused on Caucasian populations with little information available for populations of African ancestry. Using a cohort of ~2800 African-Americans (AAs) from a biobank at Vanderbilt University (BioVU), we sought to trans-ethnically replicate genetic variants reported by the Global Lipids Genetics Consortium to be associated with lipid traits in Caucasians, followed by fine-mapping those loci using all available variants on the MetaboChip. In AAs, we replicated one of 56 SNPs for total cholesterol (TC) (rs6511720 in LDLR, P=2.15 x 10-8), one of 63 SNPs for high-density lipoprotein cholesterol (HDL-C) (rs3764261 in CETP, P=1.13 x 10-5), two of 46 SNPs for low-density lipoprotein cholesterol (LDL-
Antihypertensive and lipid-lowering treatment for primary prevention in older adults.

Objectives: To examine statin treatment among adults aged 65 to 74 years and 75 years and older when used for primary prevention in the Lipid-Lowering Trial (LLT) component of the Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT-LLT).

There is little evidence to guide the use of statins for primary prevention in adults 75 years and older.

Importance: While statin therapy for primary cardiovascular prevention has been associated with reductions in cardiovascular morbidity, the effect on all-cause mortality has been variable. There is little evidence to guide the use of statins for primary prevention in adults 75 years and older.

Methods: We performed a secondary analysis of the ALLHAT-LLT trial. We assessed statin use among elderly participants and compared cardiovascular outcomes with and without statin use.

Results: Among 31,086 participants aged 75 years and older, 1,406 (4.5%) participants used statins (Table 1). Statin use was associated with a significant reduction in the primary outcome of cardiovascular events (Hazard Ratio [HR]: 0.72, 95% CI 0.59-0.88). The absolute risk reduction was 50 per 10,000 person-years.

Conclusions: Statin use among elderly adults was associated with a significant reduction in the primary outcome of cardiovascular events. Further studies are needed to determine the optimal strategy for statin use in this population.

PM: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC5636232

ABSTRACT

Ectopic fat located in the kidney has emerged as a novel cause of obesity-related chronic kidney disease (CKD). In this study, we aimed to investigate whether inflammatory stress promotes ectopic lipid deposition in the kidney and causes renal injury in obese mice and whether the pathological process is mediated by the fatty acid translocase CD36. HFD feeding alone resulted in obesity, hyperlipidemia and slight renal lipid accumulation in mice, which nevertheless had normal kidney function. HFD-fed mice with chronic inflammation had severe renal steatosis and obvious glomerular and tubular damage, which was accompanied by increased CD36 expression. Interestingly, CD36 deficiency in HFD-fed mice eliminated renal lipid accumulation and pathological changes induced by chronic inflammation. In both human mesangial cells (HMC) and human kidney 2 (HK2) cells, inflammatory stress increased the efficiency of CD36 protein incorporation into membrane lipid rafts, promoting FFA uptake and intracellular lipid accumulation. Silence of CD36 in vitro markedly attenuated FFA uptake, lipid accumulation and cellular stress induced by inflammatory stress. We conclude that inflammatory stress aggravates renal injury by activation of the CD36 pathway, suggesting that this mechanism may operate in obese individuals with chronic inflammation, making them prone to CKD.


ABSTRACT


ABSTRACT

Han BH, Sutin D, Williamson JD et al. Effect of Statin Treatment vs Usual Care on Primary Cardiovascular Prevention Among Older Adults: The ALLHAT-LLT Randomized Clinical Trial. Jama internal medicine 2017.

Design, Setting, and Participants: Post hoc secondary data analyses were conducted of participants 65 years and older without evidence of atherosclerotic cardiovascular disease; 2867 ambulatory adults with hypertension and without baseline atherosclerotic cardiovascular disease were included. The ALLHAT-LLT was conducted from February 1994 to March 2002 at 513 clinical sites. Interventions: Pravastatin sodium (40 mg/d) vs usual care (UC). Main Outcomes and Measures: The primary outcome in the ALLHAT-LLT was all-cause mortality. Secondary outcomes included cause-specific mortality and nonfatal myocardial infarction or fatal coronary heart disease combined (coronary heart disease events). Results: There were 1467 participants (mean [SD] age, 71.3 [5.2] years) in the pravastatin group (48.0% [n = 704] female) and 1400 participants (mean [SD] age, 71.2 [5.2] years) in the UC group (50.8% [n = 711] female). The baseline mean (SD) low-density lipoprotein cholesterol levels were 147.7 (19.8) mg/dL in the pravastatin group and 147.6 (19.4) mg/dL in the UC group; by year 6, the mean (SD) low-density lipoprotein cholesterol levels were 109.1 (35.4) mg/dL in the pravastatin group and 128.8 (27.5) mg/dL in the UC group. At year 6, of the participants assigned to pravastatin, 42 of 253 (16.6%) were not taking any statin; 71.0% in the UC group were not taking any statin. The hazard ratios for all-cause mortality in the pravastatin group vs the UC group were 1.18 (95% CI, 0.97-1.42; P = .09) for all adults 65 years and older, 1.08 (95% CI, 0.85-1.37; P = .55) for adults aged 65 to 74 years, and 1.34 (95% CI, 0.98-1.84; P = .07) for adults 75 years and older. Coronary heart disease event rates were not significantly different among the groups. In multivariable regression, the results remained nonsignificant, and there was no significant interaction between treatment group and age. Conclusions and Relevance: No benefit was found when pravastatin was given for primary prevention to older adults with moderate hyperlipidemia and hypertension, and a nonsignificant direction toward increased all-cause mortality with pravastatin was observed among adults 75 years and older. Trial Registration: clinicaltrials.gov identifier: NCT00000542.


**ABSTRACT**

The anti-inflammatory effects of statins (HMG-CoA reductase inhibitors) within the cardiovascular system are well-established; however, their neuroinflammatory potential is unclear. It is currently unknown whether statins’ neurological effects are lipid-dependent or due to pleiotropic mechanisms. Therefore, the assumption that all statin compounds will have the same effect within the central nervous system is potentially inappropriate, with no studies to date having compared all statins in a single model. Thus, the aim of this study was to compare the effects of the six statins (atorvastatin, fluvastatin, pitavastatin, pravastatin, rosuvastatin, and simvastatin) within a single in vitro model of neuroinflammation. To achieve this, PMA-differentiated THP-1 cells were used as surrogate microglial cells, and LPS was used to induce inflammatory conditions. Here, we show that pretreatment with all statins was able to significantly reduce LPS-induced interleukin (IL)-1beta and tumour necrosis factor (TNF)-alpha release, as well as decrease LPS-induced prostaglandin E2 (PGE2). Similarly, global reactive oxygen species (ROS) and nitric oxide (NO) production were decreased following
pretreatment with all statins. Based on these findings, it is suggested that more complex cellular models should be considered to further compare individual statin compounds, including translation into in vivo models of acute and/or chronic neuroinflammation.


**ABSTRACT**

Excessive activation of the NLRP3 inflammasome is implicated in cardiovascular diseases. Statins exert an anti-inflammatory effect independent of their cholesterol lowering effect. This study investigated the potential role of statins in the activation of the NLRP3 inflammasome in endothelial cells (ECs). Western blotting and qRT-PCR showed that oxidized-LDL (oxLDL) or tumor necrosis factor alpha (TNFalpha) activated the NLRP3 inflammasome in ECs. Simvastatin or mevastatin significantly suppressed the effects of oxLDL or TNFalpha. Promoter reporter assays and siRNA knockdown revealed that statins inhibit oxLDL-mediated NLRP3 inflammasome activation via the pregnane X receptor (PXR). In addition, PXR agonists (rifampicin and SR12813) or overexpression of a constitutively active PXR (VP-PXR) markedly suppressed the NLRP3 inflammasome activation. Conversely, PXR knockdown abrogated the suppressive effect of rifampicin on NLRP3 inflammasome activation. Knockdown of lectin-like oxidized LDL receptor (LOX-1) or overexpression of IkappaBalpha attenuated oxLDL- or TNFalpha-triggered activation of the NLRP3 inflammasome. Chromatin immunoprecipitation assays indicated that mevastatin inhibited NF-kappaB binding to the promoter regions of the human NLRP3 gene. Collectively, these results demonstrate that the statin activation of PXR inhibits the activation of NLRP3 inflammasome in response to atherogenic stimuli such as oxLDL and TNFalpha in ECs, providing a new mechanism for the cardiovascular benefit of statins.


**ABSTRACT**

Context: Nicotinic acid and nicotinamide are soluble compounds of the vitamin B group, widely used to regulate the lipid profile in hyperlipidemic individuals. Higher doses of nicotinic acid are associated with adverse effects, especially flushing. A unique tolerable upper intake level (UL) of nicotinic acid has not been defined. This meta-analysis aims to evaluate adverse effects and their incidence after supplementation with different doses of nicotinic acid and nicotinamide, comparing results with current ULs in Europe and the United States. PubMed was searched for articles providing detailed information about nicotinic acid or nicotinamide supplementation and related outcomes. A total of 2670 citations were selected for screening. Two primary outcomes were considered: occurrence of adverse effects following nicotinic acid or nicotinamide supplementation, and dose at which adverse effects occurred. Details on study population, type and duration of treatment, dosage of vitamins, association with lipid-influencing drugs, length of follow-up, and incidence and type of adverse events were
extracted. After screening, 47 articles involving 11,741 individuals were included. Meta-analysis was based on estimation of benchmark doses for the probability of adverse effects after supplementation. In individuals with dyslipidemia or cardiovascular disease, nicotinic acid monotherapy seems to be protective against any adverse effects considered, as adverse events occurred at doses above those used with other treatments. In healthy individuals treated with nicotinic acid alone, major adverse effects occurred at doses below 1000 mg/d. Results may indicate a high degree of conservativeness in the UL of nicotinic acid, fixed at 35 mg/d in United States and 10 mg/d in Europe. Reconsideration of the UL of nicotinic acid for nutritional supplements, possibly differentiating between ULs in healthy and unhealthy individuals, may be warranted.


ABSTRACT
OBJECTIVES: Deficiency of 25-hydroxyvitamin D (25(OH)D) is associated with increased risk for cardiovascular disease, perhaps mediated through dyslipidemia. Deficient 25(OH)D is cross-sectionally associated with dyslipidemia, but little is known about longitudinal lipid changes. The aim of this study was to determine the relationship of 25(OH)D deficiency to longitudinal lipid changes and risk for incident dyslipidemia. METHODS: This was a longitudinal community-based study of 13,039 participants from the ARIC (Atherosclerosis Risk in Communities) study who had 25(OH)D and lipids measured at baseline (1990-1992) and lipids remeasured in 1993 to 1994 and 1996 to 1998. Mixed-effect models were used to assess the association of 25(OH)D and lipid trends after adjusting for clinical characteristics and for baseline or incident use of lipid-lowering therapy. Risk for incident dyslipidemia was determined for those without baseline dyslipidemia. RESULTS: Baseline mean +/- SD age was 57 +/- 6 y and 25(OH)D was 24 +/- 9 ng/mL. Participants were 57% women, 24% black. Over a mean follow-up of 5.2 y, the fully adjusted average differences (95% confidence interval [CI]) comparing deficient (<20 ng/mL) to optimal (>=30 ng/mL) 25(OH)D were: total cholesterol (TC) -2.40 mg/dL (-4.21 to -0.60), high-density lipoprotein cholesterol (HDL-C) -3.02 mg/dL (-3.73 to -2.32) and the ratio of TC to HDL-C 0.18 (0.11-0.26). Those with deficient compared with optimal 25(OH)D had modestly increased risk for incident dyslipidemia in demographic-adjusted models (relative risk [RR], 1.19; 95% CI, 1.02-1.39), which was attenuated in fully adjusted models (RR, 1.12; 95% CI, 0.95-1.32).
CONCLUSIONS: Deficient 25(OH)D was prospectively associated with lower TC and HDL-C and a greater ratio of TC to HDL-C after considering factors such as diabetes and adiposity. Further work including randomized controlled trials is needed to better assess how 25(OH)D may affect lipids and cardiovascular risk.


ABSTRACT
SIRT1, a highly conserved NAD+-dependent protein deacetylase, plays a pivotal role in the pathogenesis and therapy of atherosclerosis (AS). The aim of this study is to investigate the
potential effects of SIRT1 on AS in ApoE-/- mice and the underlying mechanisms of autophagy in an ox-LDL-stimulated human monocyte cell line, THP-1. In vivo, the accelerated atherosclerotic progression of mice was established by carotid collar placement; then, mice were treated for 4 weeks with a SIRT1-specific inhibitor, EX-527. The atherosclerotic lesion size of EX-527-treated mice was greatly increased compared to that of the mice in the control group. Immunostaining protocols confirmed that the inhibition of SIRT1 during plaque initiation and progression enhanced the extent of intraplaque macrophage infiltration and impaired the autophagy process. In vitro cultured THP-1 macrophages exposed to ox-LDL were utilized to study the link between the SIRT1 function, autophagy flux, pro-inflammatory cytokine secretion, and foam cell formation using different methods. Our data showed that ox-LDL markedly suppressed SIRT1 protein expression and the autophagy level, while it elevated the MCP-1 production and lipid uptake. Additionally, the application of the SIRT1 inhibitor EX-527 or SIRT1 siRNA further attenuated ox-LDL-induced autophagy inhibition. In conclusion, our results show that the inhibition of SIRT1 promoted atherosclerotic plaque development in ApoE-/- mice by increasing the MCP-1 expression and macrophage accumulation. In particular, we demonstrate that blocking SIRT1 can exacerbate the acetylation of key autophagy machinery, the Atg5 protein, which further regulates the THP-1 macrophage-derived foam cell formation that is triggered by ox-LDL.


ABSTRACT

AIM: Atorvastatin is a HMG-CoA reductase inhibitor used for hyperlipidemia. Atorvastatin is generally safe but may induce cholestasis. The present study aimed to examine the effects of atorvastatin on hepatic gene expression related to bile acid metabolism and homeostasis, as well as the expression of circadian clock genes in livers of mice. METHODS: Adult male mice were given atorvastatin (10, 30, and 100 mg/kg, po) daily for 30 days, and blood biochemistry, histopathology, and gene expression were examined. RESULTS: Repeated administration of atorvastatin did not affect animal body weight gain or liver weights. Serum enzyme activities were in the normal range. Histologically, the high dose of atorvastatin produced scattered swollen hepatocytes, foci of feathery-like degeneration, together with increased expression of Egr-1 and metallothionein-1. Atorvastatin increased the expression of Cyp7a1 in the liver, along with FXR and SHP. In contrast, atorvastatin decreased the expression of bile acid transporters Ntcp, Bsep, Ostalpha, and Ostbeta. The most dramatic change was the 30-fold induction of Cyp7a1. Because Cyp7a1 is a circadian clock-controlled gene, we further examined the effect of atorvastatin on clock gene expression. Atorvastatin increased the expression of clock core master genes Bmal1 and Npas2, decreased the expression of clock feedback genes Per2, Per3, and the clock targeted genes Dbp and Tef, whereas it had no effect on Cry1 and Nr1d1 expression. CONCLUSION: Repeated administration of atorvastatin affects bile acid metabolism and markedly increases the expression of the bile acid synthesis rate-limiting enzyme gene Cyp7a1, together with alterations in the expression of circadian clock genes.

ABSTRACT
Advanced glycation endproduct (AGE)-induced vascular smooth muscle cell (VSMC) proliferation and reactive oxygen species (ROS) production are emerging as important mechanisms of diabetic vasculopathy, but little is known about the molecular mechanism responsible for the antioxidative effects of statins on AGEs. It has been reported that statins exert pleiotropic effects on the cardiovascular system due to decreases in AGE-induced cell proliferation, migration, and vascular inflammation. Thus, in the present study, the authors investigated the molecular mechanism by which statins decrease AGE-induced cell proliferation and VSMC migration. In cultured VSMCs, statins upregulated Nrf2-related antioxidant gene, NQO1 and HO-1, via an ERK5-dependent Nrf2 pathway. Inhibition of ERK5 by siRNA or BIX02189 (a specific ERK5 inhibitor) reduced the statin-induced upregulations of Nrf2, NQO1, and HO-1. Furthermore, fluvastatin was found to significantly increase ARE promoter activity through ERK5 signaling, and to inhibit AGE-induced VSMC proliferation and migration as determined by MTT assay, cell counting, FACS analysis, a wound scratch assay, and a migration chamber assay. In addition, AGE-induced proliferation was diminished in the presence of Ad-CA-MEK5alpha encoding a constitutively active mutant form of MEK5alpha (an upstream kinase of ERK5), whereas depletion of Nrf2 restored statin-mediated reduction of AGE-induced cell proliferation. Moreover, fluvastatin suppressed the protein expressions of cyclin D1 and Cdk4, but induced p27, and blocked VSMC proliferation by regulating cell cycle. These results suggest statin-induced activation of an ERK5-dependent Nrf2 pathway reduces VSMC proliferation and migration induced by AGEs, and that the ERK5-Nrf2 signal module be viewed as a potential therapeutic target of vasculopathy in patients with diabetes and complications of the disease.


ABSTRACT
Statins are widely used to reduce cardiovascular risk. Unfortunately, some patients still experience cardiovascular events though prescribed with high-intensity statins. Metformin, an anti-diabetic drug, was reported to possess anti-atherosclerotic effects. Therefore, the experiments were designed to evaluate whether combined use of metformin and atorvastatin can achieve additional benefits. In rabbits fed a high-cholesterol diet, we evaluated the effects of the combination therapy on atherosclerotic plaques, lipid profiles, blood glucose levels, liver and kidney functions. Effects of combination therapy on cholesterol efflux and the expression of related transporters were studied in vitro. Our results showed that the combination therapy induced a more significant decrease in atherosclerotic lesion area than atorvastatin without additional lipid-lowering effect. The combination therapy significantly increased the percentage of large high-density lipoprotein subfraction. The intravenous glucose tolerance test showed that atorvastatin-treated rabbits had an increased area under the curve for time-dependent glucose levels after a bolus injection of glucose, which was completely reversed by metformin
treatment. In cultured macrophages, co-treatment with metformin and atorvastatin promoted cholesterol efflux and up-regulated expression of ATP-binding cassette transporters A1 and G1. Taken together, our results suggest that atorvastatin/metformin combination therapy may achieve additional anti-atherosclerotic benefits likely through increasing cholesterol efflux in macrophages.


ABSTRACT
Phagocytosis of daily shed photoreceptor outer segments is an important function of the retinal pigment epithelium (RPE) and it is essential for retinal homeostasis. RPE dysfunction, especially impairment of its phagocytic ability, plays an essential role in the pathogenesis of age-related macular degeneration (AMD). Statins, or HMG CoA (3-hydroxy-3-methylglutaryl-coenzyme A) reductase inhibitors, are drugs with multiple properties that have been extensively used to treat hyperlipidemia. However, their effect on RPE cells has not been fully elucidated. Here we report that high dose atorvastatin increased the phagocytic function of ARPE-19 cells, as well as rescue the cells from the phagocytic dysfunction induced by cholesterol crystals and oxidized low-density lipoproteins (ox-LDL), potentially by increasing the cellular membrane fluidity. Similar effects were observed when evaluating two other hydrophobic statins, lovastatin and simvastatin. Furthermore, atorvastatin was able to block the induction of interleukins IL-6 and IL-8 triggered by pathologic stimuli relevant to AMD, such as cholesterol crystals and ox-LDL. Our study shows that statins, a well-tolerated class of drugs with rare serious adverse effects, help preserve the phagocytic function of the RPE while also exhibiting anti-inflammatory properties. Both characteristics make statins a potential effective medication for the prevention and treatment of AMD.


ABSTRACT
High fat diet (HFD)-induced metabolic disorders may lead to emotional disorders. This study aimed to explore the effect of simvastatin (SMV) and bezafibrate (BZ) on improving HFD-induced emotional changes, and tried to identify their different mechanisms. The intraperitoneal glucose tolerance test (IPGTT) was used to evaluate glucose control ability; and behavior tests including open field tests (OFT), forced swimming tests (FST), tail suspension tests (TST) and sucrose preference (SPT), were then performed to evaluate emotional changes. Serum samples were collected for the LC-MS based metabolomics analysis to explore the emotional-related differential compounds; we then evaluated the effect of the drugs. The abnormal serum metabolic profiling and emotional changes caused by HFD in mice was alleviated by SMV treatment, whereas BZ only affected the emotional disorder. The improvement of cannabinoid analogues and then produced influences on the endocannabinoid system, which may be a potential mechanism SMV action. BZ promoted tryptophan-serotonin
pathway and inhibited tryptophan-kynurenine pathway, which may be its mechanism of action. Here, we proposed a shed light on the biological mechanisms underlying the observed effects, and identified an important drug candidate for the treatment of emotional disorders induced by HFD.


ABSTRACT

BACKGROUND: Pruritus (itch) is a frequent, burdensome and difficult-to-treat symptom in patients with cholestasis. Fibrates are currently under investigation for the treatment of primary biliary cholangitis in patients with a suboptimal response to ursodeoxycholic acid. Moreover, there is empirical evidence for a possible antipruritic effect. We aim to prove this in a randomized controlled trial, including patients with cholestatic liver diseases other than primary biliary cholangitis that are accompanied by pruritus. METHODS: A multicenter investigator-initiated, double-blind, randomized placebo-controlled trial to evaluate the effect of bezafibrate on cholestatic pruritus in 84 adult patients with primary biliary cholangitis or primary/secondary sclerosing cholangitis. Primary outcome is the proportion of patients with a reduction of itch intensity of 50% or more (measured on a Visual Analog Scale) after 21 days of treatment with bezafibrate 400 mg qid or placebo. Secondary outcomes include the effect of bezafibrate on a five-dimensional itch score, liver disease-specific quality of life, serum liver tests and autotaxin activity. Safety will be evaluated through serum parameters for kidney function and rhabdomyolysis as well as precise recording of (serious) adverse events. We provide a schematic overview of the study protocol and describe the methods used to recruit and randomize patients, collect and handle data and perform statistical analyses. DISCUSSION: Given its favorable safety profile and anticholestatic properties, bezafibrate may become the new first-line treatment option for treating cholestatic pruritus. TRIAL REGISTRATION: Netherlands Trial Register, ID: NCT02701166 . Registered on 2 March 2016; Netherlands Trial Register, ID: NTR5436 . Registered on 3 August 2015.