

**ABSTRACT**

Statins are widely used to lower cholesterol and to reduce cardiovascular events. Whether all statins have similar effects on plaque stabilization is unknown. We aimed to investigate coronary plaque response to treatment with different statins that result in similar lipid reduction using serial multimodality intracoronary imaging. Patients with de novo coronary artery disease requiring intervention were randomized to rosuvastatin 10 mg (R10) or atorvastatin 20 mg (A20) daily. Optical coherence tomography and intravascular ultrasound were performed at baseline, 6 months, and 12 months. Untreated nonculprit plaques were analyzed by optical coherence tomography for thin-cap fibroatheroma, minimum fibrous cap thickness, lipid arc, and lipid length. Total and percent atheroma volume, respectively were analyzed by intravascular ultrasound. Forty-three patients completed the protocol (R10: 24 patients, 31 plaques; A20: 19 patients, 30 plaques). The decrease in serum lipids was similar. From baseline to 6 months to 12 months, minimum fibrous cap thickness increased in the R10 group (61.4 +/- 15.9 microm to 120.9 +/- 57.9 microm to 171.5 +/- 67.8 microm, p <0.001) and the A20 group (60.8 +/- 18.1 microm to 99.2 +/- 47.7 microm to 127.0 +/- 66.8 microm, p <0.001). Prevalence of thin-cap fibroatheroma significantly decreased in the R10 and A20 groups (-48% and -53%, respectively, p <0.001 for intragroup comparisons). Only the R10 group had a decrease in macrophage density (-23%, p=0.04) and microvessels (-12%, p=0.002). Total atheroma volume decreased in the R10 group (109.2 +/- 62.1 mm(3) to 101.8 +/- 61.1 mm(3) to 102.5 +/- 62.2 mm(3), p=0.047) but not in the A20 group (83.3 +/- 48.5mm(3) to 77.6 +/- 43.0 mm(3) to 77.9 +/- 48.6 mm(3), p=0.07). In conclusion, although both statins demonstrated similar reductions in lipid profiles, the rosuvastatin group showed more rapid and robust plaque stabilization, and regression of plaque volume compared to the atorvastatin group.


**ABSTRACT**

Glucagon-like peptide-1 receptor agonists (GLP-1RAs) exert potent glucose lowering effects without increasing risks for hypoglycemia and weight gain. Preclinical studies have demonstrated direct anti-atherogenic effects of GLP-1RAs in normoglycemic animal models; however, the underlying mechanisms in hyperglycemic conditions have not been fully clarified. Here, we aimed to elucidate the role of AMP-activated protein kinase (AMPK) in anti-atherogenic effects of GLP-1RAs in hyperglycemic mice. Streptozotocin-induced hyperglycemic apolipoprotein E-null mice were treated with vehicle, low-dose liraglutide (17 nmol/kg/day), or high-dose liraglutide (107 nmol/kg/day) in Experiment 1, and the AMPK inhibitor dorsomorphin, dorsomorphin + low-dose liraglutide, or dorsomorphin + high-dose liraglutide in Experiment 2. Four weeks after treatment, aortas were collected to assess atherosclerosis. In Experiment 1, metabolic parameters were similar between the groups. Assessment of atherosclerosis revealed that high-dose liraglutide treatments reduced lipid deposition on the
aortic surface and plaque volume and intra-plaque macrophage accumulation at the aortic sinus. In Experiment 2, liraglutide-induced AMPK phosphorylation in the aorta was abolished by dorsomorphin; however, anti-atherogenic effects of high-dose liraglutide were preserved. In cultured human umbilical vein endothelial cells, liraglutide suppressed tumor necrosis factor-induced expression of pro-atherogenic molecules; these effects were maintained under small interfering RNA-mediated knockdown of AMPKalpha1 and in the presence of dorsomorphin. Conversely, in human monocytic U937 cells, anti-inflammatory effects of liraglutide were abolished by dorsomorphin. In conclusion, liraglutide exerted AMPK-independent anti-atherogenic effects in hyperlipidemic mice with STZ-induced hyperglycemia, with the possible involvement of AMPK-independent suppression of pro-atherogenic molecules in vascular endothelial cells.


ABSTRACT
Age-related alterations in endothelium and the resulting vascular dysfunction critically contribute to a range of pathological conditions associated with old age. To rationally develop therapies that improve vascular health and thereby increase health span and lifespan in older adults, it will be essential to understand the cellular and molecular mechanisms contributing to vascular aging. Pre-clinical studies in model organisms demonstrate that NAD(+) availability decreases with age in multiple tissues and that supplemental NAD(+) precursors can ameliorate many age-related cellular impairments. Here we provide a comprehensive overview of NAD(+) dependent pathways (including the NAD(+) utilizing sirtuins and poly (ADP-ribose) polymerase enzymes) and the potential consequences of endothelial NAD(+) deficiency in vascular aging. The multifaceted vasoprotective effects of treatments that reverse the age-related decline in cellular NAD(+) levels are discussed. The preventive and therapeutic potential of NAD(+) intermediates as effective, clinically relevant interventions in older adults at risk for ischemic heart disease, vascular cognitive impairment and other common geriatric conditions and diseases that involve vascular pathologies (e.g. sarcopenia, frailty) is critically discussed. We propose that NAD(+) precursors (e.g., nicotinamide riboside, nicotinamide mononucleotide, niacin) should be considered as a critical component of combination therapies to slow the vascular aging process and increase cardiovascular health span.


ABSTRACT
Objective- Heterozygous familial hypercholesterolemia (FH) is the most common genetic disorder associated with premature atherosclerotic cardiovascular disease (CVD). Circulating microvesicles (cMV) are released when cells are activated. We investigated whether cMV could
provide information on coronary calcification and atherosclerosis in FH patients. Approach and Results- Eighty-two patients (mean of 44+-9 years old) with molecular diagnosis of heterozygous FH and asymptomatic cardiovascular disease were investigated. Atherosclerotic plaque characterization was performed by computed tomography angiography, and Agatston coronary calcium score and plaque composition sum were calculated. cMV were quantified by flow cytometry using AV (annexin V) and cell surface-specific antibodies. Of the 82 FH patients, 48 presented atherosclerotic plaque. Patients with atherosclerosis were men and older in a higher percentage than patients without atherosclerotic plaque. FH patients with atherosclerotic plaque showed higher levels of total AV(+) cMV, cMV AV(+) from platelet origin, from granulocytes and neutrophils, and cMV AV(+/-) from endothelial cells than FH-patients without atherosclerotic plaque. Plaque composition sum correlated with platelet- and endothelial-derived cMV, and Agatston coronary calcium score correlated with granulocyte-, platelet-, and endothelial-derived cMV. Receiver operating characteristic curve analyses indicated that the cluster of platelet-, granulocyte-, neutrophil, and endothelial-derived cMV considered together, added significant predictive value to the specific SAFEHEART risk equation for plaque presence (area under the curve=0.866, 95% CI, 0.775-0.958; P<0.0001, P=0.030 for the increment of the area under the curve). Conclusions- Endothelial, granulocyte-, neutrophil- and platelet-derived cMV discriminate and map coronary atherosclerotic plaque and calcification in asymptomatic patients with FH. Liquid biopsy of cMV may be a surrogate biomarker of coronary atherosclerotic plaque burden in FH patients.


ABSTRACT
Homozgyous familial hypercholesterolemia developed into severe cardiovascular consequences early. Untreated HoFH usually cannot survive over 30 years old. Acute coronary syndrome(ACS) caused by plaque rupture is one of the main causes of death in HoFH. As the highest resolution intravascular imaging technique, optical coherence tomography(OCT) can clearly show the thickness and structural characteristics of atherosclerotic plaque caps. In this study, a Chinese male HoFH received percutaneous coronary intervention for unstable angina. After analyzed his genetic and follow-up data, OCT was performed during interventional therapy. Multiple lipid rich plaques accompanied with inflammatory cell infiltration and a thin-cap fibroatheroma(TCFA) were noted, which reflected the vulnerability of plaques. The utility of OCT had certain guiding significance for strategy of interventional therapy and the long-term drug management. And this case suggested that it was important to undergo OCT examination for patients with HoFH who required percutaneous coronary intervention.


ABSTRACT
AIMS: To investigate the status of familial hypercholesterolemia (FH) research and the characteristics of patients with FH in China. METHODS: Published papers in Chinese or English language from PubMed, SinoMed and CNKI databases from 1971 to March 2018 were searched using 'Familial hypercholesterolemia', 'Chinese' and 'Han' as keywords. A systematic review of studies on familial hypercholesterolemia was then conducted. RESULTS: A total of 391 articles were found, in which 22% were in English and 78% were in Chinese; approximately 43% are case reports and 34% are genetic reports according to the study type; 52% discussed the status of the disease and 11% investigated the subclinical status according to the study content. Furthermore, 96% of the articles were published by tertiary hospitals and 46% were conducted by cardiologists. The first expert consensus was issued in February 2018. Of the 163 case reports published before 2018, 48.7% used the Chinese FH clinical diagnostic criteria and 34.4% did not clearly indicate the diagnostic criteria. The incidence rates of low-density lipoprotein receptor (LDLR) and apolipoprotein B (APOB) mutations were 82% and 9%, and proprotein convertase subtilisin/kexin type 9 (PCSK9) mutations were rare in Chinese patients with FH. However, the data on lipid-lowering treatment rates, compliance rates and cardiovascular events in FH remain insufficient. CONCLUSIONS: Large-scale epidemiological investigation of FH has not been demonstrated, the recognition of FH remains rudimentary, and the guidelines are incomplete in China. The diagnosis and management of Chinese FH needs to be improved.


ABSTRACT

BACKGROUND AND AIMS: There remains a substantial residual risk of ischaemic heart disease (IHD) despite optimal low-density lipoprotein cholesterol (LDLC) reduction. Part of this risk may be attributable to remnant cholesterol, which is carried in triglyceride-rich lipoproteins. We evaluated the relationship between remnant cholesterol and coronary atherosclerotic plaque burden assessed non-invasively by computed tomography coronary angiography (CTCA) in patients with suspected coronary artery disease (CAD). METHODS AND RESULTS: This was a multicentre study of 587 patients who had a CTCA and fasting lipid profile within 3 months. Calculated remnant cholesterol was total cholesterol minus LDLC minus high-density lipoprotein cholesterol (HDLC). Significant coronary atherosclerotic burden was defined as CT-Leaman score >5 (CT-LeSc), an established predictor of cardiac events. Mean age was 61+/-12 years and mean pretest probability of CAD was 23.2+/19.8%. LDLC levels were <1.8mmol/L in 134 patients (23%), of whom 82% were statin-treated. Patients with CT-LeSc >5 had higher mean remnant cholesterol than those with CT-LeSc <=5 (0.76+/-0.36mmol/L vs. 0.58+/-0.33mmol/L, p=0.01). On univariable analysis, remnant cholesterol (p=0.01), LDLC (p=0.002) and HDLC (p<0.001) levels predicted CT-LeSc >5, whilst triglycerides (p=0.79) had no association with CT-LeSc >5. On multivariable analysis in the subset of patients with optimal LDLC levels, remnant cholesterol levels remained predictive of CT-LeSc >5 (OR 3.87, 95% confidence interval 1.34-7.55, p=0.004), adjusted for HDLC and traditional risk factors. CONCLUSIONS: Remnant cholesterol levels are associated with significant coronary atherosclerotic burden as assessed by
CTCA, even in patients with optimal LDLC levels. Future studies examining whether lowering of remnant cholesterol can reduce residual IHD risk are warranted.


ABSTRACT
Nonalcoholic fatty liver disease (NAFLD) describes a spectrum of alcohol-like hepatic histological changes, which occur in the absence of any competing causes of chronic liver disease, notably including significant alcohol consumption. A close and bi-directional relationship links NAFLD with the metabolic syndrome (MetS), and concurrent MetS will hasten the progression to more severe forms of NAFLD, including cirrhosis and hepatocellular carcinoma (HCC). Patients with NAFLD will typically exhibit atherogenic dyslipidemia and increased cardiovascular risk (CVR). Statins are among the most widely prescribed lipid-lowering drugs. Their use has historically been hampered, in individuals with liver disease, owing to the fear of hepatotoxicity. However, studies suggest that statins are not only effective in reducing cardiovascular events, but may also exert multiple beneficial effects on the liver. CVR in those with NAFLD has extensively been covered by our group and others. This updated clinical narrative review will critically examine the effects of statins on the pathogenesis of NAFLD, including the key elementary pathological lesions of NAFLD, i.e. steatosis, inflammation and fibrosis, and its liver-related complications, i.e. cirrhosis, portal hypertension and HCC.


ABSTRACT
OBJECTIVE: The objective of this study is to determine whether coronary atherosclerotic plaque composition is associated with cardiovascular disease (CVD) risk in Chinese adults. METHODS: We performed a cross-sectional analysis in 549 subjects without previous diagnosis or clinical symptoms of CVD in a community cohort of middle-aged Chinese adults. The participants underwent coronary computed tomography (CT) angiography for the evaluation of the presence and composition of coronary plaques. CVD risk was evaluated by the Framingham risk score (FRS) and the 10-year atherosclerotic cardiovascular disease (ASCVD) risk score. RESULTS: Among the 549 participants, 267 (48.6%) had no coronary plaques, 201 (36.6%) had noncalcified coronary plaques, and 81 (14.8%) had calcified or mixed coronary plaques. The measures of CVD risk including FRS and ASCVD risk score and the likelihood of having elevated FRS significantly increased across the groups of participants without coronary plaques, with noncalcified coronary plaques, and with calcified or mixed coronary plaques. However, only calcified or mixed coronary plaques were significantly associated with an elevated ASCVD risk score [odds ratio (OR) 2.41; 95% confidence interval (CI) 1.09-5.32] compared with no coronary plaques, whereas no significant association was found for noncalcified coronary plaques and elevated ASCVD risk score (OR 1.25; 95% CI 0.71-2.21) after multivariable adjustment.
CONCLUSION: Calcified or mixed coronary plaques might be more associated with an elevated likelihood of having CVD than noncalcified coronary plaques.


ABSTRACT
BACKGROUND: With development of cholesterol management guidelines by the American College of Cardiology/American Heart Association (ACC/AHA), more individuals at risk of cardiovascular disease may be eligible for statin therapy. It is not known how this affects statin eligibility in the Africa and Middle East Region. METHODS: Data were used from the Africa Middle East Cardiovascular Epidemiological (ACE) study. The percentage of subjects eligible for statins per the ACC/AHA 2013 cholesterol guidelines and the 2002 National Cholesterol Education Program-Adult Treatment Panel (NCEP-ATP III) recommendations were compared. Analyses were carried out according to age, gender, community (urban/rural), and country income categories based on World Bank definitions. RESULTS: According to the ACC/AHA recommendations, 1695 out of 4378 subjects (39%; 95% confidence interval [CI], 37-40%) satisfied statin eligibility criteria vs. 1043/4378 (24%; 95% CI, 23-25%) per NCEP-ATP recommendations, representing a 63% increase in statin eligibility. Consistent increases in eligibility for statin therapy were seen according to the ACC/AHA vs. NCEP-ATP guidelines across sub-groups of age, gender, community, and country income. Notable increases for statin eligibility according to ACC/AHA vs. NCEP-ATP were seen, respectively, in subjects aged >/=65 years (86% vs. 39%), in males (46% vs. 25%), in low-income countries (28% vs. 14%), and rural communities (37% vs. 19%). CONCLUSION: An increase in statin eligibility was seen applying ACC/AHA cholesterol guidelines compared with previous NCEP-ATP recommendations in the Africa Middle East region. The economic consequences of these guideline recommendations will need further research. TRIAL REGISTRATION: The ACE trial is registered under NCT01243138.


ABSTRACT
Background and Aims: We aimed to assess whether chronic statins used (> 6 months) were protective of the development of esophagitis in patients with gastroesophageal reflux disease. In the presence of esophagitis, complications such as strictures, Barrett's esophagus, and adenocarcinoma were the most common. Statins, lipid lowering drugs with a pleiotropic effect, are recently implicated in various pathologies. Nevertheless, the possible impact of statins in esophagitis development has never been assessed. Methods: We performed a retrospective, cross-sectional, single center study that included 4148 gastroesophageal reflux disease patients from 2014 and 2018 at EMMS Nazareth Hospital. We divided the patients into 5 groups. The
groups were split into positive control group, which was the nonesophagitis group, and the other 4 groups were A-D (as per Los Angeles classification). Results: Overall, out of the 4148 patients included, 48% were males and 2840 patients were in the control group. In groups A, B, C, and D there were 818, 402, 72, and 16 patients, respectively. Logistic regression analysis revealed that chronic statins usage is protective by preventing development esophagitis (OR 0.463 [95%CI 0.370-0.579], p < 0.0001). NSAIDS use, Hiatus hernia, and H. pylori were promoting factors (OR, 1.362, 1.779, and 1.811; 95% CI, 1.183-1.569, 1.551-2.040, and 1.428-2.298; P<0.0001, P<0.0001, and P<0.0001, respectively). Conclusion: Using chronic statins was protective to the development of esophagitis among GERD patients. Our findings of potential clinical application mandate further randomized controlled trials to better assess the impact of statins on esophagitis.


ABSTRACT
The proprotein convertases family is involved in several physiological processes such as cell growth, migration, and angiogenesis, and also in different pathological conditions. Evolocumab, an inhibitor of proprotein convertase subtilisin/kexin type 9 (PCSK9), has recently been approved for treatment of hypercholesterolemia. This study aimed to investigate the effect of evolocumab on angiogenesis in human umbilical vein endothelial cells (HUVECs). Cell proliferation and migration were evaluated using 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide and Transwell methods. In vitro angiogenesis was assessed by tube formation assay. Vascular endothelial growth factor (VEGF) secretion by HUVECs was also determined using an enzyme-linked immunosorbent assay kit. Evolocumab significantly increased HUVECs viability at 100 mug/mL. Significant enhancement in cell migration, and mean tubes length and size was observed at the concentrations of 10 and 100 mug/mL and also in mean number of junctions at the concentration of 100 mug/mL. Administration of evolocumab at the concentration of 10 mug/mL increased VEGF release into supernatants of HUVECs. Findings of this investigation provided in vitro evidence for pro-angiogenic activity of evolocumab through promoting cell proliferation, migration, tubulogenesis, and VEGF secretion in HUVECs.


ABSTRACT
In previous studies we found that low carbohydrate (CHO) diets reduced the incidence of tumors in mice genetically predisposed to cancer. However, since more than 90% of human cancers arise via carcinogen-induced somatic mutations we investigated, herein, the role that different types and levels of CHO, protein and lipid play in lung cancer induced by the tobacco-specific carcinogen, nicotine-derived nitrosamine ketone (NNK) in A/J mice. We found lowering CHO levels significantly reduced lung nodules and blood glucose levels. We also found that soy
protein was superior to casein and that coconut oil was ineffective at reducing lung nodules. Diets containing amylose or inulin (at 15% of total calories), soy protein (at 35%), and fat (at 50%, 30% being fish oil) were the most effective at reducing lung nodules. These fish oil-containing diets increased plasma levels of the ketone body, beta-hydroxybutyrate, while reducing both insulin and 8-isoprostane in plasma and bronchoalveolar IL-12 and lung PGE2 levels. After only 2 weeks on this diet, the levels of gamma-H2AX were significantly reduced, 24 hours after NNK treatment. Housing these mice in two-tiered rat cages with exercise wheels led to similar mouse weights on the different diets, while keeping mice in standard mouse cages led to both significant weight differences between the low CHO, soy protein, fish oil diet and Western diet and substantially more lung nodules than in the two-tiered cages. Our results suggest that low CHO, soy protein, fish oil containing diets, together with exercise, may reduce the incidence of lung cancer.


ABSTRACT

INTRODUCTION: The apolipoprotein A1 (apoA1) remnant ratio has been identified as an independent cardiovascular (CV) risk factor. Higher apoA1 remnant ratios may predict lower CV risk in some patients. This analysis aimed to evaluate the effects of evolocumab on the change from baseline in the apoA1 remnant ratio compared with placebo. METHODS: This pooled post hoc analysis included 2464 patients with mixed dyslipidemia treated with evolocumab 140 mg every 2 weeks (Q2W) or 420 mg once monthly (QM) in three phase 3 evolocumab trials. The apoA1 remnant ratio was calculated by dividing apoA1 by the difference between non-high-density lipoprotein cholesterol (non-HDL-C) and low-density lipoprotein cholesterol (LDL-C). ApoA1 remnant ratio strata were generated using previously published tertile (< 4.7, 4.7-6.8, and > 6.8) and partitioning categories (< 3.6, 3.6-6.0, and > 6.0). RESULTS: The baseline apoA1 remnant ratio in evolocumab and placebo treatment arms was 7.1 and 7.3, respectively. At week 12, evolocumab 140 mg Q2W and 420 mg QM increased the apoA1 remnant ratio by 25.0% and 33.6%, respectively, versus placebo (p < 0.0001 for both groups). When patients were categorized by week 12 apoA1 remnant ratio thresholds (< 3.6 vs. > 3.6, and < 4.7 vs. > 4.7), those with higher week 12 apoA1 remnant ratios were significantly more likely to have also achieved a target non-HDL-C level of < 100 mg/dl. In the subset of women > 50 years of age, the proportion of patients at apoA1 remnant ratio thresholds < 3.6, 3.6-6.0, and > 6.0 at baseline shifted toward or remained at higher thresholds at week 12. CONCLUSIONS: This post hoc analysis suggests that evolocumab increases the apoA1 remnant ratio. FUNDING: Amgen Inc. Plain language summary available for this article.


ABSTRACT
The authors have retracted this article [1] because they have identified serious errors in their data analysis which change the conclusions of their study. All authors agree with this retraction.


**ABSTRACT**

Elevated levels of lipoprotein(a) (Lp(a)) contribute to the risk of early and severe cardiovascular disease (CVD) and Lp(a) is acknowledged as a risk factor to be included in risk assessment. The established lipid-modifying medical therapies do not lower Lp(a) except niacin but no data of endpoint trials are available. Of the new lipid-modifying drugs a few have some impact on Lp(a). Whether the Lp(a) lowering effect contributes to the reduction of CVD events would have to be shown in Lp(a) dedicated trials. None of the available agents is indicated to lower Lp(a). Lipoprotein apheresis lowers levels of Lp(a) significantly by >60% per treatment. Trial data and data of the German Lipoprotein Apheresis Registry show that regular apheresis reduces cardiovascular events. The Apo(a) antisense oligonucleotide is the only approach to specifically lower Lp(a). The IONIS-APO(a)Rx phase 1 and 2 trials showed very substantial decreases of Lp(a) and good tolerability. The hepatospecific variant IONIS-APO(a)-LRx is 30 times more potent. The results of the IONIS-APO(a)-LRx phase 2 trial were presented recently. The highest dosages reduced Lp(a) by 72 and 80%; in about 81 and 98% Lp(a) levels <50mg/dl were achieved. Tolerability and safety were confirmed, whereby injection site reactions were the most common side effects. This raises hope that the planned phase 3 trial will reproduce these findings and show a reduction of cardiovascular events.


**ABSTRACT**

Purpose: Peripheral artery disease (PAD) causes narrowing of arteries in the limbs, leading to tissue ischemia, gangrene, and eventually limb amputation. The presence of diabetes greatly exacerbates the course of PAD, accounting for the majority of lower limb amputations. Therapeutic strategies focussing on macrovascular repair are less effective in diabetic patients where smaller vessels are affected, and proangiogenic therapies offer a viable adjunct to improve vascularisation in these at risk individuals. The purpose of the current study was to assess the proangiogenic effects of drugs routinely used to treat cardiovascular disease in a diabetic murine model of hind limb ischemia longitudinally using multimodal imaging. 

**Procedures:** Diabetic mice underwent surgical intervention to induce hind limb ischemia and were treated with simvastatin, metformin, or a combination orally for 28 days and compared to diabetic and nondiabetic mice. Neovascularisation was assessed using [(18)F]FtRGD PET imaging, and macrovascular volume was assessed by quantitative time of flight MRI. At each imaging time point, VEGF expression and capillary vessel density were quantified using immunohistochemical analysis, and functional recovery and disease progression were assessed. 

**Results:** Combined use of simvastatin and metformin significantly increased neovascularisation
above levels measured with either treatment alone. Early angiogenic events were accurately assessed using PET [(18)F]FtRGD, showing maximal retention in the ischemic hind limb by day 8, which translated to a sustained increase in vascular volume at later time points. Immunohistochemical analysis shows that combined therapy significantly increased VEGF expression and capillary density (CD31(+)) in a similar time course and also slowed disease progression while simultaneously improving functional foot use. Conclusions: Combined treatment with simvastatin and metformin led to a significant improvement in limb angiogenesis, vascular volume, and sustained functional recovery in a diabetic murine model of HLI. PET imaging with [(18)F]FtRGD provides a robust method for early detection of these proangiogenic effects preclinically and may be useful for the assessment of proangiogenic therapies used clinically to treat diabetic PAD patients.


ABSTRACT
PURPOSE OF REVIEW: Atherosclerotic cardiovascular disease (ASCVD) is caused by elevated levels of low-density lipoprotein cholesterol (LDL-C). Although statins significantly reduce ASCVD risk, there remains a high degree of residual risk in statin-treated patients. Proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibition has emerged as a significant therapeutic target for further lowering of LDL-C when used in combination with statins. The purpose of this review is to provide an update on recent evidence supporting the use of PCSK9 inhibitors in patients with ASCVD. RECENT FINDINGS: Alirocumab and evolocumab were approved by the US Food and Drug Administration in 2015. Multiple phase II and III studies have demonstrated that these agents reduce LDL-C levels by up to 60% and are relatively safe, with the exception of injection site reactions. Additionally, two randomized controlled clinical trials have demonstrated that both alirocumab and evolocumab reduce ASCVD events when used in combination with statin therapy compared to statin alone. In light of this evidence, the 2018 Cholesterol Guideline incorporated PCSK9 inhibitors into the treatment algorithm for select secondary prevention patients unable to achieve an LDL-C below 70 mg/dL despite maximally tolerated statin plus ezetimibe. Although PCSK9 inhibitors provide substantial reductions in LDL-C levels and reduce ASCVD events in secondary prevention populations, the cost-effectiveness of alirocumab and evolocumab limit widespread use. Additional research is needed to explore the role of PCSK9 inhibitors in other populations, including primary prevention, patients unable to tolerate statins, and acute myocardial infarction.


ABSTRACT
Purpose: Coexistence of hypertension (HTN) and hypercholesterolemia is a major synergistic and modifiable risk factor for cardiovascular disease (CVD). Thus, a fixed-dose combination
(FDC) of anti-HTN drugs and statins may be useful for treating CVD. This study evaluated the efficacy of an FDC of irbesartan and atorvastatin (Rovelito(R)) in Korean patients. Patients and methods: Patients with HTN and hypercholesterolemia were screened for this prospective, observational, descriptive, multi-center, phase IV study. Eligible patients were administered with Rovelito for 3 months. Dose adjustment was allowed based on the physician's discretion. Blood pressure (BP) goal was <140/90 mmHg, and blood lipid goal was based on Adult Treatment Panel III. Compliance with therapeutic lifestyle modification and safety of the study drugs were evaluated. Results: Of the 2,777 patients enrolled in this study, 931 were analyzed for clinical efficacy. BP and low-density lipoprotein cholesterol (LDL-C) goals were achieved in 801 (86.04%) and 797 (85.61%) patients, respectively. For the BP goal, higher baseline BP and higher body mass index were risk factors for treatment failure. For LDL-C goal, baseline LDL-C level, number of concomitant drugs, smoking status, and alcohol consumption were risk factors for treatment failure. Of the 931 participants, 694 (74.54%) achieved the treatment goals for both BP and LDL-C. Smoking status, alcohol consumption, number of concomitant drugs, and higher baseline LDL-C and BP levels were risk factors for treatment failure in both BP and LDL-C goals. Adherence with Rovelito was 97.90%+/-5.79%, and incidence of adverse events was 4.19% (116). Conclusion: FDC of irbesartan and atorvastatin (Rovelito) could be extremely helpful in treating patients with both HTN and hypercholesterolemia. Poor metabolic profiles were risk factors for poor treatment response and the reason for choosing Rovelito. Therapeutic lifestyle modification should still be underscored despite the 75% treatment success rate with Rovelito for both conditions.


ABSTRACT
BACKGROUND: The effects of increasing high-density lipoprotein cholesterol on cardiovascular outcomes remain uncertain. DESIGN: We conducted a meta-analysis to investigate the effects of high-density lipoprotein cholesterol modifiers (niacin, fibrates and cholesteryl ester transfer protein inhibitors) on cardiovascular outcomes. METHODS: Thirty-one randomized controlled trials (154,601 patients) with a follow-up of 6 months or more and a sample size of 100 or more patients were selected using MEDLINE, EMBASE and CENTRAL database (inception January 2018). RESULTS: High-density lipoprotein cholesterol modifiers had no statistically significant effect on cardiovascular mortality in terms of relative risk (RR) (RR 0.94, 95% confidence interval (CI) 0.89-1.00, P = 0.05, I(2) = 13%) or absolute risk (risk difference -0.0001, 95% CI -0.0014, 0.0011, P = 0.84, I(2) = 28%). High-density lipoprotein cholesterol modifiers reduced the RR of myocardial infarction (RR 0.87, 95% CI 0.82-0.93, P < 0.001, I(2) = 37%). This significant effect was derived by the use of fibrates (RR 0.80, 95% CI 0.73-0.87, P < 0.001, I(2) = 22%) and meta-regression analysis showed that this benefit was consistent with an absolute reduction in low-density lipoprotein cholesterol. High-density lipoprotein cholesterol modifiers had no effect on stroke (RR 1.00, 95% CI 0.93-1.09, P = 0.94, I(2) = 25%) or all-cause mortality (RR 1.02, 95% CI 0.97-1.08, P = 0.48, I(2) = 49%). Meta-regression analyses failed to demonstrate a significant association of pharmacologically increased high-density lipoprotein cholesterol with key
endpoints. In studies with background statin therapy, high-density lipoprotein cholesterol modifiers had no statistically significant impact on cardiovascular mortality, myocardial infarction, stroke or all-cause mortality (P > 0.05). CONCLUSION: The use of high-density lipoprotein cholesterol modifying treatments had no significant effect on cardiovascular mortality, stroke or all-cause mortality. The beneficial effect on myocardial infarction was lost when drugs were used with statin therapy.


ABSTRACT
AIMS: Local wall shear stress (WSS) plays an important role in the onset of atherosclerotic plaque formation, however it does not fully explain plaque progression and destabilization. We are the first to investigate the influence of multidirectional WSS features on plaque progression and plaque composition changes in human coronary arteries. METHODS AND RESULTS: Coronary artery imaging using biplane angiography and virtual-histology intravascular ultrasound (VH-IVUS) was performed in twenty patients with coronary artery disease at baseline and after six-month follow-up. 3D surfaces of the coronary arteries were generated using the coronary imaging and together with patient-specific flow measurements different WSS features (multidirectional and conventional time-averaged WSS (TAWSS)) were determined at baseline using computational fluid dynamics (CFD). The changes in plaque component area over the six-month period were determined from VH-IVUS. Changes in plaque composition rather than plaque size were primarily associated with the (multidirectional) WSS at baseline. Interestingly, regions simultaneously exposed to low TAWSS and low multidirectional WSS showed the greatest plaque progression (p<0.001). CONCLUSIONS: In this patient study, several multidirectional WSS features were found to significantly contribute to coronary plaque progression and changes in plaque composition.


ABSTRACT
Background: Associations of both common and rare genetic variants with fasting blood lipids have been extensively studied. However, most of the rare coding variants associated with lipids are population-specific, and exploration of genetic data from diverse population samples may enhance the identification of novel associations with rare variants. Results: We searched for novel coding genetic variants associated with fasting lipid levels in 894 samples from the Genetics of Lipid Lowering Drugs and Diet Network (GOLDN) with exome-wide sequencing-based genotype data. In single variant tests, one variant (rs11171663 in ITGA7) was associated with fasting triglyceride levels (P = 7.66E-08), explaining approximately 3.2% of the total trait variance. In gene-based tests, we found statistically significant associations between ITGA7 (P =
1.77E-07) and SLCO2A1 (P = 7.18E-07) and triglycerides, as well as between POT1 (P = 3.00E-07) and low-density lipoprotein cholesterol. In another independent replication cohort consisting of 3,183 African American samples from Hypertension Genetic Epidemiology Network (HyperGEN) and the Genetic Epidemiology Network of Arteriopathy (GENOA), the top genes achieved P-values of 0.04 (ITGA7), 0.08 (SLCO2A1), and 0.02 (POT1). In GOLDN, gene transcript levels of ITGA7 and SLCO2A1 were associated with fasting triglycerides (P = 0.07 and P = 0.02), highlighting functional relevance of our findings. Conclusion: In this study, we present preliminary evidence of novel rare variant determinants of fasting lipids, and reveal potential underlying molecular mechanisms. Moreover, these results were replicated in an independent cohort. Our findings may inform novel biomarkers of disease risk and treatment targets.


ABSTRACT
Background: Medication non-adherence remains a significant problem for the health care system with clinical, humanistic and economic impact. Dispensing data is a valuable and commonly utilized measure due accessibility in electronic health data. The purpose of this study was to analyze the changes on adherence implementation rates before and after a community pharmacist intervention integrated in usual real life practice, incorporating big data analysis techniques to evaluate Proportion of Days Covered (PDC) from pharmacy dispensing data.

Methods: Retrospective observational study. A de-identified database of dispensing data from 20,335 patients (n = 11,257 on rosuvastatin, n = 6,797 on irbesartan, and n = 2,281 on desvenlafaxine) was analyzed. Included patients received a pharmacist-led medication adherence intervention and had dispensing records before and after the intervention. As a measure of adherence implementation, PDC was utilized. Analysis of the database was performed using SQL and Python. Results: Three months after the pharmacist intervention there was an increase on average PDC from 50.2% (SD: 30.1) to 66.9% (SD: 29.9) for rosuvastatin, from 50.8% (SD: 30.3) to 68% (SD: 29.3) for irbesartan and from 47.3% (SD: 28.4) to 66.3% (SD: 27.3) for desvenlafaxine. These rates declined over 12 months to 62.1% (SD: 32.0) for rosuvastatin, to 62.4% (SD: 32.5) for irbesartan and to 58.1% (SD: 31.1) for desvenlafaxine. In terms of the proportion of adherent patients (PDC >= 80.0%) the trend was similar, increasing after the pharmacist intervention from overall 17.4 to 41.2% and decreasing after one year of analysis to 35.3%. Conclusion: Big database analysis techniques provided results on adherence implementation over 2 years of analysis. An increase in adherence rates was observed after the pharmacist intervention, followed by a gradual decrease over time. Enhancing the current intervention using an evidence-based approach and integrating big database analysis techniques to a real-time measurement of adherence could help community pharmacies improve and sustain medication adherence.

Literature update week 11 (2019)

ABSTRACT
Atherosclerotic cardiovascular disease (ASCVD) is the leading cause of death worldwide. Despite the clinical long-term and near-term benefits of lowering cholesterol in, respectively, primary and secondary prevention of ASCVD, cholesterol levels remain under-treated, with many patients not achieving their recommended targets. The present article will review the latest updates on lipid management with emphases on the different classes of cholesterol-lowering agents and their clinical uses.


ABSTRACT
Lowering total and, in particular, LDL cholesterol reduces cardiovascular risk and clinical events. Cholesterol-lowering strategies are manifold. Better diets and positive lifestyle changes are the foremost approach; the use of functional foods, of food supplements/nutraceuticals, and pharmaceutical treatment must be considered in patients with increasing lipid abnormalities and or increasing cardiovascular risk. Here, we briefly review the most frequently occurring cholesterol-lowering substances found in functional foods or nutraceuticals, i.e. plant sterols and stanols, monacolin K found in red yeast rice, berberine and beta-glucans. We intentionally use a colloquial style to convey our message, which physicians can forward to their patients. We underscore that these preparations are effective either alone or in combination, but that patients should use them after careful discussion with primary care physicians or specialists.


ABSTRACT
Background While there is clear evidence for the benefit of statins in the secondary prevention of cardiovascular and cerebrovascular events, there is a lack of research on the effects of statin regimens in older patients aged 75 years and over. Objectives To compare the effectiveness of statin regimens in the secondary prevention of ischemic cardiovascular and cerebrovascular events among patients aged 75 years and over. Setting Claims data from the South Korean National Health Insurance Database from 2006 to 2014. Methods This retrospective cohort study included patients aged 75-100 years with a prior history of cardiovascular or cerebrovascular disease who began statin therapy in 2009-2011. Propensity score matching and the Cox proportional hazards regression model were used to compare the effectiveness of the statin regimens in secondary prevention. Main outcome measure The hazard ratios for ischemic cardiovascular and cerebrovascular events and all-cause mortality. Results Neither high nor low-intensity statin therapy significantly differed from moderate-intensity statin therapy in preventing ischemic cardiovascular and cerebrovascular events or all-cause mortality. Of the moderate-intensity statin therapies, the use of 10 mg rosvastatin was more strongly associated with a reduced risk of ischemic cardiovascular and cerebrovascular events than was 10 mg atorvastatin [HR 0.79 (95% CI 0.64-0.98), p = 0.029]. Subgroup analysis revealed that the
protective effects of 10 mg rosuvastatin against ischemic cardiovascular and cerebrovascular events were more obvious for patients who were 75-79 years old, those who were statin-adherent, those who did not have diabetes mellitus at baseline, and those who were non-adherent to aspirin or antiplatelet drugs during the selection and follow-up periods. Conclusion The results of this study support the preferential prescription of moderate-intensity rosuvastatin over moderate-intensity atorvastatin for the secondary prevention of ischemic cardiovascular and cerebrovascular events in older patients aged >/= 75 years.


ABSTRACT

BACKGROUND: Eukaryotic cells can respond to diverse stimuli by converging at serine-51 phosphorylation on eukaryotic initiation factor 2 alpha (eIF2alpha) and activate the integrated stress response (ISR). This is a key step in translational control and must be tightly regulated; however, persistent eIF2alpha phosphorylation is observed in mouse and human atheroma. OBJECTIVES: Potent ISR inhibitors that modulate neurodegenerative disorders have been identified. Here, the authors evaluated the potential benefits of intercepting ISR in a chronic metabolic and inflammatory disease, atherosclerosis. METHODS: The authors investigated ISR’s role in lipid-induced inflammasome activation and atherogenesis by taking advantage of 3 different small molecules and the ATP-analog sensitive kinase allele technology to intercept ISR at multiple molecular nodes. RESULTS: The results show lipid-activated eIF2alpha signaling induces a mitochondrial protease, Lon protease 1 (LONP1), that degrades phosphatase and tensin-induced putative kinase 1 and blocks Parkin-mediated mitophagy, resulting in greater mitochondrial oxidative stress, inflammasome activation, and interleukin-1beta secretion in macrophages. Furthermore, ISR inhibitors suppress hyperlipidemia-induced inflammasome activation and inflammation, and reduce atherosclerosis. CONCLUSIONS: These results reveal endoplasmic reticulum controls mitochondrial clearance by activating eIF2alpha-LONP1 signaling, contributing to an amplified oxidative stress response that triggers robust inflammasome activation and interleukin-1beta secretion by dietary fats. These findings underscore the intricate exchange of information and coordination of both organelles’ responses to lipids is important for metabolic health. Modulation of ISR to alleviate organelle stress can prevent inflammasome activation by dietary fats and may be a strategy to reduce lipid-induced inflammation and atherosclerosis.


ABSTRACT
Background The impairment of endothelium-dependent vasodilation, increased endothelial permeability, and glycocalyx degradation are all important pathophysiological components of endothelial dysfunction. However, it is still not clear whether in atherosclerosis, glycocalyx injury precedes other features of endothelial dysfunction or these events coincide. Methods and Results Herein, we demonstrate that in 4- to 8-week-old apolipoprotein E/low-density lipoprotein receptor-deficient mice, at the stage before development of atherosclerotic plaques, impaired acetylcholine-induced vasodilation, reduced NO production in aorta, and increased endothelial permeability were all observed; however, flow-mediated dilation in the femoral artery was fully preserved. In 4-week-old mice, glycocalyx coverage was reduced and endothelial stiffness was increased, whereas glycocalyx length was significantly decreased at 8 weeks of age. Early changes in endothelial function were also featured by increased plasma concentration of biomarkers of glycocalyx disruption (endocan), biomarkers of endothelial inflammation (soluble vascular cell adhesion molecule 1), increased vascular permeability (angiopoietin 2), and alterations in hemostasis (tissue plasminogen activator and plasminogen activator inhibitor 1). In 28-week-old mice, at the stage of advanced atherosclerotic plaque development, impaired NO production and nearly all other features of endothelial dysfunction were changed to a similar extent, compared with the preatherosclerotic plaque phase. The exceptions were the occurrence of acetylcholine-induced vasoconstriction in the aorta and brachiocephalic artery, impaired flow-mediated vasodilation in the femoral artery, and further reduction of glycocalyx length and coverage with a concomitant further increase in endothelial permeability. Conclusions In conclusion, even at the early stage before the development of atherosclerotic plaques, endothelial dysfunction is a complex multifactorial response that has not been previously appreciated.


ABSTRACT
Achieving blood pressure (BP) control is associated with lower cardiovascular disease (CVD) risk, but less is known about CVD risk associated with sustained BP control over time. This observational analysis of the Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT) was restricted to participants with four to seven visits with systolic BP (SBP) measurements during a 22-month period (n = 24 309). The authors categorized participants as having sustained BP control (SBP < 140 mm Hg) at 100%, 75% to <100%, 50% to <75%, and <50% of visits during this period. Outcomes included fatal coronary heart disease (CHD)/nonfatal myocardial infarction (MI), stroke, heart failure (HF), a composite CVD outcome (fatal CHD/nonfatal MI, stroke, or HF), and mortality. Hazard ratios (HRs) for the association of category of sustained BP control for each outcome were obtained using proportional hazards models. SBP control was present among 20.0% of participants at 100%, 16.4% at 75% to less than 100%, 50% to <75%, and <50% of visits during this period. Outcomes included fatal coronary heart disease (CHD)/nonfatal myocardial infarction (MI), stroke, heart failure (HF), a composite CVD outcome (fatal CHD/nonfatal MI, stroke, or HF), and mortality. Hazard ratios (HRs) for the association of category of sustained BP control for each outcome were obtained using proportional hazards models. SBP control was present among 20.0% of participants at 100%, 16.4% at 75% to less than 100%, 27.0% at 50% to less than 75%, and 36.6% at less than 50% of visits. Compared to those with SBP control at 100% visits, adjusted HR (95% CI) among those with SBP control at <50% of visits was 1.16 (0.93-1.44) for fatal CHD/nonfatal MI, 1.71 (1.26-2.32) for stroke, 1.63 (1.30-2.06) for HF, 1.39 (1.20-1.62) for the composite CVD outcome, and 1.14 (0.99-1.30) for...
mortality. Sustained SBP control may be beneficial for preventing stroke, HF, and CVD outcomes in adults taking antihypertensive medication.


**ABSTRACT**

We report a new variant in the LDLRAP1 gene associated with autosomal recessive hypercholesterolemia in a woman of central European ancestry.


**ABSTRACT**

Dyslipidemias and leukocytosis are associated with cardiovascular disease and immune disorders. Mechanistic studies have shown lipoprotein metabolism to play a significant role in the regulation of atherosclerosis development and leukocyte activation, whereas lipid-lowering treatments have been shown to exert beneficial anti-inflammatory and immunomodulatory effects in clinical trials. However, the relationship between clinical markers of lipid metabolism and leukocyte counts has not been extensively evaluated at the population level. We aimed to determine whether clinical blood lipid measures are associated with leukocyte counts in the general U.S. population represented in the National Health and Nutrition Examination Survey (NHANES) 1999(-)2004, and whether differences exist between men and women (n = 5647). We observed a strong positive linear trend between serum triglycerides vs. blood lymphocyte and basophil counts in both men and women, whereas a positive trend between monocytes vs. triglycerides and lymphocytes vs. total cholesterol and LDL-cholesterol (LDL-C) was only detected in women. Conversely, HDL-C was inversely associated with a greater number of leukocyte subsets in men, whereas inverse trends between HDL-C vs. lymphocytes were observed in both men and women. In multiple regression models, a 10% increase in total cholesterol, LDL-C, and triglycerides was associated with a predicted 1.6%, 0.6%, and 1.4% increase in blood lymphocyte counts in women, respectively, whereas no relationship was observed in men. In both men and women, a 10% increase in triglycerides was additionally associated with higher lymphocyte, neutrophil, and basophil counts, whereas 10% increases in HDL-cholesterol were associated with significantly lower lymphocyte, neutrophil, eosinophil, and basophil counts in men, in addition to lower lymphocyte and monocyte counts in women. These findings suggest that clinical lipid markers may be used to predict blood leukocyte distributions, and that a gender-specific relationship exists between distinct classes of serum lipids and immune cell subsets.

Increasing evidence shows that statins increase the risk of new-onset diabetes mellitus, but the exact mechanism is not clearly known. Free fatty acid receptor 1 (FFA1) has been recognized to mediate insulin secretion, and pioglitazone has direct effects on glucose-stimulated insulin secretion in addition to the reversion of insulin resistance. In this study, we found that atorvastatin decreased potassium-stimulated insulin secretion and inhibited the expression of FFA1, PDX-1, and BETA2/NeuroD in INS-1 cells. Further study demonstrated that pioglitazone prevented the impairment of insulin secretion induced by atorvastatin and enhanced the expression of FFA1, PDX-1, and BETA2/NeuroD reduced by atorvastatin in INS-1 cells. In addition, the preventive effect of pioglitazone on atorvastatin-induced impairment of insulin secretion and the enhancement of the expression of PDX-1 and BETA2/NeuroD was abolished by knockdown of FFA1 using siRNA or the PLC inhibitor, U-73122, respectively. Ultimately, FFA1 may mediate the atorvastatin-induced pancreatic beta-cell dysfunction and pioglitazone may ameliorate this deleterious effect through the upregulation of FFA1 expression.


ABSTRACT
Familial hypercholesterolaemia (FH) is a devastating genetic disease that leads to extremely high cholesterol levels and severe cardiovascular disease, mainly caused by mutations in any of the main genes involved in low-density lipoprotein cholesterol (LDL-C) uptake. Among these genes, mutations in the LDL receptor (LDLR) are responsible for 80%-90% of the FH cases. The severe homozygous variety (HoFH) is not successfully treated with standard cholesterol-lowering therapies, and more aggressive strategies must be considered to mitigate the effects of this disease, such as weekly/biweekly LDL apheresis. However, development of new therapeutic approaches is needed to cure HoFH. Because HoFH is mainly due to mutations in the LDLR, this disease has been proposed as an ideal candidate for gene therapy. Several preclinical studies have proposed that the transference of functional copies of the LDLR gene reduces circulating LDL-C levels in several models of HoFH, which has led to the first clinical trials in humans. Additionally, the recent development of clustered regularly interspaced short palindromic repeat/CRIOSPR-associated 9 technology for genome editing has opened the door to therapies aimed at directly correcting the specific mutation in the endogenous LDLR gene. In this article, we review the genetic basis of the FH disease, paying special attention to the severe HoFH as well as the challenges in its diagnosis and clinical management. Additionally, we discuss the current therapies for this disease and the new emerging advances in gene therapy to target a definitive cure for this disease.

**ABSTRACT**
Mounting evidence has shown that inflammation might drive Alzheimer's disease (AD) pathology and contribute to its exacerbation. Previous studies have indicated that indomethacin or atorvastatin are beneficial in treating AD; however, no significant clinical effects have been shown. Furthermore, no study has investigated the efficacy of combining these agents for treating AD. This study sought to determine the effect of a combination of indomethacin and atorvastatin in the PrP-hAbetaPPsw/PS1(DeltaE9) (APP/PS1) transgenic AD mouse model. Treatment with indomethacin and atorvastatin ameliorated impairments in spatial learning and memory, and the active avoidance response in APP/PS1 mice. Moreover, we found a suppression of Abeta plaques and decreased concentration of Abeta1-42 in the hippocampus of APP/PS1 mice following treatment. In addition, indomethacin and atorvastatin ameliorated abnormal cytokine secretion, lymphocyte subset disorder, and hypothalamic-pituitary-adrenal (HPA) and hypothalamic-pituitary-gonadal (HPG) axis imbalances in APP/PS1 mice. The combination of indomethacin and atorvastatin restored immune and neuroendocrine processes, attenuated pathologic changes and cognitive impairments in APP/PS1 transgenic mice, and could thus be a potential therapeutic agent for AD.


**PM:** http://www.ncbi.nlm.nih.gov/pubmed/?term=30856465

**ABSTRACT**
Endothelial dysfunction is an early and central feature of atherosclerosis. Dietary resveratrol (RSV), a class of flavonoid compounds, have been demonstrated to exert several beneficial effects on human body. In this study, we investigated the protective effects of RSV on high fat diet-induced endothelial dysfunction. Human aortic endothelial cells (HAECs) were treated with RSV to evaluate the gene expression of the endothelial nitric oxide synthase (eNOS). Apolipoprotein E (apoE(-/-)) mice were fed a high-fat, high-cholesterol diet (HCD) or HCD supplemented with RSV for 8 weeks. Treatment of cultured HAECs with RSV dose-dependently upregulated the eNOS expression as assessed by quantitative RT-PCR and Western blot, respectively. In addition, RSV increased the promoter activity of the human eNOS gene, as determined by luciferase assays of the eNOS promoter gene. The cAMP-response element binding protein (CREB) was identified as the target transcription factor involved in the RSV mediated upregulation of eNOS expression. RSV increased phosphorylation of CREB through protein kinase A (PKA) activation, which induced a CREB-mediated upregulation of eNOS transcription. Consequently, RSV treatment significantly reversed the deleterious effects of oxidized LDL (oxLDL)-induced oxidative stress in HAECs. In vivo, treatment with RSV improves endothelial dysfunction and attenuates atherosclerotic plaque formation in apoE(-/-) mice through PKA-CREB-dependent pathway. Our findings demonstrate that RSV has an effect of activating eNOS expression, contributing to the prevention of dyslipidemia-induced endothelial dysfunction and atherosclerosis.

The prevalence of obesity, insulin resistance, and diabetes is increasing rapidly. Most patients with these disorders have hypertriglyceridemia and increased plasma levels of fatty acids, which are taken up and stored in lipid droplets in the heart. Intramyocardial lipids that exceed the capacity for storage and oxidation can be lipotoxic and induce non-ischemic and non-hypertensive cardiomyopathy, termed diabetic or lipotoxic cardiomyopathy. The clinical features of diabetic cardiomyopathy are cardiac hypertrophy and diastolic dysfunction, which lead to heart failure, especially heart failure with preserved ejection fraction (HFpEF). Although the pathogenesis of the cardiomyopathy is multifactorial, diabetic dyslipidemia and intramyocardial lipid accumulation are the key pathologic features, triggering cellular signaling and modifications of proteins and lipids via generation of toxic metabolic intermediates. Most clinical studies have shown no beneficial effect of anti-diabetic agents and statins on outcomes in heart failure patients without atherosclerotic diseases, indicating the importance of identifying underlying mechanisms and early interventions for diabetic cardiomyopathy. Here, we summarize the molecular mechanisms of diabetic cardiomyopathy, with a special emphasis on cardiac lipotoxicity, and discuss the role of PPARalpha and dysregulated fatty acid metabolism as potential therapeutic targets. Molecular Mechanisms of Diabetic Cardiomyopathy. Obesity, insulin resistance, and diabetes promote myocardial accumulation of toxic metabolic intermediates and production of pro-inflammatory cytokines through altered plasma fatty acid composition, hypertriglyceridemia, hyperglycemia, adipose tissue inflammation and activated immune cells. These effectors induce mitochondrial dysfunction, endoplasmic reticulum (ER) stress, altered Ca(2+) handling, fibrosis, and energy deficiency, thereby leading to cardiac hypertrophy and diastolic/systolic dysfunction, namely diabetic cardiomyopathy. LPL, lipoprotein lipase; OXPhos, oxidative phosphorylation; ROS, reactive oxygen species; TCA, tricarboxylic acid cycle. This article is protected by copyright. All rights reserved.


CONTEXT: Fenofibrate is used to treat elevated serum triglyceride (TG) concentrations (e.g. >150 mg/dl). The lipoprotein profile of most individuals with spinal cord injury (SCI) would not satisfy conventional criteria to initiate lipid-lowering therapies. Serum TG concentrations of 115 and 137 mg/dl were recently identified as potential intervention thresholds for persons with a SCI proximal to the 4th and below the 5th thoracic vertebrae, respectively. Fenofibrate therapy has not been tested for safety in persons with SCI. METHODS: An open-label trial was performed in 15 persons with SCI to determine the safety profile of 4 months of once-daily fenofibrate (145 mg tablet) treatment when initiated using modified intervention thresholds. Fasting blood tests and a review of systems were performed monthly to determine changes in liver and kidney function, as well as overall health status. RESULTS: Fifteen subjects participated and 4 had an adverse event (e.g. 2 with gastrointestinal distress; 2 with elevated liver enzymes).
Three subjects discontinued the trial within the first month and one participant remained in the trial with no further adverse events. Two participants were discontinued from fenofibrate after 2 months after not responding to treatment, as per protocol, and 10 participants completed the 4-month trial without experiencing an adverse event. CONCLUSION: In persons with SCI, 4 months of fenofibrate therapy initiated at lower threshold serum TG concentrations did not result in an increased incidence of adverse events compared to that reported in the general population. Fenofibrate therapy appears to be well tolerated in persons with SCI.


**ABSTRACT**
Steady increase in the prevalence of chronic kidney disease (CKD) is a serious public health problem, since CKD potentially leads to the development of end-stage renal disease (ESRD) that requires high-cost replacement therapy and is closely associated with increased risk of developing cardiovascular diseases (CVD), which are the cause of death in most patients. Progression of renal dysfunction and development of CVD are significantly affected by hyper- and dyslipidemia. This review contains results of studies evaluating the effect of hypolipidemic therapy on reduction of cardiovascular risk and slowdown of renal dysfunction in patients with CKD at pre-dialysis and dialysis stages of renal failure, as well as in patients with kidney transplant. In addition, recommendations on nutrition and new therapeutic approaches to lipid-lowering therapy in patients with CKD, as well as prospects for the usage of new hypolipidemic drugs are also presented.


**ABSTRACT**
Energy-dense foods can alter gut microbial diversity. However, the physiological effects of diet-induced microbial changes on the development of nonalcoholic fatty liver disease (NAFLD) remain debatable. We hypothesized that high-fat intake for 6 weeks would promote intestinal dysbiosis by increasing gram-positive bacteria, inducing the intestinal production of proinflammatory cytokines and subsequent hepatic lipid infiltration in young male rats. Six-week old male Sprague-Dawley rats were divided into two groups and fed either a standard rodent chow or a 60% high-fat diet (HFD) for 6 weeks. Chromogenic endotoxin quantification assays indicate an increase in lipopolysaccharide concentration in the plasma of HFD rats (p = 0.032). Additionally, Western blot analyses of the cecum showed significantly greater protein expression of the transcription factor, nuclear factor kappa B (NF-kB), (p = 0.037) and the proinflammatory cytokine, interleukin-1beta (IL-1beta), (p = 0.042) in rats fed HFD. Linear discriminate analysis of effect size (LEfSe) showed greater abundance of Firmicutes and Actinobacteria in the samples collected from the cecum of HFD rats compared to chow. Consistent with the development of steatosis, the Oil-Red-O-stained area was increased in liver sections from HFD rats. Hepatic triacylglycerol concentrations (p < 0.001) and plasma alanine aminotransferase (p < 0.001) were significantly increased in HFD-fed animals compared to
chow. These findings show that a short duration of high-fat consumption can have profound deleterious effects on gastrointestinal health and the inflammatory state of these young male Sprague-Dawley rats.


ABSTRACT

Glycogen storage disease type Ia (GSD Ia) is a rare inherited disease caused by mutations in the glucose-6-phosphatase (G6Pase) catalytic subunit gene (G6PC). Absence of G6Pase causes life-threatening hypoglycemia and long-term complications because of the accumulations of metabolic intermediates. Bezafibrate, a pan-peroxisome proliferator-activated receptor (PPAR) agonist, was administered in the context of genome editing with a zinc-finger nuclease-containing vector (AAV-ZFN) and a G6Pase donor vector (AAV-RoG6P). Bezafibrate treatment increased survival and decreased liver size (liver/body mass, p < 0.05) in combination with genome editing. Blood glucose has higher (p < 0.05) after 4 h of fasting, and liver glycogen accumulation (p < 0.05) was lower in association with higher G6Pase activity (p < 0.05). Furthermore, bezafibrate-treated mice had increased numbers of G6PC transgenes (p < 0.05) and higher ZFN activity (p < 0.01) in the liver compared with controls. PPAR-alpha expression was increased and PPAR-gamma expression was decreased in bezafibrate-treated mice. Therefore, bezafibrate improved hepatocellular abnormalities and increased the transduction efficiency of AAV vector-mediated genome editing in liver, whereas higher expression of G6Pase corrected molecular signaling in GSD Ia. Taken together, bezafibrate shows promise as a drug for increasing AAV vector-mediated genome editing.


ABSTRACT


ABSTRACT

BACKGROUND: Short-term studies have shown that bempedoic acid, an inhibitor of ATP citrate lyase, reduces levels of low-density lipoprotein (LDL) cholesterol. Data are limited regarding the safety and efficacy of bempedoic acid treatment in long-term studies involving patients with hypercholesterolemia who are receiving guideline-recommended statin therapy. METHODS: We conducted a randomized, controlled trial involving patients with atherosclerotic cardiovascular disease, heterozygous familial hypercholesterolemia, or both. Patients had to have an LDL cholesterol level of at least 70 mg per deciliter while they were receiving maximally tolerated statin therapy with or without additional lipid-lowering therapy. (Maximally tolerated statin therapy was defined as the highest intensity statin regimen that a patient was able to...
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maintain, as determined by the investigator.) Patients were randomly assigned in a 2:1 ratio to receive bempedoic acid or placebo. The primary end point was safety, and the principal secondary end point (principal efficacy end point) was the percentage change in the LDL cholesterol level at week 12 of 52 weeks. RESULTS: The trial involved 2230 patients, of whom 1488 were assigned to receive bempedoic acid and 742 to receive placebo. The mean (±SD) LDL cholesterol level at baseline was 103.2±29.4 mg per deciliter. The incidence of adverse events (1167 of 1487 patients [78.5%] in the bempedoic acid group and 584 of 742 [78.7%] in the placebo group) and serious adverse events (216 patients [14.5%] and 104 [14.0%], respectively) did not differ substantially between the two groups during the intervention period, but the incidence of adverse events leading to discontinuation of the regimen was higher in the bempedoic acid group than in the placebo group (162 patients [10.9%] vs. 53 [7.1%]), as was the incidence of gout (18 patients [1.2%] vs. 2 [0.3%]). At week 12, bempedoic acid reduced the mean LDL cholesterol level by 19.2 mg per deciliter, representing a change of -16.5% from baseline (difference vs. placebo in change from baseline, -18.1 percentage points; 95% confidence interval, -20.0 to -16.1; P<0.001). Safety and efficacy findings were consistent, regardless of the intensity of background statin therapy. CONCLUSIONS: In this 52-week trial, bempedoic acid added to maximally tolerated statin therapy did not lead to a higher incidence of overall adverse events than placebo and led to significantly lower LDL cholesterol levels. (Funded by Esperion Therapeutics; CLEAR Harmony ClinicalTrials.gov number, NCT02666664.).


ABSTRACT

Stroke is the second leading cause of death worldwide and accounts for >2 million deaths annually in China(1,2). Ischemic stroke (IS) and intracerebral hemorrhage (ICH) account for an equal number of deaths in China, despite a fourfold greater incidence of IS(1,2). Stroke incidence and ICH proportion are higher in China than in Western populations(3-5), despite having a lower mean low-density lipoprotein cholesterol (LDL-C) concentration. Observational studies reported weaker positive associations of LDL-C with IS than with coronary heart disease (CHD)(6,7), but LDL-C-lowering trials demonstrated similar risk reductions for IS and CHD(8-10). Mendelian randomization studies of LDL-C and IS have reported conflicting results(11-13), and concerns about the excess risks of ICH associated with lowering LDL-C(14,15) may have prevented the more widespread use of statins in China. We examined the associations of biochemically measured lipids with stroke in a nested case-control study in the China Kadoorie Biobank (CKB) and compared the risks for both stroke types associated with equivalent differences in LDL-C in Mendelian randomization analyses. The results demonstrated positive associations of LDL-C with IS and equally strong inverse associations with ICH, which were confirmed by genetic analyses and LDL-C-lowering trials. Lowering LDL-C is still likely to have net benefit for the prevention of overall stroke and cardiovascular disease in China.

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ABSTRACT
The current analyses used data from the Canadian Community Health Survey-Nutrition 2015 to investigate grain-based food (GBF) dietary patterns of consumptions among 6,400,000 Canadian children and adolescents 2 to 18 years old. Nutrient intakes, socioeconomic differences, body mass index (BMI) z-scores, and intakes of several food groups were examined across the identified grain patterns of consumption. We employed k-mean cluster analysis to identify the consumption patterns of grain products. Based on the contributions of 21 grain food groups to the total energy intake of each individual, seven GBF consumption patterns were identified including other bread; salty snacks; pasta; rice; cakes and cookies; white bread; and mixed grains. Individuals having less than one serving of grain products were also separately categorized as no-grain consumers. Mean energy intake (kcal/day) was lowest for the "no-grain" consumers and greatest in children/adolescents consuming a "salty snacks" pattern when all GBF patterns were compared. Children and adolescents with "no-grain" and "rice" GBF consumption patterns had significantly lower intakes of several nutrients including dietary fiber, folate, magnesium, calcium, iron, zinc, thiamin, niacin, and riboflavin. No associations were observed with any of the identified GBF patterns and BMI z-scores. In addition, the socioeconomic status (SES) indicators such as household incomes and immigration status of participants were shown to be significantly different across the identified clusters.


ABSTRACT
OBJECTIVES: Sepsis is a severe organic dysfunction caused by an infection that affects the normal regulation of several organ systems, including the central nervous system. Inflammation and oxidative stress play crucial roles in the development of brain dysfunction in sepsis. The aim of this study was to determine the effect of a fish oil (FO)-55-enriched lipid emulsion as an important anti-inflammatory compound on brain dysfunction in septic rats. METHODS: Wistar rats were subjected to sepsis by cecal ligation and perforation (CLP) or sham (control) and treated orally with FO (600 microL/kg after CLP) or vehicle (saline; sal). Animals were divided into sham+sal, sham+FO, CLP+sal and CLP+FO groups. At 24 h and 10 d after surgery, the hippocampus, prefrontal cortex, and total cortex were obtained and assayed for levels of interleukin (IL)-1beta and IL-10, blood-brain barrier permeability, nitrite/nitrate concentration, myeloperoxidase activity, thiobarbituric acid reactive species formation, protein carbonyls, superoxide dismutase and catalase activity, and brain-derived neurotrophic factor levels. Behavioral tasks were performed 10 d after surgery. RESULTS: FO reduced BBB permeability in the prefrontal cortex and total cortex of septic rats, decreased IL-1beta levels and protein carbonylation in all brain structures, and diminished myeloperoxidase activity in the hippocampus and prefrontal cortex. FO enhanced brain-derived neurotrophic factor levels in the hippocampus and prefrontal cortex and prevented cognitive impairment. CONCLUSIONS: FO diminishes the negative effect of polymicrobial sepsis in the rat brain by reducing inflammatory and oxidative stress markers.
High LDL-cholesterol concentrations constitute a risk for atherosclerotic cardiovascular disease. By consensus, cholesterol-lowering therapy is initiated with a statin that reduces endogenous cholesterol synthesis, upregulates hepatic LDL receptor activity, increases LDL clearance and lowers LDL-cholesterol concentrations in the bloodstream. The efficacy of statin treatment is dose dependent and achieves a risk reduction of up to 50%. However, a substantial body of evidence suggests that a quarter of statin-treated patients do not respond adequately as a result of low endogenous cholesterol synthesis. In humans fractional cholesterol absorption varies from 20% to 80%. High cholesterol absorbers which are characterized by a low to normal cholesterol synthesis exhibit poor responsiveness to statin treatment. On the other hand, the cholesterol absorption inhibitor ezetimibe reduces serum cholesterol levels in these patients effectively. On this background, we suggest to "get personal" and individualize cholesterol-lowering therapies according to the individual status of cholesterol synthesis and absorption.

PCSK9 protein is a key regulator of LDL receptor activity. Gain-of-function mutations in PCSK9 are one of the genetic causes of familial hypercholesterolemia. Conversely, loss-of-function mutations are associated with lower levels of LDL cholesterol and reduced coronary heart disease. Monoclonal antibodies targeting PCSK9 are highly efficacious in lowering LDL-C levels, with a good tolerability and safety profile. Two PCSK9 inhibitors, alirocumab and evolocumab, have demonstrated a cardiovascular benefit in addition to statin therapy in patients with established cardiovascular disease. A recent European consensus has defined the candidates for PCSK9 inhibitors, e.g., patients with established cardiovascular disease and patients with familial hypercholesterolemia in primary prevention, with substantially elevated LDL-C levels despite maximally tolerated statin with or without ezetimibe therapy.

The indication for carotid artery stenosis treatment is based primarily on the severity of internal carotid stenosis. There is increasing evidence that unstable plaques in the extracranial carotid artery can be responsible for ischemic stroke or transient ischemic attacks as the source of emboli, even if in the presence of a moderate stenosis. Physicians should be aware that morphological characteristics of the carotid plaques that indicate recent intra-plaque hemorrhage might require intervention in the absence of severe stenosis. This report details a
patient with an unstable plaque in the common carotid artery who met clinical criteria for intervention because of the risk for future stroke.


ABSTRACT

Background: Thinning of the fibrous cap of atherosclerotic plaque is a major component of plaque vulnerability. The high resolution of optical coherence tomography (OCT) provides an accurate measurement of fibrous-cap thickness. Endothelial dysfunction is associated with inflammation and enhanced local expression of matrix metalloproteinases. We investigated the association between endothelial dysfunction and OCT-derived thin-cap fibroatheroma (TCFA) in patients with acute coronary syndromes (ACS). Methods: Seventy-four patients with ACS, who underwent both OCT examinations of the culprit lesion before percutaneous coronary intervention and peripheral endothelial function assessment as assessed by logarithmic value of reactive hyperemia index (Ln_RHI), were enrolled. Age-, sex-, hypertension-, and diabetes-matched non-coronary artery disease (non-CAD) patients were also enrolled (n=15). Results: Ln_RHI levels were significantly lower in ACS patients compared with non-CAD patients (0.56+/-.0.26 vs 0.74+/-.0.22, P=0.01). Furthermore, the Ln_RHIs of ACS patients with TCFA (n=44) were significantly lower than those of ACS patients without TCFA (n=30) (0.50+/-.0.24 vs 0.65+/-.0.26, P=0.01). There was a weak but significant positive correlation between Ln_RHI and fibrous-cap thickness (Spearman’s rho=0.25, P=0.03). Multivariate logistic regression analysis identified lower Ln_RHI as an independent factor associated with TCFA in ACS patients (OR per 0.1 increase in Ln_RHI: 0.78 [95% CI: 0.62-0.98], P=0.03). Conclusion: Advanced endothelial dysfunction significantly correlates with a thin fibrous cap of coronary plaques in patients with ACS.


ABSTRACT

Rhabdomyolysis is characterized by elevation of plasma creatine phosphokinase (CPK) level, and multiple organ disorders, especially renal failure, as well as approximately 50% of acquired rhabdomyolysis are caused by pharmaceuticals. Statins are known to cause rhabdomyolysis, and its incidence is >/=10 times higher with coadministration of statin and fibrate. The purpose of this study is to establish a mouse model of drug-induced rhabdomyolysis by coadministration of statin and fibrate to clarify the mechanisms of its myotoxicity. We administered lovastatin (LV) and gemfibrozil (GF) with a glutathione synthesis inhibitor, L-buthionine-(S,R)-sulfoximine (BSO), to C57BL/6 J female mice once daily for 3 days. The plasma levels of CPK and aspartate aminotransferase (AST) were prominently increased, and the increase in plasma miR-206-3p and miR-133-3p levels, not the increase of miR-122-5p and miR-208-3p levels, suggested skeletal muscle-specific toxicity. The caspase 3/7 activity and mRNA levels of oxidative stress-
related factors were elevated in skeletal muscle. Pharmacokinetic parameters showed that blood levels of statin were significantly increased by coadministered GF. The possibility of kidney injury was examined as in clinical rhabdomyolysis. In histological examination, vacuoles were observed in renal proximal tubules, and the plasma renal injury marker, lipocalin 2/neutrophil gelatinase-associated lipocalin (Lcn2/Ngal), was markedly increased in the mice coadministered LV and GF, suggesting mild complications of acute kidney injury. A quantitative comparison of the myotoxic potential of various statins was successfully performed using the present method. In this study, a rhabdomyolysis mouse model was established by coadministration of the clinically using statin and fibrate. This mouse model may be useful to identify drugs that have high risk for rhabdomyolysis.


ABSTRACT
The prevalence of coronary artery disease in young adults (&lt;45 years of age) has been increasing steadily in recent decades. Although traditional cardiovascular risk factors can be identified in most cases, newly recognized associations are becoming progressively more relevant. The relationship between the factor V Leiden mutation and atherosclerosis has been a matter of debate due to conflicting data presented in previous studies. Presently described is the case of a previously asymptomatic 37-year-old woman with a significant family history of coronary artery disease who developed rapidly progressive angina within 1 month. After a positive non-invasive evaluation, coronary angiography demonstrated a significant obstruction in the proximal left anterior descending artery. Optical coherence tomography revealed a highly vulnerable lipid-rich atherosclerotic plaque. Coronary angioplasty followed by the implantation of 1 drug-eluting stent was successfully performed. A subsequent thrombophilia screening identified a heterozygous factor V R506Q mutation (factor V Leiden). Since there was no history of thromboembolic events, the patient was discharged using only aspirin, clopidogrel, atorvastatin, and atenolol. Further studies are needed to define the most appropriate management of young patients who manifest clinically significant atherosclerotic disease in association with hereditary thrombophilia.