**ABSTRACT**

Clofibric acid derivatives called fibrates, are quite commonly used lipid-lowering drugs, so it is necessary to know beneficial and adverse effects of these compounds on the body. The European Medicines Agency's Committee for Medicinal Products for Human Use (CHMP) has concluded that benefits of four fibrates such as: bezafibrate, ciprofibrate, fenofibrate and gemfibrozil continue outweigh their risk in treatment of people with blood lipid disorders. According to recommendations of the CHMP fibrates should not be used as first-line drugs, except in patients with severe hypertriglyceridemia and patients who cannot use statins. In this paper, we focused on effect of clofibric acid derivatives on lipid metabolism, in particular on apoproteins and regulatory enzymes.

**ABSTRACT**

Atorvastatin reduces morbidity and mortality due to cardiovascular events. This study was conducted to assess the prices and pharmaceutical quality of innovator atorvastatin 20 mg with its locally available generics in Palestine and to assess the suitability of their interchangeability. The prices of innovator and generic atorvastatin 20 mg were determined and compared. Innovator atorvastatin and four generic products were tested for their pharmaceutical quality. Tablets were tested for their drug contents, weight uniformity, hardness, disintegration and dissolution. Three out of four generics were less expensive than the innovator. Pharmaceutical quality assessments were satisfactory and within limits for all atorvastatin tested products. The average weight ranged from 206.6 +/- 8.40 to 330 +/- 3.92 mg and the %RSDs were within the permitted limits as per USP. Tablet hardness ranged from 102 +/- 1.41 to 197.4 +/- 6.88 kg and drug contents ranged from 92.2% to 105.3%. All products disintegrated within permitted time limits and showed very rapid dissolution. Products released more than 85% of their drug contents in less than 15 min. Our results showed that all tested innovator and generic atorvastatin products were of good pharmaceutical quality. Despite the lack of in vivo evaluation, our results indicate that these products are equivalent in vitro. Considering the in vitro release characteristics, these products might be used interchangeably. However, regulatory authorities permit the use of in vitro data in establishing similarity between immediate release oral dosage forms containing biopharmaceutical classification system class I and III drugs only.

**ABSTRACT**


ABSTRACT

INTRODUCTION: The aim of the study was to examine changes in carotid intima-media thickness (CIMT) and carotid plaque morphology in patients receiving multifactorial cardiovascular disease (CVD) risk factor management in a community-based prevention clinic. Quantitative changes in CIMT and qualitative changes in carotid plaque morphology may be measured non-invasively by ultrasound.

MATERIAL AND METHODS: This is a retrospective study on a cohort of 324 patients who received multifactorial cardiovascular risk reduction treatment at a community prevention clinic. All patients received lipid-lowering medications (statin, niacin, and/or ezetimibe) and lifestyle modification. All patients underwent at least one follow-up CIMT measurement after starting their regimen. Annual biomarker, CIMT, and plaque measurements were analyzed for associations with CVD risk reduction treatment.

RESULTS: Median time to last CIMT was 3.0 years. Compared to baseline, follow-up analysis of all treatment groups at 2 years showed a 52.7% decrease in max CIMT, a 3.0% decrease in mean CIMT, and an 87.0% decrease in the difference between max and mean CIMT (p < 0.001). Plaque composition changes occurred, including a decrease in lipid-rich plaques of 78.4% within the first 2 years (p < 0.001). After the first 2 years, CIMT and lipid-rich plaques continued to decline at reduced rates.

CONCLUSION: In a cohort of patients receiving comprehensive CVD risk reduction therapy, delipidation of subclinical carotid plaque and reductions in CIMT predominantly occurred within 2 years, and correlated with changes in traditional biomarkers. These observations, generated from existing clinical data, provide unique insight into the longitudinal on-treatment changes in carotid plaque.


ABSTRACT

INTRODUCTION: It remains controversial whether statins have a beneficial effect on pulmonary arterial hypertension (PAH). This study is intended to evaluate whether statin, co-administered with Rho-kinase inhibitor, could enhance its efficacy. Although Rho-kinase inhibitors, including fasudil, have been reported to improve pulmonary hypertension in experimental and clinical studies, the combination of these agents has not been tested in the treatment of pulmonary hypertension (PH). MATERIAL AND METHODS: The effects of such a regimen on hemodynamics, right ventricle hypertrophy, and Rho-associated protein kinase (ROCK) activity in experimental monocrotaline (MCT)-induced pulmonary hypertension were examined. Fourteen days after monocrotaline injection (60 mg/kg), male rats were treated orally for another 14 days with fasudil (15 mg/kg per day), or with a combination of fasudil + rosuvastatin (10 mg/kg per day). RESULTS: The drug combination reversed the MCT-induced increase in right ventricle pressure (RVP) and reduced right ventricular hypertrophy (RV/LV + S ratio) more than Rho kinase inhibitor alone. The simultaneous administration of fasudil and rosuvastatin caused a further decrease of RhoA kinase activity in isolated lung tissues as compared to fasudil alone. CONCLUSIONS: The results indicate that rosuvastatin intensifies the beneficial effects of Rho-kinase inhibitor on the
Rho/Rho-kinase pathway and such a combination may represent an option for the treatment of pulmonary arterial hypertension.


ABSTRACT

BACKGROUND AND AIMS: Proprotein convertase subtilisin kexin type 9 (PCSK9) induces degradation of the low-density lipoprotein-receptor (LDLR). Smooth muscle cells (SMCs) in human atherosclerotic plaques and cultured SMCs express PCSK9. The present study aimed at defining the role of PCSK9 on vascular response to injury. METHODS: Carotid neointimal lesions were induced by positioning a non-occlusive collar in PCSK9 knock-out (PCSK9-/−) and wild type littermate (PCSK9+/+) mice. RESULTS: In PCSK9-/− mice, we observed a significantly less intimal thickening (p < 0.05), a lower intimal media ratio (p < 0.02), and a tendency to higher lumen area, compared to PCSK9+/+ mice. When compared with PCSK9-/−, lesions of PCSK9+/+ mice had a higher content of SMCs (p < 0.05) and collagen (p < 0.05), while no difference was observed in the accumulation of macrophages. PCSK9 was detectable in both left and right carotids artery in regions occupied by medial and neointimal SMCs. SMCs freshly isolated from PCSK9-/−, when compared to PCSK9+/+ cells, showed higher levels of alpha-smooth muscle actin (alpha-SMA; 2.24 +/- 0.36 fold; p < 0.01) and myosin heavy chain II (MHC-II; 8.65 +/- 1.55 fold; p < 0.01), and lower levels of caldesmon mRNA(-54 +/- 14%; p < 0.01). PCSK9-/− cells also showed a slower proliferation rate, and an impaired migratory capacity and G1/S progression of the cell cycle. The reconstitution of PCSK9 expression, by retroviral infection of PCSK9-/− SMCs, led to a downregulation of alpha-SMA (-56 +/- 2%; p < 0.01), MHC-II (-45% +/- 25.5 fold: p = 0.06) and calponin (-25% +/- 0.8 fold: p < 0.05) and induction of caldesmon mRNA (1.46 +/- 0.3 fold; p < 0.05). Proliferation rate of SMCs PCSK9-/− was significantly lower compared to PCSK9 reconstituted cells. CONCLUSIONS: Taken together, the present results suggest that PCSK9, by sustaining SMC synthetic phenotype, proliferation, and migration, may play a pro-atherogenic role in the arterial wall.


ABSTRACT

Age-related Macular Degeneration (AMD) is the leading cause of blindness among the elderly in western societies. While antioxidant micronutrient treatment is available for intermediate non-neovascular disease, and effective anti-vascular endothelial growth factor treatment is available for neovascular disease, treatment for early AMD is lacking due to an incomplete understanding of the early molecular events. The role of lipids, which accumulate in the macula, and their oxidation, has emerged as an important factor in disease development. These oxidized lipids can either directly contribute to tissue injury or react with amine on proteins to form oxidation-specific epitopes, which can induce an innate
immune response. If inadequately neutralized, the inflammatory response from these epitopes can incite tissue injury during disease development. This review explores how the accumulation of lipids, their oxidation, and the ensuing inflammatory response might contribute to the pathogenesis of AMD. This article is part of a Special Issue entitled: Lipid modification and lipid peroxidation products in innate immunity and inflammation edited by Christoph J. Binder.


ABSTRACT

Non-alcoholic steatohepatitis (NASH) is viewed as the hepatic manifestation of the metabolic syndrome and is a condition hallmarked by lipid accumulation in the liver (steatosis) along with inflammation (hepatitis). Currently, the etiology and mechanisms leading to obesity-induced liver inflammation are not clear and, as a consequence, strategies to diagnose or treat NASH in an accurate manner do not exist. In the current review, we put forward the concept of oxidized lipids as a significant risk factor for NASH. We will focus on the contribution of the different types of oxidized lipids as part of the oxidized low-density lipoprotein (oxLDL) to the hepatic inflammatory response. Furthermore, we will elaborate on the underlying mechanisms linking oxLDL to inflammatory responses in the liver and on how these cascades can be used as therapeutic targets to combat NASH. This article is part of a Special Issue entitled: Lipid modification and lipid peroxidation products in innate immunity and inflammation edited by Christoph J. Binder.


ABSTRACT


ABSTRACT

AIMS: Two anti-proprotein convertase subtilisin/kexin type 9 (PCSK9) monoclonal antibodies, alirocumab and evolocumab, have been approved for the treatment of hypercholesterolaemia in certain patients. We reviewed data from phase 3 studies to evaluate the efficacy and safety of these antibodies. METHODS: We systematically reviewed phase 3 English-language studies in patients with hypercholesterolaemia, published between 1 January 2005 and 20 October 2015. Congress proceedings
from 16 November 2012 to 16 November 2015 were also reviewed. RESULTS: We identified 12 studies of alirocumab and nine of evolocumab, including over 10,000 patients overall. Most studies enrolled patients with hypercholesterolaemia and used anti-PCSK9 antibodies with statins. The ODYSSEY FH I, FH II and HIGH FH alirocumab studies and the RUTHERFORD-2 evolocumab study exclusively recruited patients with heterozygous familial hypercholesterolaemia. Two evolocumab studies focused mainly on homozygous familial hypercholesterolaemia (HoFH): TESLA Part B and TAUSSIG (a TESLA sub-study); only data for HoFH are reported here. All comparator studies demonstrated a reduction in LDL cholesterol (LDL-C) with the anti-PCSK9 antibodies. No head to head studies were conducted between alirocumab and evolocumab. Up to 87% of patients receiving alirocumab and up to 98% receiving evolocumab reached LDL-C goals. Both antibodies were effective and well tolerated across a broad population of patients and in specific subgroups, such as those with type 2 diabetes. CONCLUSIONS: Using anti-PCSK9 antibodies as add-on therapy to other lipid-lowering treatments or as monotherapy for patients unable to tolerate statins may help patients with high cardiovascular risk to achieve their LDL-C goals.


ABSTRACT

BACKGROUND: PCSK9 inhibition is a new powerful cholesterol-lowering strategy. Recently, it was reported that CETP inhibitors influence PCSK9 levels as an off-target effect. We explored the relationship between circulating PCSK9 levels and CETP activity in patients with metabolic disease who were not on lipid-lowering therapy. METHODS: Plasma CETP activity and PCSK9 levels were measured in 450 participants (median age, 58 years; 49 % women) who attended the metabolism unit because of metabolic syndrome (MetS) (78 %), atherogenic dyslipidemia (32 %), obesity (50 %), type 2 diabetes mellitus (72 %), and other risk factors (13 %). A 6 week lipid-lowering drug wash-out period was established in treated patients. RESULTS: Both PCSK9 levels and CETP activity were higher in patients with an increasing number of MetS components. PCSK9 levels were positively correlated with CETP activity in the entire cohort (r = 0.256, P < 0.0001) independent of age, gender, body mass index (BMI), systolic blood pressure (SBP), LDL cholesterol (LDL-C), triglycerides and glucose. Individuals with the loss-of-function PCSK9 genetic variant rs11591147 (R46L) had lower levels of PCSK9 (36.5 %, P < 0.0001) and LDL-C (17.8 %, P = 0.010) as well as lower CETP activity (10.31 %, P = 0.009). This association remained significant in the multiple regression analysis even after adjusting for gender, age, BMI, LDL-C, triglycerides, glucose, lecithin-cholesterol acyltransferase, SBP and MetS (P = 0.003). CONCLUSIONS: Our data suggest a metabolic association between PCSK9 and CETP independent of lipid-lowering treatment. The clinical implications of this metabolic relationship could be relevant for explaining the effect of PCSK9 and CETP inhibition on overall lipid profiles.

Ischemia-induced brain damage leads to apoptosis like delayed neuronal death in selectively vulnerable regions, which could further result in irreversible damages. Previous studies have demonstrated that neurons in the CA1 area of hippocampus are particularly sensitive to ischemic damage. Atorvastatin (ATV) has been reported to attenuate cognitive deficits after stroke, but precise mechanism for neuroprotection remains unknown. Therefore, the aims of this study were to investigate the neuroprotective mechanisms of ATV against ischemic brain injury induced by cerebral ischemia reperfusion. In this study, four-vessel occlusion model was established in rats with cerebral ischemia. Rats were divided into five groups: sham group, I/R group, I/R+ATV group, I/R+ATV+LY, and I/R+SP600125 group. Cresyl violet staining was carried out to examine the neuronal death of hippocampal CA1 region. Immunoblotting was used to detect the expression of the related proteins. Results showed that ATV significantly protected hippocampal CA1 pyramidal neurons against cerebral I/R. ATV could increase the phosphorylation of protein kinase B (Akt1) and nNOS, diminished the phosphorylation of JNK3 and c-Jun, and further inhibited the activation of caspase-3. Whereas, all of the aforementioned effects of ATV were reversed by LY294002 (an inhibitor of Akt1). Furthermore, pretreatment with SP600125 (an inhibitor of JNK) diminished the phosphorylation of JNK3 and c-Jun, and further inhibited the activation of caspase-3 after cerebral I/R. Taken together, our results implied that Akt-mediated phosphorylation of nNOS is involved in the neuroprotection of ATV against ischemic brain injury via suppressing JNK3 signaling pathway that provide a new experimental foundation for stroke therapy.


BACKGROUND: Omega-3 fatty acids from fish oil have been associated with beneficial cardiovascular effects, but their role in modifying cardiac structures and tissue characteristics in patients who have had an acute myocardial infarction while receiving current guideline-based therapy remains unknown. METHODS: In a multicenter, double-blind, placebo-controlled trial, participants presenting with an acute myocardial infarction were randomly assigned 1:1 to 6 months of high-dose omega-3 fatty acids (n=180) or placebo (n=178). Cardiac magnetic resonance imaging was used to assess cardiac structure and tissue characteristics at baseline and after study therapy. The primary study endpoint was change in left ventricular systolic volume index. Secondary endpoints included change in noninfarct myocardial fibrosis, left ventricular ejection fraction, and infarct size. RESULTS: By intention-to-treat analysis, patients randomly assigned to omega-3 fatty acids experienced a significant reduction of left ventricular systolic volume index (-5.8%, P=0.017), and noninfarct myocardial fibrosis (-5.6%, P=0.026) in comparison with placebo. Per-protocol analysis revealed that those patients who achieved the highest quartile increase in red blood cell omega-3 index experienced a 13% reduction in left ventricular systolic
volume index in comparison with the lowest quartile. In addition, patients in the omega-3 fatty acid arm underwent significant reductions in serum biomarkers of systemic and vascular inflammation and myocardial fibrosis. There were no adverse events associated with high-dose omega-3 fatty acid therapy. CONCLUSIONS: Treatment of patients with acute myocardial infarction with high-dose omega-3 fatty acids was associated with reduction of adverse left ventricular remodeling, noninfarct myocardial fibrosis, and serum biomarkers of systemic inflammation beyond current guideline-based standard of care. CLINICAL TRIAL REGISTRATION: URL: http://www.clinicaltrials.gov/. Unique identifier: NCT00729430.


ABSTRACT

BACKGROUND: -Evidence for treating hypertension in patients with asymptomatic aortic valve stenosis (AS) is scarce. We used data from the Simvastatin Ezetimibe in Aortic Stenosis (SEAS) trial to assess what blood pressure (BP) would be optimal. METHODS: -1767 patients with asymptomatic AS and no manifest atherosclerotic disease were analyzed. Outcomes were all-cause mortality, cardiovascular death, heart failure, stroke, myocardial infarction (MI) and aortic valve replacement (AVR). Blood pressure was analyzed in Cox models as the cumulative average of serially measured BP as well as a time-varying covariate. RESULTS: -The incidence of all-cause mortality was highest for average follow up systolic BP >/= 160 mmHg (4.3 per 100 person-year with 95% CI from 3.1 to 6.0) and lowest for average systolic BP 120-139 (2.0 per 100 person-year from 1.6 to 2.6). In multivariable analysis all-cause mortality was associated with average systolic BP < 120 mmHg (HR 3.4 with 95% CI from 1.9 to 6.1), diastolic BP >/= 90 mmHg (HR 1.8 with 95% CI from 1.1 to 2.9) and pulse pressure < 50 mmHg (HR 1.8 with 95% CI from 1.1 to 2.9) taking systolic BP 120-139, diastolic BP 70-79 and pulse pressure 60-69 mmHg as reference. Low systolic and diastolic BP increased risk in patients with moderate AS. Using a time-varying systolic BP from 130 to 139 mmHg as reference, mortality was increased for systolic BP >/= 160 mmHg (hazard ratio 1.7, p=0.033) and BP 120-129 mmHg (hazard ratio 1.6, p=0.039). CONCLUSIONS: -Optimal BP seems to be systolic 130-139 mmHg and diastolic 70-90 mmHg in these patients with asymptomatic AS and no manifest atherosclerotic disease or diabetes. Clinical Trial Registration-http://www.clinicaltrials.gov/NCT00092677.


ABSTRACT
Literature update week 32 (2016)


ABSTRACT

Cardiovascular disease (CVD) remains one of the commonest sources of morbidity and mortality in the world. Lipids and especially low density lipoprotein cholesterol (LDL-C) contribute to the risk of CVD events. Statins are the primary therapy for hypercholesterolaemia and recent evidence supports the use of ezetimibe as a second-line agent. Pro-protein convertase subtilisin kexin 9 (PCSK9) is a regulator of LDL receptor expression. Activating mutations in PCSK9 give rise to a form of familial hypercholesterolaemia, while inactivating mutations lead to lower LDL-C levels and fewer CVD events. Therapies to inhibit PCSK9 are in development and two antibody-based therapies - alirocumab and evolocumab - have recently been licensed. This article reviews the actions of PCSK9, the novel therapeutics targeted on this molecule and how they are likely to be used in clinical practice until large scale CVD outcome studies with PCSK9 inhibitors are published.


ABSTRACT

Cardiovascular (CV) risk may remain despite statin treatment, and there is a need to address this risk with add-on therapy. The lipid effects of two different prescription omega-3 fatty acid therapies are described in a 55-year-old statin- and niacin-treated female with severe dyslipidemia and high CV risk. The patient was initially treated with omega-3-acid ethyl esters (eicosapentaenoic acid [EPA] and docosahexaenoic acid) 4 g/day. Due to persistently elevated low-density lipoprotein cholesterol (LDL-C), she was switched to icosapent ethyl (high-purity EPA ethyl ester) 4 g/day. Approximately 28 months after switching to icosapent ethyl, her LDL-C decreased by 69% to 52 mg/dL, triglycerides decreased by 35% to 119 mg/dL, non-high-density lipoprotein cholesterol (non-HDL-C) decreased by 63% to 76 mg/dL, total cholesterol decreased by 44% to 137 mg/dL, and HDL-C increased by 45% to 61 mg/dL. Total and small dense LDL particle concentrations decreased by 60 and 59%, respectively. Treatment was well tolerated, with improvements maintained over two years.


ABSTRACT
BACKGROUND: Age-related macular degeneration (AMD) is a progressive, late-onset disorder of the macula affecting central vision. It is the leading cause of blindness in people over 65 years in industrialized countries. Recent epidemiologic, genetic, and pathological evidence has shown that AMD shares a number of risk factors with atherosclerosis, leading to the hypothesis that statins may exert protective effects in AMD. OBJECTIVES: The objective of this review was to examine the effectiveness of statins compared with other treatments, no treatment, or placebo in delaying the onset and progression of AMD. SEARCH METHODS: We searched the Cochrane Central Register of Controlled Trials (CENTRAL) (which contains the Cochrane Eyes and Vision Trials Register) (2016, Issue 3), Ovid MEDLINE, Ovid MEDLINE In-Process and Other Non-Indexed Citations, Ovid MEDLINE Daily, Ovid OLDMEDLINE (January 1946 to March 2016), EMBASE (January 1980 to March 2016), Latin American and Caribbean Health Sciences Literature Database (LILACS) (January 1982 to March 2016), PubMed (January 1946 to March 2016), the metaRegister of Controlled Trials (mRCT) (http://www.controlled-trials.com/) (last searched 5 June 2014), ClinicalTrials.gov (http://www.clinicaltrials.gov/), and the WHO International Clinical Trials Registry Platform (ICTRP) (http://www.who.int/ictrp/search/en). We did not use any date or language restrictions in the electronic searches for trials. We last searched the electronic databases on 31 March 2016. SELECTION CRITERIA: We included randomized controlled trials (RCTs) and quasi-randomized trials that compared statins with other treatments, no treatment, or placebo in people who were diagnosed as having the early stages of AMD. DATA COLLECTION AND ANALYSIS: We used standard methodological procedures expected by Cochrane. Two review authors independently evaluated the search results against the selection criteria, abstracted data, and assessed risk of bias. We did not perform meta-analysis due to heterogeneity in the interventions and outcomes between the included studies. MAIN RESULTS: Two RCTs with a total of 144 participants met the selection criteria. Both trials compared simvastatin versus placebo in older people (older than 50 or 60 years) with high risk of developing AMD (drusen present on examination). Overall, we judged the quality of the evidence to be low, as we downgraded all outcomes due to limitations in the designs of the trials and insufficient outcome reporting. The larger trial, with 114 participants, was conducted in Australia and used a higher dose (40 mg daily) of simvastatin for three years. Participants and study personnel in this trial were adequately masked, however data were missing for 30% of participants at three years’ follow-up. The smaller trial, with 30 participants, was conducted in Italy and used a lower dose (20 mg) of simvastatin for three months. This trial reported insufficient details to assess the risk of bias. Neither trial reported data for change in visual acuity. Low-quality evidence from the smaller trial, with 30 participants, did not show a statistically significant difference between the simvastatin and placebo groups in visual acuity values at three months of treatment (decimal visual acuity 0.21 +/- 0.56 in simvastatin group and 0.19 +/- 0.40 in placebo group) or 45 days after the completion of treatment (decimal visual acuity 0.20 +/- 0.50 in simvastatin group and 0.19 +/- 0.48 in placebo group). The lack of a difference in visual acuity was not explained by lens or retina status, which remained unchanged during and after the treatment period for both groups. Preliminary analyses of 42 participants who had completed 12 months’ follow-up in the larger trial did not show a statistically significant difference between simvastatin and the placebo groups for visual acuity, drusen score, or visual function (effect estimates and confidence intervals were not available). Complete data for these outcomes at three years’ follow-up were not reported. At three years, low-quality evidence showed an effect of simvastatin in slowing progression of AMD compared with placebo to be uncertain (odds ratio 0.51, 95% confidence interval 0.23 to 1.09). One trial did not report adverse outcomes. The second trial reported no difference between groups in terms of adverse events such as death, muscle aches, and acute hepatitis. AUTHORS’ CONCLUSIONS: Evidence from
currently available RCTs is insufficient to conclude that statins have a role in preventing or delaying the onset or progression of AMD.


ABSTRACT

While statins significantly reduce cholesterol levels and thereby reduce the risk of cardiovascular disease, the development of myopathy with statin use is a significant clinical side effect. Recent guidelines recommend increasing inclusion criteria for statin treatment in diabetic individuals; however, the impact of statins on skeletal muscle health in those with diabetes (who already suffer from impairments in muscle health) is ill defined. Here, we investigate the effects of fluvastatin treatment on muscle health in wild type (WT) and streptozotocin (STZ)-induced diabetic mice. WT and STZ-diabetic mice received diet enriched with 600 mg/kg fluvastatin or control chow for 24 days. Muscle morphology, intra and extracellular lipid levels, and lipid transporter content were investigated. Our findings indicate that short-term fluvastatin administration induced a myopathy that was not exacerbated by the presence of STZ-induced diabetes. Fluvastatin significantly increased ectopic lipid deposition within the muscle of STZ-diabetic animals, findings that were not seen with diabetes or statin treatment alone. Consistent with this observation, only fluvastatin-treated diabetic mice downregulated protein expression of lipid transporters FAT/CD36 and FABPpm in their skeletal muscle. No differences in FAT/CD36 or FABPpm mRNA content were observed. Altered lipid compartmentalization resultant of a downregulation in lipid transporter content in STZ-induced diabetic skeletal muscle was apparent in the current investigation. Given the association between ectopic lipid deposition in skeletal muscle and the development of insulin-resistance, our findings highlight the necessity for more thorough investigations into the impact of statins in humans with diabetes.


ABSTRACT

PURPOSE: The American College of Cardiology/American Heart Association (ACC/AHA) guidelines are based on studies with a limited number of Asian subjects; therefore, they are difficult to apply to Asian patients, including Korean patients. MATERIALS AND METHODS: Data were extracted from the clinical data warehouse system of Seoul St. Mary's hospital (January 2010 - December 2012) to determine the percent change in low-density lipoprotein cholesterol (LDL-C) levels at an average 3 and 6 months from baseline. Statins with statistically similar lowering effects were placed in one group (group A, B, or C). The proportions of patients who achieved LDL-C < 100 mg/dL were compared between baseline LDL-C levels: low (< 130 mg/dL), medium (130 - 160 mg/dL), and high (> 160 mg/dL). RESULTS: The majority of the 9 statins of various doses (2,349 patients) were effective at 3 months, with additional, smaller
ABSTRACT

Milk-based emulsions have been used commercially as a carrier for phytosterols, but there is limited knowledge on the effect of added plant sterols on the properties of a system. In this study, phytosterols dispersed in milk fat at levels of 0.3% or 0.6% were homogenized with an aqueous dispersion of whey protein isolate (WPI). The particle size, morphology, zeta-potential, and stability of the emulsions were investigated. Emulsion crystallization properties were examined through the use of differential scanning calorimetry (DSC) and Synchrotron X-ray scattering at both small and wide angles. Phytosterol enrichment influenced particle size and physical appearance of the emulsion droplets, but did not impact the stability or charge of the dispersed particles. DSC data demonstrated that, at the higher level of phytosterol addition, crystallization of milk fat was delayed while, at the lower level, phytosterol enrichment induced nucleation and emulsion crystallization. These differences were attributed to the formation of separate phytosterol crystals within the emulsions at the high phytosterol concentration, as characterized by Synchrotron X-ray measurements. X-ray scattering patterns demonstrated the ability of the phytosterol to integrate within the milk fat triacylglycerol matrix, with a concomitant increase in longitudinal packing and system disorder. Understanding the consequences of adding phytosterols, on the physical and crystalline behavior of emulsions, enables the functional food industry to design more physically and chemically stable products.


ABSTRACT

AIM: Clinical trials suggest that residual risks remain for coronary artery disease (CAD) during low-density lipoprotein cholesterol (LDL-C) lowering therapy. We aimed to investigate the role of exogenous lipids in the prognosis of CAD after percutaneous coronary intervention (PCI). METHODS: A total of 145 patients with CAD, who underwent elective PCI, and 82 non-CAD (control) patients were enrolled in this
study. CAD patients underwent follow-up coronary angiography 6-9 months after PCI, and were classified into three groups: 1) patients who showed in-stent restenosis (ISR) in the original stented segment, 2) patients with other non-target coronary atherosclerotic lesions (de novo), and 3) patients with neither ISR nor a de novo lesion. Biochemical analyses were performed on fasting serum samples at the time of follow-up coronary angiography. RESULTS: Despite the controlled serum LDL-C levels, CAD patients with statin showed elevated cholesterol absorption marker campessterol/total cholesterol (TC), synthesis marker lathosterol/TC, campessterol/lathosterol ratio, and apolipoprotein B48 (apoB48) concentration compared with non-CAD patients. The high campessterol/TC, campessterol/lathosterol ratio, and apoB48 concentration were associated with de novo lesion progression after PCI. In stepwise multivariate logistic regression analysis, campessterol/TC and apoB48 concentrations were independent risk factors for de novo lesion progression in statin-treated CAD patients after PCI. CONCLUSION: The increase of cholesterol absorption marker and apoB48 concentration may lead to the progression of de novo lesions, and these markers may represent a residual risk during statin treatment after PCI.


ABSTRACT

The information on the potential hazardous effects of gemfibrozil (GEM) on marine fish is extremely scarce. In the current study, molecular, endocrine and biochemical parameters were assessed in Sparus aurata after 96h waterborne exposure to a GEM concentration range. Hepatic mRNA levels of target genes known to be regulated via peroxisome proliferator-activated receptor alpha (pparalpha) in mammals, such as apolipoprotein AI (apoa1) and lipoprotein (lpl) were significantly increased, without a concomitant activation of the ppar pathways. GEM (15mugL-1) induced an upregulation in mRNA levels of interleukin 1beta (il1beta), tumour necrosis factor-alpha (tnfalpha) and caspase 3 (casp3), suggesting an activation of proinflammatory processes in S. aurata liver. However, mRNA levels of genes related with the antioxidant defence system and cell-tissue repair were unaltered under the tested experimental conditions. Higher levels of GEM induced a cortisol rise, an indication that it is recognized as a stressor by S. aurata. Cortisol levels and the mRNA levels of il1beta, tnfalpha and casp3 may be suggested as potential biomarkers of GEM effects in marine fish.


ABSTRACT

Capsular fibrosis and contracture occurs in most breast reconstruction patients who undergo radiotherapy, and there is no definitive solution for its prevention. Simvastatin was effective at reducing fibrosis in various models. Peri-implant capsular formation is the result of tissue fibrosis development in
Irradiated breasts. The purpose of this study was to examine the effect of simvastatin on peri-implant fibrosis in rats. Eighteen male Sprague-Dawley rats were allocated to an experimental group (9 rats, 18 implants) or a control group (9 rats, 18 implants). Two hemispherical silicone implants, 10 mm in diameter, were inserted in subpanniculus pockets in each rat. The next day, 10-Gy of radiation from a clinical accelerator was targeted at the implants. Simvastatin (15 mg/kg/day) was administered by oral gavage in the experimental group, while animals in the control group received water. At 12 weeks post-implantation, peri-implant capsules were harvested and examined histologically and by real-time polymerase chain reaction. The average capsular thickness was 371.2 mum in the simvastatin group and 491.2 mum in the control group. The fibrosis ratio was significantly different, with 32.33% in the simvastatin group and 58.44% in the control group (P < 0.001). Connective tissue growth factor (CTGF) and transforming growth factor (TGF)-beta1 gene expression decreased significantly in the simvastatin group compared to the control group (P < 0.001). This study shows that simvastatin reduces radiation-induced capsular fibrosis around silicone implants in rats. This finding offers an alternative therapeutic strategy for reducing capsular fibrosis and contracture after implant-based breast reconstruction.


ABSTRACT

This double-blind, randomized, placebo-controlled, cross-over intervention-study was conducted in healthy volunteers to evaluate the effects of plant sterol ester supplemented margarine on cholesterol, non-cholesterol sterols and oxidative stress in serum and monocytes. Sixteen volunteers, average age 34 years, with no or mild hypercholesterolemia were subjected to a 4 week period of daily intake of 3g plant sterols per day supplied via a supplemented margarine on top of regular eating habits. After a wash-out period of one week, volunteers switched groups. Compared to placebo, a diet supplementation with plant sterols increased serum levels of plant sterols such as campesterol (+0.16+/−0.19mg/dL, p=0.005) and sitosterol (+0.27+/−0.18mg/dL, p<0.001) and increased markers of cholesterol synthesis such as desmosterol (+0.05+/−0.07mg/dL, p=0.006) as well as lathosterol (+0.11+/−0.16mg/dL, p=0.012). Cholesterol serum levels, however, were not changed significantly (+18.68mg/dL, p=0.052). These findings could not be verified in isolated circulating monocytes. Moreover, there was no effect on monocyte activation and no differences with regard to redox state after plant sterol supplemented diet. Therefore, in a population of healthy volunteers with no or mild hypercholesterolemia, consumption of plant sterol ester supplemented margarine results in increased concentrations of plant sterols and cholesterol synthesis markers without affecting total cholesterol in the serum, activation of circulating monocytes or redox state.


ABSTRACT

Importance: Low-density lipoprotein cholesterol (LDL-C) is causally related to coronary artery disease (CAD), but the relevance of high-density lipoprotein cholesterol (HDL-C) and triglycerides (TGs) is uncertain. Lowering of LDL-C levels by statin therapy modestly increases the risk of type 2 diabetes, but it is unknown whether this effect is specific to statins. Objective: To investigate the associations of 3 routinely measured lipid fractions with CAD and diabetes through mendelian randomization (MR) using conventional MR and making use of newer approaches, such as multivariate MR and MR-Egger, that address the pleiotropy of genetic instruments where relevant. Design, Setting, and Participants: Published data from genome-wide association studies were used to construct genetic instruments and then applied to investigate associations between lipid fractions and the risk of CAD and diabetes using MR approaches that took into account pleiotropy of genetic instruments. The study was conducted from March 12 to December 31, 2015. Main Outcomes and Measures: Coronary artery disease and diabetes. Results: Genetic instruments composed of 130 single-nucleotide polymorphisms (SNPs) were used for LDL-C (explaining 7.9% of its variance), 140 SNPs for HDL-C (6.6% of variance), and 140 SNPs for TGs (5.9% of variance). A 1-SD genetically instrumented elevation in LDL-C levels (equivalent to 38 mg/dL) and TG levels (equivalent to 89 mg/dL) was associated with higher CAD risk; odds ratios (ORs) were 1.68 (95% CI, 1.51-1.87) for LDL-C and 1.28 (95% CI, 1.13-1.45) for TGs. The corresponding OR for HDL-C (equivalent to a 16-mg/dL increase) was 0.95 (95% CI, 0.85-1.06). All 3 lipid traits were associated with a lower risk of type 2 diabetes. The ORs were 0.79 (95% CI, 0.71-0.88) for LDL-C and 0.83 (95% CI, 0.76-0.90) for HDL-C per 1-SD elevation. For TG, the MR estimates for diabetes were inconsistent, with MR-Egger giving an OR of 0.83 (95% CI, 0.72-0.95) per 1-SD elevation. Conclusions and Relevance: Routinely measured lipid fractions exhibit contrasting associations with the risk of CAD and diabetes. Increased LDL-C, HDL-C, and possibly TG levels are associated with a lower risk of diabetes. This information will be relevant to the design of clinical trials of lipid-modifying agents, which should carefully monitor participants for dysglycemia and the incidence of diabetes.


ABSTRACT

Fish oil-based lipid emulsions (FOLEs) have been used to treat cholestasis in children with intestinal failure-associated liver disease (IFALD). When FOLEs are dosed at 1 g/kg/d, essential fatty acid (EFA) deficiency typically does not occur. We describe the clinical course of a severely malnourished parenteral nutrition-dependent infant with IFALD. Baseline EFA panels were normal upon starting FOLE at 1 g/kg/d. Despite biochemical improvement in IFALD, weight velocity was below target and biochemical EFA status worsened, even after correction for other factors affecting weight. The FOLE dose was increased to 1.5 g/kg/d, resulting in improvement of weight velocity and EFA status. This suggests that in severely malnourished infants being treated for IFALD, higher doses of FOLE may be required for adequate growth and to prevent EFA deficiency.


ABSTRACT

BACKGROUND AND OBJECTIVES: We assessed plaque erosion of culprit lesions in patients with acute coronary syndrome in real world practice. SUBJECTS AND METHODS: Culprit lesion plaque rupture or plaque erosion was diagnosed with optical coherence tomography (OCT). Intravascular ultrasound (IVUS) was used to determine arterial remodeling. Positive remodeling was defined as a remodeling index (lesion/reference EEM [external elastic membrane area]) >1.05. RESULTS: A total of 90 patients who had plaque rupture showing fibrous-cap discontinuity and ruptured cavity were enrolled. 36 patients showed definite OCT-plaque erosion, while 7 patients had probable OCT-plaque erosion. Overall, 26% (11/43) of definite/probable plaque erosion had non-ST elevation myocardial infarction (NSTEMI) while 35% (15/43) had ST elevation myocardial infarction (STEMI). Conversely, 14.5% (13/90) of plaque rupture had NSTEMI while 71% (64/90) had STEMI (p<0.0001). Among plaque erosion, white thrombus was seen in 55.8% (24/43) of patients and red thrombus in 27.9% (12/43) of patients. Compared to plaque erosion, plaque rupture more often showed positive remodeling (p=0.003) with a larger necrotic core area examined by virtual histology (VH)-IVUS, while negative remodeling was prominent in plaque erosion. Overall, 65% 28/43 of plaque erosions were located in the proximal 30 mm of a culprit vessel-similar to plaque ruptures (72%, 65/90, p=0.29). CONCLUSION: Although most of plaque erosions show nearly normal coronary angiogram, modest plaque burden with negative remodeling and an uncommon fibroatheroma might be the nature of plaque erosion. Multimodality intravascular imaging with OCT and VH-IVUS showed fundamentally different pathoanatomic substrates underlying plaque rupture and erosion.


ABSTRACT

BACKGROUND AND OBJECTIVES: There is controversy surrounding whether or not high dose statin administration before percutaneous coronary intervention (PCI) decreases peri-procedural microvascular injury. We performed a prospective randomized study to investigate the mechanisms and effects of pre-treatment high dose atorvastatin on myocardial damage in patients with non-ST-segment elevation acute coronary syndrome (NSTEMI-ACS) undergoing PCI. SUBJECTS AND METHODS: Seventy seven patients with NSTE-ACS were randomly assigned to either the high dose group (atorvastatin 80 mg loading 12 to 24 h before PCI with a further 40 mg loading 2 h before PCI, n=39) or low dose group (atorvastatin 10 mg administration 12 to 24 h before PCI, n=38). Index of microcirculatory resistance
(IMR) was measured after stent implantation. Creatine kinase-myocardial band (CK-MB) and high sensitivity C-reactive protein (CRP) levels were measured before and after PCI. RESULTS: The baseline characteristics were not different between the two patient groups. Compared to the low dose group, the high dose group had lower post PCI IMR (14.1+/−5.0 vs. 19.2+/−9.3 U, p=0.003). Post PCI CK-MB was also lower in the high dose group (median: 1.40 ng/mL (interquartile range [IQR: 0.75 to 3.45] vs. 4.00 [IQR: 1.70 to 7.37], p=0.002) as was the post-PCI CRP level (0.09 mg/dL [IQR: 0.04 to 0.16] vs. 0.22 [IQR: 0.08 to 0.60], p=0.001). CONCLUSION: Pre-treatment with high dose atorvastatin reduces peri-PCI microvascular dysfunction verified by post-PCI IMR and exerts an immediate anti-inflammatory effect in patients with NSTE-ACS.


**ABSTRACT**

Overproduction of reactive oxygen species (ROS) by NADPH oxidase (NOX) activation has been considered the essential mechanism induced by hyperglycemia in various tissues. However, there is no comprehensive study on the role of NOXs in high glucose (HG)-induced toxic effect in neural tissues. Recently, a therapeutic strategy in oxidative related pathologies has been introduced by blocking the undesirable actions of NOX enzymes by small molecules. The protective roles of Statins in ameliorating oxidative stress by NOX inhibition have been shown in some tissues except neural. We hypothesized then, that different NOXs may have role in HG-induced neural cell injury. Furthermore, we postulate that Atorvastatin as a small molecule may modulate this NOXs activity to protect neural cells. Undifferentiated PC12 cells were treated with HG (140 mM/24 h) in the presence and absence of Atorvastatin (1 μM/96 h). The cell viability was measured by MTT assay and the gene and protein expressions profile of NOX (1-4) were determined by RT-PCR and western blotting, respectively. Levels of ROS and malondialdehyde (MDA) were also evaluated. Gene and protein expression levels of NOX (1-4) and consequently ROS and MDA levels were elevated in HG-treated PC12 cells. Atorvastatin could significantly decrease HG-induced NOXs, ROS and MDA elevation and improve impaired cell viability. It can be concluded that HG could elevate NOXs activity, ROS and MDA levels in neural tissues and Atorvastatin as a small molecule NOX inhibitor drug may prevent and delay diabetic complications, particularly neuropathy.


**ABSTRACT**

The aim of the present study was to establish an endothelial cell model of endothelium-specific insulin resistance to evaluate the effect of atorvastatin on insulin resistance-associated endothelial dysfunction.
and to identify the potential pathway responsible for its action. Cultured human umbilical vein endothelial cells (HUVECs) were pretreated with different concentrations of glucose with, or without, 105 M insulin for 24 h, following which the cells were treated with atorvastatin. The tyrosine phosphorylation of insulin receptor (IR) and insulin receptor substrate-1 (IRS1), the production of nitric oxide (NO), the activity and phosphorylation level of endothelial NO synthase (eNOS) on serine1177, and the mRNA levels of endothelin1 (ET1) were assessed during the experimental procedure. Treatment of the HUVECs with 30 mM glucose and 105 M insulin for 24 h impaired insulin signaling, with reductions in the tyrosine phosphorylation of IR and protein expression of IRS1 by almost 75 and 65%, respectively. This, in turn, decreased the activity and phosphorylation of eNOS on serine1177, and reduced the production of NO by almost 80%. By contrast, the mRNA levels of ET1 were upregulated. All these changes were ameliorated by atorvastatin. Taken together, these results demonstrated that high concentrations of glucose and insulin impaired insulin signaling leading to endothelial dysfunction, and that atorvastatin ameliorated these changes, acting primarily through the phosphatidylinositol 3-kinase/Akt/eNOS signaling pathway.


ABSTRACT

Atorvastatin, a lipid-lowering medication, provides neuroprotective effects, although the precise mechanisms of action remain unclear. Our previous studies confirmed activated autophagy following spinal cord injury, which was conducive to recovery of neurological functions. We hypothesized that atorvastatin could also activate autophagy after spinal cord injury, and subsequently improve recovery of neurological functions. A rat model of spinal cord injury was established based on the Allen method. Atorvastatin (5 mg/kg) was intraperitoneally injected at 1 and 2 days after spinal cord injury. At 7 days post-injury, western blot assay, reverse transcription-polymerase chain reaction, and terminal deoxynucleotidyl transferase-mediated dUTP nick-end labeling (TUNEL) staining results showed increased Beclin-1 and light chain 3B gene and protein expressions in the spinal cord injury + atorvastatin group. Additionally, caspase-9 and caspase-3 expression was decreased, and the number of TUNEL-positive cells was reduced. Compared with the spinal cord injury + saline group, Basso, Beattie, and Bresnahan locomotor rating scale scores significantly increased in the spinal cord injury + atorvastatin group at 14-42 days post-injury. These findings suggest that atorvastatin activated autophagy after spinal cord injury, inhibited apoptosis, and promoted recovery of neurological function.


ABSTRACT
BACKGROUND/AIMS: Vitamin D has been investigated for many non-skeletal effects. The objective of this study was to determine whether circulating lipids, systemic inflammation, and biomarkers of endothelial cell activation varied with the vitamin D status of older Australians. METHODS: One hundred and one participants were proportionately and randomly sampled across tertiles of 25 hydroxy vitamin D (25(OH)D) from a larger cohort of free living older adults (T1 median = 97; T2 median = 74.5; T3 median = 56.8 nmol/L). Overnight fasting blood samples were assayed for 25(OH)D, parathyroid hormone (PTH), insulin, triacylglycerol (TAG), total cholesterol (TC), low density lipoprotein cholesterol (LDL-C) and high density lipoprotein cholesterol (HDL-C). Markers of systemic inflammation (high sensitivity C-reactive protein (hsCRP), tumour necrosis factor-alpha (TNF-alpha)) and endothelial activation (hepatocyte growth factor (HGF), P-selectin and soluble vascular cell adhesion molecule (sVCAM), soluble intracellular adhesion molecule (sICAM)) were determined. A general linear model multivariate analysis with a backward elimination procedure was performed. RESULTS: Eighty-three participants (48 women, 35 men), aged 65 +/- 7.7 years, BMI 28 +/- 4.5 kg/m(2), with complete data were analyzed. The final parsimonious model controlled for age, gender, BMI, and McAuley's index, but excluded season, medications, and PTH. There were significant differences across 25(OH)D tertiles in TC (T1 < T3, p = 0.003; T2 < T3, p = 0.001), LDL-C (T1 < T3, p = 0.005; T2 < T3, p = 0.001), TAG (T2 < T3, p = 0.026), HGF (T1 > T3, p = 0.009) and sVCAM (T1 > T3, P = 0.04). CONCLUSIONS: Higher vitamin D status may protect the endothelium through reduced dyslipidaemia and increased HGF.


ABSTRACT

Considerable evidence suggests that "the lower the better" is a reasonable approach for reducing cardiovascular risk by lowering LDL cholesterol levels. Despite the reduction in cardiovascular events and mortality achieved by statin therapy, significant residual risk remains, especially in severe hereditary hypercholesterolemia, such as familial hypercholesterolemia. Some new strategies to achieve even lower LDL levels are now available, including the addition of cholesterol absorption inhibitor ezetimibe, and the recently available Proprotein convertase subtilisin/kexin type 9 monoclonal antibodies. In addition, new LDL drugs may be effectively administrated in those individuals who are unable to tolerate statins. The authors summarize the efficacy and clinical indications of these new agents and review the currently available guidelines. Orv. Hetil., 2016, 157(31), 1219-1223.


ABSTRACT

Familial hypercholesterolemia (FH) is an autosomal co-dominant genetic disorder characterized by elevated low-density lipoprotein cholesterol levels and increased risk for premature cardiovascular disease. It is under diagnosed, yet early detection and treatment are critical to limit premature
atherosclerotic disease. High-intensity statins are the mainstay of treatment, which should be started as early as possible in homozygous FH and as soon as the diagnosis of heterozygous FH is made in adults. Combination therapy is often necessary in FH patients and can include the addition of ezetimibe and bile acid sequestrants. Lipoprotein apheresis is used when pharmacotherapy is inadequate, especially for those with homozygous FH and some patients with severe heterozygous FH. Mipomersen and lomitapide are also indicated for patients with homozygous FH. The recently approved PCSK9 inhibitors, alirocumab and evolocumab, are a promising treatment and outcome studies are ongoing. This article reviews the pathophysiology, diagnosis, and management of FH.


ABSTRACT

INTRODUCTION AND OBJECTIVES: To estimate the health benefits and cost-effectiveness of a polypill intervention (aspirin 100 mg, atorvastatin 20 mg, ramipril 10 mg) compared with multiple monotherapy for secondary prevention of cardiovascular events in adults with a history of myocardial infarction from the perspective of the Spanish National Health System. METHODS: An adapted version of a recently published Markov model developed and validated in Microsoft Excel was used to compare the cost-effectiveness of the polypill with that of its combined monocomponents over a 10-year time horizon. The population included in the model had a mean age of 64.7 years; most were male and had a history of myocardial infarction. The input parameters were obtained from a systematic literature review examining efficacy, adherence, utilities, and costs. The results of the model are expressed in events avoided, incremental costs, incremental life years, incremental quality-adjusted life years, and the incremental cost-effectiveness ratio. RESULTS: Over a 10-year period, use of the cardiovascular polypill instead of its monocomponents simultaneously would avoid 46 nonfatal and 11 fatal cardiovascular events per 1000 patients treated. The polypill would also be a more effective and cheaper strategy. Probabilistic analysis of the base case found a 90.9% probability that the polypill would be a cost-effective strategy compared with multiple monotherapy at a willingness-to-pay of 30000 euros per quality-adjusted life year. CONCLUSIONS: The polypill would be a cost-effective strategy for the Spanish National Health System with potential clinical benefits.


ABSTRACT

Hyperlipidemia is a well-known risk factor for coronary heart disease, the leading cause of death for both men and women. Current lipid-lowering treatment is not always efficient, therefore new
pharmacological interventions that reduce LDL cholesterol (LDL-C) have been developed. This paper presents new class of specific LDL lipid-lowering drugs under investigation in phase II or III clinical trials. The inhibition of proprotein convertase subtilisin/kexin type 9 (PCSK9), a key enzyme in cholesterol homeostasis, improve the liver’s ability to clear LDL from the plasma, reducing LDL-C levels. Currently, three monoclonal antibodies PCSK9 inhibitors (alirocumab, evolocumab and bococizumab) are evaluated in clinical outcome trials. ALN-PCSsc, the new first-in-class therapeutic RNA interference (RNAi) inhibitor of proprotein convertase subtilisin/kexin type 9 (PCSK9) is also the first-in-class investigational medicine that acts by turning off PCSK9 synthesis in the liver. The development leadership of ALN-PCSsc has now transferred from Alnylam Pharmaceuticals to The Medicines Company, who has initiated the ORION-1 Phase II study at the beginning of 2016. ALN-PCSsc has significant potential given its highly competitive profile as compared with monoclonal antibodies anti-PCSK9 MAbs, a recently approved class of LDL-C lowering drugs.


ABSTRACT