ABSTRACT
Clinical and epidemiological studies during the last 7 decades indicated that elevated low-density lipoprotein cholesterol (LDL-C) levels and reduced high-density lipoprotein cholesterol (HDL-C) levels correlate with the pathogenesis and progression of atherosclerotic lesions in the arterial wall. This observation led to the development of LDL-C-lowering drugs for the prevention and treatment of atherosclerosis, some with greater success than others. However, a body of recent clinical evidence shows that a substantial residual cardiovascular risk exists even at very low levels of LDL-C, suggesting that new therapeutic modalities are still needed for reduction of atherosclerosis morbidity and mortality. Unfortunately, HDL-C-raising drugs developed toward this goal had disappointing results thus far. Here, we critically review the literature presenting available evidence and challenges that need to be met and discuss possible new avenues for the development of novel lipid pharmacotherapeutics to reduce the burden of atherosclerosis.

ABSTRACT
AIMS: To assess the relationship between physical frailty and cognitive function among elderly men with a history of cardiovascular disease (CVD). METHODS: Three-hundred-twenty-four community-dwelling men with chronic CVD (mean age 77.2 +/- 6.4 years) who previously participated in the Beazafibrate Infarction Prevention (BIP) trial (1990-1998) underwent assessment of frailty and cognitive function between 2011 and 2013. Physical frailty was assessed using the Fried phenotypic model, and cognitive performance overall and in memory, executive function, visuospatial and attention domains was evaluated using a validated set of computerized cognitive tests. Linear regression models were used to assess the cross-sectional relationship of frailty status and its components (gait speed, grip strength, weight loss, exhaustion and activity) with cognitive function overall and in specific domains, adjusting for age, education, smoking status, physical activity, history of myocardial infarction, hypertension, diabetes and dyslipidemia, systolic blood pressure, BMI and depression. RESULTS: Of the 324 men, 91 (28%) were frail and 121 (37%) were pre-frail. After controlling for potential confounders, severity of frailty was strongly associated with global cognitive function (beta=-8.0, 95%CI=-11.9,-4.1 and beta=-3.3, 95%CI=-6.0,-0.5 comparing frail and pre-frail to non-frail, respectively), with the most profound associations observed in executive function and attention. Gait speed was associated with overall cognitive performance and with all cognitive domains assessed in this study, and activity with none. CONCLUSION: Cognitive function is poor among frail and pre-frail men with CVD, particularly in non-memory domains. Future research is warranted to address mechanisms and to assess the efficacy of interventions to improve physical and cognitive health.


**ABSTRACT**

OBJECTIVE: Inhibition of PCSK9 (proprotein convertase subtilisin/kexin type 9) and statins are known to lower plasma LDL (low-density lipoprotein)-cholesterol concentrations. However, the comparative effects of these treatments on the postprandial metabolism of TRLs (triglyceride-rich lipoproteins) remain to be investigated. APPROACH AND RESULTS: We performed a 2-by-2 factorial trial of the effects of 8 weeks of subcutaneous evolocumab (420 mg every 2 weeks) and atorvastatin (80 mg daily) on postprandial TRL metabolism in 80 healthy, normolipidemic men after ingestion of an oral fat load. We evaluated plasma total and incremental area under the curves for triglycerides, apo (apolipoprotein)B-48, and VLDL (very-LDL)-apoB-100. We also examined the kinetics of apoB-48 using intravenous D3-leucine administration, mass spectrometry, and multicompartmental modeling. Atorvastatin and evolocumab independently lowered postprandial VLDL-apoB-100 total area under the curves (P<0.001). Atorvastatin, but not evolocumab, reduced fasting plasma apoB-48, apoC-III, and angiopoietin-like 3 concentrations (P<0.01), as well as postprandial triglyceride and apoB-48 total area under the curves (P<0.001) and the incremental area under the curves for plasma triglycerides, apoB-48, and VLDL-apoB-100 (P<0.01). Atorvastatin also independently increased TRL apoB-48 fractional catabolic rate (P<0.001) and reduced the number of apoB-48-containing particles secreted in response to the fat load (P<0.01). In contrast, evolocumab did not significantly alter the kinetics of apoB-48. CONCLUSIONS: In healthy, normolipidemic men, atorvastatin decreased fasting, and postprandial apoB-48 concentration by accelerating the catabolism of apoB-48 particles and reducing apoB-48 particle secretion in response to a fat load. Inhibition of PCSK9 with evolocumab had no significant effect on apoB-48 metabolism.


**ABSTRACT**


**ABSTRACT**

Background: Murine models of atherosclerosis have been invaluable to gain mechanistic understanding of this chronic disease. Induction of atherosclerosis with relative ease in ApoE-/ and Ldlr-/ mice fed a Western-type diet to cause hyperlipidaemia has provided researchers with popular tools to manipulate and characterise the action of genes that affect atherogenesis. Seminal studies and reviews have discussed key phenotypic differences between different models and “target levels of hyperlipidaemia” have also been published. However, despite widespread use of these models and firm beliefs about differences in severity between them, there has been no meta-analysis and critical appraisal of published literature reporting
Aims: Currently, efficient regimens to reverse atherosclerotic plaques are not available in the clinic. Here, we present sonodynamic therapy (SDT) as a novel methodology to rapidly inhibit progression of atherosclerotic plaques. Methods and Results: In atherosclerotic rabbit and apoE-deficient mouse models, SDT efficiently decreased the atherosclerotic burden within one week, revealing a decrease in the size of the atherosclerotic plaque and enlarged lumen. The shrunken atherosclerotic plaques displayed compositional alterations, with a reduction in lesional macrophages and lipids. The rapid efficacy of SDT may be due to its induction of macrophage apoptosis, enhancement of efferocytosis and amelioration of inflammation in the atherosclerotic plaque. Compared with atorvastatin, the standard of care for atherosclerosis, SDT showed more significant plaque shrinkage and lumen enlargement during one-week treatment. Furthermore, SDT displayed good safety without obvious side effects. In a pilot clinical trial recruiting the patients suffering atherosclerotic peripheral artery disease, combination therapy of SDT with atorvastatin efficiently reduced progression of atherosclerotic plaque within four weeks, and its efficacy was able to last for at least 40 weeks. Conclusion: SDT is a non-invasive and efficacious regimen to inhibit atherosclerotic plaque progression.


ABSTRACT
AIM: PCSK9 inhibitors (PCSK9i) effectively lower cholesterol levels in randomized trials with reduction in cardiovascular outcomes and favorable safety profile. However, the access to PCSK9i is limited due to high cost and data regarding the use of PCSK9i in real-world practice is
limited. METHODS: Data on all patients submitted for approval of PCSK9i at a regional lipid clinic, outside of clinical trials. Patients' profile, approval rates, low-density lipoprotein cholesterol (LDL-C) reduction rates and adverse events were evaluated. RESULTS: Recommendation for PCSK9i was given to 133 patients; 16 did not receive insurance approval and additional 16 were approved but did not initiate therapy. Of the 101 treated patients (47% females; mean age 61 +/- 11 years), 52 had probable/definite familial hypercholesterolemia (FH) (peak LDL-C level 305 +/- 87 mg/dl vs. non-FH 204 +/- 39 mg/dl) and 62% had an established cardiovascular disease. Statin intolerance was reported by 77%. Follow-up lipid panel was available in 66/101 patients: mean LDL-C reduction was 59% +/- 19. Subjects with heterozygous FH had similar LDL-C decrease than those with non-FH (59% +/- 22 vs 60% +/- 14, p=0.792). LDL-C <100 mg/dl was achieved by 76%, LDL-C <70 mg/dl by 58% and LDL-C <40 mg/dl by 18% of those with follow-up data. Side effects were reported by 10%, mainly musculoskeletal complaints and flu-like symptoms, and 15% have discontinued treatment. CONCLUSIONS: Patient selection by a regional lipid clinic resulted in a high real-world PCSK9i insurance approval, with efficacy and safety comparable to randomized clinical trials. Cost and medication non-adherence are potential barriers to successful implementation of therapy in routine clinical care. This article is protected by copyright. All rights reserved.


ABSTRACT
Oleanolic acid (OA) is a pentacyclic triterpenoid compound extracted from olea europaeal, a traditional Chinese medicine herb. OA has been used in the clinic as a hepatoprotective medicine in China since 1970s. In our previous study, we observed that OA could ameliorate hyperlipidemia in animal models. In the present study, we conducted a small-scale clinical trial to evaluate the hypolipidemia effect of OA in hyperlipidemic patients. Hyperlipidemic patients were administrated with OA for four weeks (4 tablets once, three times a day). The blood samples of the patients were collected before and after OA treatment. The biological parameters were measured. Furthermore, three patients' blood samples were studied with DNA microarray. After OA administration, the TC, TG, and HDLC levels in serum decreased significantly. DNA microarray analysis results showed that the expressions of 21 mRNAs were significantly changed after OA treatment. Bioinformatics analysis showed 17 mRNAs were up-regulated and 4 mRNAs were down-regulated significantly after OA treatment. Five mRNAs (CACNA1B, FCN, STEAP3, AMPH, and NR6A1) were selected to validate the expression levels by qRT-PCR. Therefore, OA administration differentially regulated the expression of genes involved in lipid metabolism. The data showed a clinical evidence that OA could improve hyperlipidemia and also unveiled a new insight into the molecular mechanisms underlying the pharmacological effect of OA on hyperlipidemia.

ABSTRACT

BACKGROUND: Low birthweight has been associated with a higher risk of hypertension, type 2 diabetes mellitus (T2D), and cardiovascular disease. The Barker hypothesis posits that intrauterine growth restriction resulting in lower birthweight is causal for these diseases, but causality is difficult to infer from observational studies. METHODS: We performed regression analyses to assess associations of birthweight with cardiovascular disease and T2D in 237,631 individuals from the UK Biobank. Further, we assessed the causal relationship of such associations using Mendelian randomization. RESULTS: In the observational analyses, birthweight showed inverse associations with systolic and diastolic blood pressure (beta, -0.83 and -0.26; per raw unit in outcomes and SD change in birthweight; 95% confidence interval [CI], -0.90 to -0.75 and -0.31 to -0.22, respectively), T2D (odds ratio, 0.83; 95% CI, 0.79-0.87), lipid-lowering treatment (odds ratio, 0.84; 95% CI, 0.81-0.86), and coronary artery disease (hazard ratio, 0.85; 95% CI, 0.78-0.94), whereas the associations with adult body mass index and body fat (beta, 0.04 and 0.02; per SD change in outcomes and birthweight; 95% CI, 0.03-0.04 and 0.01-0.02, respectively) were positive. The Mendelian randomization analyses indicated inverse causal associations of birthweight with low-density lipoprotein cholesterol, 2-hour glucose, coronary artery disease, and T2D and positive causal association with body mass index but no associations with blood pressure. CONCLUSIONS: Our study indicates that lower birthweight, used as a proxy for intrauterine growth retardation, is causally related with increased susceptibility to coronary artery disease and T2D. This causal relationship is not mediated by adult obesity or hypertension.


ABSTRACT

INTRODUCTION: The human scavenger receptor class B type 1 (hSR-B1), which serves as a high affinity receptor for HDL, is expressed on platelet surface and mediates various anti-atherogenic functions. Based on the anti-thrombotic effects of HDL and the importance of HDL-SR-B1 in the formation of atherosclerotic plaque, the present study was aimed to investigate and compare the expression level of hSR-B1 on platelets of CAD patients with that of normal controls. METHODS: The expressions of the hSR-B1 on platelets of 31 CAD patients with atherosclerotic plaque and 20 healthy controls were detected using flowcytometry and western blotting. Moreover, platelet function in response to the agonists was examined by aggregometry, and the lipid panel tests were assayed using chemistry autoanalyzer. RESULTS: Our findings showed that the expression of hSR-B1 was significantly reduced on the surface of platelets from CAD patients with atherosclerotic disease, as compared with healthy controls (6/8% vs. 13/6%) (P < 0.001). Of particular interest, we also found that the formation of aggregates after stimulation of the platelets with ADP was higher in patients with atherosclerotic disease than the controls; indicating an inverse relationship between hSR-B1 expression and the function of human platelets. CONCLUSION: Taken together, the results of the present study raise the possibility that the measurement of hSR-B1 expression on human
platelets may provide a valuable insight that reflects the status of RCT in patients with atherosclerosis.


**ABSTRACT**
Atherosclerotic cardiovascular disease (ASCVD) is the number one cause of morbidity and mortality worldwide. Low-density lipoprotein cholesterol (LDL-C) has been implicated as one of the major risk factors causing ASCVD based on multiple hierarchical levels of evidence. The advent of powerful LDL-C lowering therapies, such as the proprotein convertase subtilisin/kexin type 9 inhibitor, have raised the question of how low to target LDL-C and whether there are any adverse safety events associated with a very low LDL-C level. The present review summarizes the available evidence and concludes that even a very low LDL-C is associated with cardiovascular benefit, although the magnitude of benefit depends on baseline ASCVD risk and the absolute change in LDL-C with pharmacologic therapy. The safety data in patients treated to very low LDL-C is reassuring, although it is inconsistent and requires longer-term follow-up. This article is protected by copyright. All rights reserved.


**ABSTRACT**
Background The Low Density Lipoprotein (LDL) Receptor (LDL-R) is a transmembrane protein playing a crucial role in effective lipid homeostasis. Various therapeutic agents has been used in management of dyslipidemias, however the outcome of therapeutic target is debated. Objective The aim of this review is to summarize and fully understand the current concept regarding LDL-R and its molecular properties, metabolic pathway, factors affecting LDL-R activity and all available pharmacological interventions. Additionally, non-lipid related properties of LDL-R are also referred. Methods Literature from the PubMed database was extracted to identify papers between 1984 to 2017 regarding LDL-R and therapeutic agents on dyslipidemia management. Results We analyzed basic data regarding agents associated with LDL-R (Sterol Regulating Element-Binding Proteins - SREBPs, Protein ARH, IDOL, Thyroid Hormones, Haematologic Disorders, Protein convertase subtilisin kexintype 9 - PCSK-9, ApoC-III) as well as non-lipid related properties of LDL-R, while all relevant (common and novel) pharmacological interventions (statins, fibrates, cholesterol absorption inhibitors, bile acid sequestrants and PCSK-9) are also referred. Conclusion LDL-R and its molecular properties are involved in lipid homeostasis, so potentially sets the therapeutic goals in cardiovascular patients, which is usually debated. Further research is needed in order to fully understand its properties, as well as to find the potential pharmacological interventions that could be beneficial in cholesterol homeostasis and various morbidities in order to reach the most appropriate therapeutic goal.

ABSTRACT

BACKGROUND: Proprotein convertase subtilisin/kexin type 9 (PCSK9) is a circulating protein that promotes degradation of the low density lipoprotein receptor. PCSK9 has emerged as a target for lipid-lowering therapy, but the predictive value of the serum level of PCSK9 for the severity of coronary disease is largely unknown. METHODS: From December 2009 to July 2012, 121 individuals who underwent coronary angiography (CAG) because of clinically suspected acute coronary syndrome were enrolled in this study. Serum levels of PCSK9 and metabolic parameters were measured. SYNTAX (SYNergy between percutaneous coronary intervention with [paclitaxel-eluting] TAXUS stent and cardiac surgery) and GRACE (Global Registry of Acute Coronary Events) scores were calculated. RESULTS: Individuals with CAG lesions (n=100) had significantly higher levels of PCSK9 than those without lesions (n=21). The study population was stratified into three groups according to serum levels of PCSK9. The odds ratio for occurrence of one or more CAG lesions was significantly higher in the group with the highest level of PCSK9 (odds ratio, 7.468; P=0.011) than in the group with the lowest level of PCSK9. Serum PCSK9 was positively associated with the number of involved coronary arteries. Multivariable linear regression indicated that levels of PCSK9 were positively correlated with GRACE risk scores and SYNTAX scores. CONCLUSION: Serum PCSK9 concentrations are higher in patients with coronary artery lesions, and are associated with SYNTAX and GRACE scores, suggesting that PCSK9 is a potential biomarker of the severity of coronary artery disease.


ABSTRACT

Proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitors reduce the risk of cardiovascular events and all-cause mortality in patients at high risk of cardiovascular disease (CVD). Due to high costs and unknown long-term adverse effects, critical evaluation of patients considered for PCSK9 inhibitors is important. It has been proposed that measuring low-density lipoprotein (LDL) subfractions, or LDL particle numbers (LDL-P), could be of value in CVD risk assessment and may identify patients at high risk of CVD. This review evaluates the evidence for the use of LDL subfractions, or LDL-P, when assessing CVD risk in patients for whom PCSK9 inhibitors are considered as a lipid-lowering therapy. Numerous methods for measuring LDL subfractions and LDL-P are available, but several factors limit their availability. A lack of standardization makes comparison between the different methods challenging. Longitudinal population-based studies have found an independent association between different LDL subfractions, LDL-P, and an increased risk of cardiovascular events, but definitive evidence that these measurements add predictive value to the standard risk markers is lacking. No studies have proven that these measurements improve clinical outcomes. PCSK9 inhibitors seem to be effective at lowering all LDL subfractions and LDL-P, but any evidence that measuring LDL subfractions and LDL-P yield clinically useful information is lacking. Such analyses are currently
not recommended when considering whether to initiate PCKS9 inhibitors in patients at risk of CVD.


ABSTRACT
BACKGROUND AND AIMS: Few studies have shown the direct effect of familial hypercholesterolemia (FH) on myocardial systolic function. Studies focused on heterozygote FH patients but not homozygote ones, and they did not perform genetic analyses. We aimed to evaluate all types of patients with FH using the potentially more sensitive speckle tracking echocardiography (STE) technique to identify early left ventricular (LV) dysfunction. METHODS: Genetic analyses of patients with FH were conducted for LDL-receptor, PCSK9, and ApoB100. Nine homozygote, two compound heterozygote, and 82 heterozygote FH patients and 85 healthy subjects were prospectively studied. Longitudinal and circumferential strain measurements and conventional echocardiography findings were obtained. RESULTS: LV ejection fractions were similar for all (homozygote, heterozygote, and control) groups. The LV average longitudinal strain (aLS) and average circumferential strain (aCS) levels were significantly reduced in the homozygote and heterozygote groups when compared with the controls (for aLS, P = .008 (<.001); for aCS, P <= .001). A significant inverse correlation was found between LDL-C levels and LS (P < .001, r = .728) and CS (P < .001, r = .642) for all FH patients. CONCLUSIONS: This study demonstrates the potential of using systolic strain values obtained using 2D STE for determining lipotoxicity in the myocardium owing to hypercholesterolemia. Our study found that cardiac functions of homozygote patients who had the highest cholesterol levels were disrupted at very early ages. Therefore, starting lipid reduction treatment and early reverse LV remodelling therapy at early ages may be beneficial for high-risk patients.


ABSTRACT


ABSTRACT

OBJECTIVE: Intraplaque hemorrhage (IPH) and ulceration of carotid atherosclerotic plaques have been associated with vulnerability while calcification has been conventionally thought protective. However, studies suggested calcification size and location may increase plaque vulnerability. This study explored the association between calcium configurations and
ulceration with IPH. METHODS: One hundred thirty-seven consecutive symptomatic patients scheduled for carotid endarterectomy were recruited. CTA and CTP were performed prior to surgery. Plaque samples were collected for histology. According to the location, calcifications were categorized into superficial, deep and mixed types; according to the size and number, calcifications were classified as thick and thin, multiple and single. RESULTS: Seventy-one plaques had IPH (51.8%) and 83 had ulceration (60.6%). The appearance of IPH and ulceration was correlated ($r = 0.49; p < 0.001$). The incidence of multiple, superficial and thin calcifications was significantly higher in lesions with IPH and ulceration compared with those without. After adjusting factors including age, stenosis and ulceration, the presence of calcification (OR (95% CI), 3.0 (1.1-8.2), $p = 0.035$), multiple calcification [3.9 (1.4-10.9), $p = 0.009$] and superficial calcification [3.4 (1.1-10.8), $p = 0.001$] were all associated with IPH. ROC analysis showed that the AUC of superficial and multiple calcifications in detecting IPH was 0.63 and 0.66, respectively ($p < 0.05$). When the ulceration was combined, AUC increased significantly to 0.82 and 0.83, respectively. Results also showed that patients with lesions of both ulceration and IPH have significantly reduced brain perfusion in the area ipsilateral to the infarction.

CONCLUSIONS: Superficial and multiple calcifications and ulceration were associated with carotid IPH, and they may be a surrogate for higher risk lesions. KEY POINTS: * CTA-defined superficial and multiple calcifications in carotid atherosclerotic plaques are independently associated with the presence of intraplaque hemorrhage. * The combination of superficial and multiple calcifications and ulceration is highly predictive of carotid intraplaque hemorrhage. * Patients with lesions of both ulceration and intraplaque hemorrhage have significantly reduced brain perfusion in the area ipsilateral to the infarction.


**ABSTRACT**

Evidence suggests that oxidative stress is involved in the pathogenesis of Parkinson disease (PD). Simvastatin has been suggested to protect against oxidative stress in several diseases. However, the molecular mechanisms by which simvastatin protects against neuropathology and oxidative damage in PD are poorly elucidated. In this study, we aimed to investigate the potential neuroprotective effects of simvastatin owing to its anti-oxidative properties in 6-hydroxydopamine (6-OHDA)-treated SH-SY5Y cells and mice. The results of 2',7'-dichlorodihydrofluorescein diacetate (DCFH-DA) fluorescence and CCK-8 assay demonstrated that simvastatin reduced intracellular reactive oxygen species (ROS) levels and reversed apoptosis in 6-OHDA-treated SH-SY5Y cells. Mechanistic studies revealed that 6-OHDA-induced activation of nicotinamide adenine dinucleotide phosphate (NADPH) oxidase/p38 mitogen-activated protein kinase (MAPK) pathway was inhibited and nuclear factor-kappaB (NF-kappaB) nuclear transcription decreased in SH-SY5Y cells after simvastatin treatment. Enhanced expression levels of superoxide dismutase (SOD), heme oxygenase-1 (HO-1), peroxisome proliferator-activated receptor-gamma coactivator-1alpha (PGC-1alpha) and glutamate-cysteine ligase modifier subunit (GCLM) were observed after simvastatin treatment in 6-OHDA-treated SH-SY5Y cells. In vivo studies revealed that administration of simvastatin by gavage
Literature update week 23 (2018)

depressed limb-use asymmetry and apomorphine-induced rotations in 6-OHDA-lesioned mice. Simvastatin increased dopaminergic neurons and reduced protein tyrosine nitration and glia in the midbrain of PD mice. An inhibitory effect on activation of the NADPH oxidase/p38 MAPK was observed, and increased antioxidant protein expression in the midbrain were seen in the simvastatin plus 6-OHDA group compared with the 6-OHDA-lesioned group. Taken together, these results demonstrate that simvastatin might inhibit the activation of NADPH oxidase/p38 MAPK pathway, enhance antioxidant protein expression and protect against oxidative stress, thereby providing a novel antioxidant mechanism that has therapeutic validity.


ABSTRACT
Alternative therapies are needed to reduce the use of antibiotics and incidence of drug-resistant Salmonellosis. Previous studies have revealed important roles of statins in regulating innate immunity. Therefore, we investigated the effects of statins on innate immunity in Salmonella-infected intestinal epithelial cells (IECs), which are involved in mucosal innate immunity. SW480 cells and Akt siRNA- or vitamin D receptor (VDR) siRNA-transfected SW480 cells were infected by wild-type S. Typhimurium strain SL1344 in the presence or absence of statins. The mRNA or protein expression was analyzed by real-time quantitative PCR or western blot analysis, respectively. Simvastatin or fluvastatin caused IL-8 (interleukin-8) suppression, but increased hBD-2 mRNA expression in Salmonella-infected SW480 cells. Both statins enhanced phosphorylated Akt and VDR expressions. Akt or VDR knockdown by siRNA counteracted the suppressive effect of simvastatin on IL-8 expression, whereas VDR knockdown diminished the enhanced hBD-2 expression in Salmonella-infected SW480 cells. Therefore, we observed differential regulation of statins on inflammatory IL-8 and anti-microbial hBD-2 expressions in Salmonella-infected IECs via PI3K/Akt signaling and VDR protein expression, respectively. The enhanced activity of antimicrobial peptides by statins in Salmonella-infected IECs could protect the host against infection, and modulation of pro-inflammatory responses could prevent the detrimental effects of overwhelming inflammation in the host.


ABSTRACT
Statement 1. Familial hypercholesterolemia (FH) is an autosomal hereditary disease with the 3 major clinical features of hyper-LDL-cholesterolemia, premature coronary artery disease and tendon and skin xanthomas. As there is a considerably high risk of coronary artery disease, in addition to early diagnosis and intensive treatment, family screening (cascade screening) is required (Recommendation level A). 2. For a diagnosis of FH, at least 2 of the following criteria should be satisfied: 1 in circle LDL-C >/= 180 mg/dL, 2 in circle Tendon/skin xanthomas, 3 in circle History of FH or premature coronary artery disease (CAD) within second degree blood relatives (Recommendation level A) 3. Intensive lipid-lowering therapy is necessary for the treatment of
FH. First-line drug should be statin. (Recommendation level A, evidence level 3) 4. Screening for coronary artery disease as well as asymptomatic atherosclerosis should be conducted periodically in FH patients. (Recommendation level A) 5. For homozygous FH, consider LDL apheresis and treatment with PCSK9 inhibitors or MTP inhibitors. (Recommendation level A) 6. For severe forms of heterozygous FH who have resistant to drug therapy, consider PCSK9 inhibitors and LDL apheresis. (Recommendation level A) 7. Refer FH homozygotes as well as heterozygotes who are resistant to drug therapy, who are children or are pregnant or have the desire to bear children to a specialist. (Recommendation level A).


ABSTRACT
Xanthomas are visibly deforming cholesterol deposits that develop after long-term exposure to high serum low-density lipoprotein cholesterol concentrations. We present the case of a 10-year-old boy suffering from homozygous familial hypercholesterolemia with generalized atherosclerosis and large xanthomas. The case impressively demonstrates the potential of low-density lipoprotein cholesterol lowering to rapidly regress pathologic cutaneous manifestations of hypercholesterolemia.


ABSTRACT
Aberrant lipid accumulation in both endothelial cells and macrophage foam cells as well as atherogenic inflammation in the atherosclerotic lesions, if left untreated, eventually lead to plaque rupture and arterial damage, causing devastating consequences. In this report, we explore a dual cell therapy modality by designing a dual-targeting core-shell nanoplatform to deliver LOX-1 siRNA and atorvastatin (AT) to control lipid trafficking to and from endothelial cells and macrophages in the atherosclerotic lesions selectively and sequentially. The core-shell nanoparticles are composed of a PLGA core for AT encapsulation and siRNA complexation and three external lipid layers: a lipid bilayer as the inner layer for cholesterol receiving, apolipoprotein A-I (apoA-I) as the intermediate layer for macrophage targeting, and hyaluronic acid (HA)-DOPE as the outermost layer for endothelial cell targeting. The nanoplatform is designed such that it can shed the HA-DOPE layer extracellularly upon encountering HAase type II (Hyal-2) to expose the intermediate apoA-I layer for enhanced entry into macrophages. We thoroughly characterized dual-targeting bifunctional core-shell nanoparticles and studied the dual-targeting mechanism and biofunctions of the nanoplatform both in vitro and in vivo. Following a 12-week biweekly dosing regimen, the core-shell nanoparticles coated with high molecular weight HA (200kDa) exhibited the most potent anti-atherosclerotic activities as evidenced by 39% plaque size reduction, 63% decrease in lipid accumulation, 68% reduction in CD68(+) macrophage content and 74% reduction in MCP-1 content compared with the baseline.
group. Taken together, the dual-targeting bifunctional core-shell nanoparticles exert a synergistic therapeutic effect on both endothelial cells and macrophages as a dual cell therapy modality to regress atherosclerotic plaques.


ABSTRACT
Considering a non-statin intervention? Choose one that upregulates LDL-C-receptor expression. Adding a PCSK9 inhibitor to statin therapy is effective, but expensive.


ABSTRACT


ABSTRACT
The optimization of a new class of small molecule PCSK9 mRNA translation inhibitors is described. The potency, physicochemical properties and the off-target pharmacology associated with the hit compound (1) were improved by changes to two regions of the molecule. The last step in the synthesis of the congested amide center was enabled by three different routes. Subtle structural changes yielded significant changes in pharmacology and off-target margins. These efforts led to the identification of 7l and 7n with overall profiles suitable for in vivo evaluation. In a 14-day toxicology study, 7l demonstrated an improved safety profile vs. lead 7f. We hypothesize that the improved safety profile is related to diminished binding of 7l to non-translating ribosomes and an apparent improvement in transcript selectivity due to the lower strength of 7l stalling of off-target proteins.


ABSTRACT
BACKGROUND: Scavenger receptor class B type I (SR-BI) plays a key role in high density lipoproteins (HDL) metabolism. SR-BI deficiency in mice results in enhanced susceptibility to atherosclerosis with abnormal large, cholesterol enriched, and functional impaired HDL. This study was to characterize the protein markers of dysfunctional HDL in SR-BI deficient (SR-BI(-/-)) mice and to test if the defective of HDL might be affected by probucol treatment. METHODS: Shotgun proteomics and 2-D gel electrophoresis were performed to examine the profile of HDL protein and distribution of HDL particles isolated from SR-BI(-/-) mice. HDL's cell-function,
paraoxonase 1 (PON1) and myeloperoxidase activity were assessed. The mice were treated with 1.2 mg/g/day probucol for 6 weeks and the impact on HDL protein markers was analyzed. The differential proteins were quantified by Western blotting. RESULTS: The relative amount of protein in SR-BI(-/-) HDL was decreased by about 25% compared to that in HDL from wild type (WT) mice. Compared to WT HDL, relative protein abundance of representative apoAI and PON1 in SR-BI(-/-) HDL were significantly reduced, whereas acute-phase protein serum amyloid A (SAA) and apoAIV, proteinase inhibitor proteins alpha-1-antitrypsin (A1AT) were increased. The distribution of plasma apoAI-containing HDL particles in SR-BI(-/-) mice was also dramatically altered, although plasma apoAI level was no difference. The protein alterations were accompanied with dysfunction of SR-BI(-/-) HDL, evidenced by impaired cholesterol homeostasis in macrophages, and reduced anti-oxidative and anti-inflammatory effects. Probucol treatment of SR-BI(-/-) mice could restored the relative contents of critical proteins including apoAI, PON1, SAA, apoAIV and A1AT on HDL, and improve HDL dysfunction despite decreased HDL-C level. CONCLUSION: SR-BI deficiency leading to dysfunctional HDL is closely related to alteration of HDL protein, suggesting that identification of apoAI, PON1, SAA, apoAIV, and A1AT may serve as the valuable protein markers for diagnosis and therapeutics of dysfunctional HDL-related metabolic diseases.


ABSTRACT
PURPOSE: To study adherence to therapy with statins and its relation to development of cardiovascular complications (CVC) in patients with stable angina after elective percutaneous coronary intervention (PCI) at five-year observation. MATERIALS AND METHODS: This study comprised 574 patients with stable angina (81 % men, mean age 60.3 years) hospitalized for elective PCI. All patients were prescribed therapy in accordance with recommendations on management of stable angina including statins. Adherence to statin therapy after PCI was assessed in 1 year at telephone interview and in 5 years at ambulatory examination and by filling of an adherence questionnaire. The following CVCs were registered during follow-up after hospital discharge: deaths from all causes, cardiovascular deaths, nonfatal myocardial infarctions and strokes, repetitive myocardial revascularizations. Associations of these events with adherence to hypolipidemic therapy were finally analyzed. RESULTS: Mean duration of follow-up was 53.5 (from 3.4 to 67.6) months. In 1 year 490 patients (84.5 %) declared that they continued to take statins. In 5 years number of patients who continued taking statins was 380 (66.2 %). Doses of statins were low (mean for simvastatin 17.4, atorvastatin - 15.8, rosuvastatin - 12.1 mg). Only in 8.7 % of patients level of low density lipoprotein cholesterol (LDLC) was.


ABSTRACT
BACKGROUND At present, a constant progress in pathophysiology understanding and treatment of the chronic heart failure (CHF) is arising. Meanwhile, hyperhomocysteinemia (HHcy) has been linked to impaired left ventricular function and clinical class in patients with CHF. Atorvastatin therapy can reduce the incidence of sudden cardiac death in patients with advanced CHF. Folic acid could enhance endothelial function in vascular disease states. The present study aims to investigate the effect of atorvastatin and folic acid combined on the cardiac function and ventricular remodeling in CHF patients with HHcy. MATERIAL AND METHODS Elderly CHF patients with HHcy were divided into four groups: routine, routine + atorvastatin, routine + folic acid, and routine + atorvastatin + folic acid groups. Serum homocysteine (Hcy) level was detected using enzymatic cycling methods, and N-terminal pro brain natriuretic peptide (NT-proBNP) level by ELISA. The cardiac function indexes and left ventricular early diastolic peak flow velocity/atrial systolic peak flow velocity (E/A) ratio were evaluated. The six-minute walk test was performed to measure the six-minute walk distance (6MWD). RESULTS 6MWD increased, the serum Hcy and NT-proBNP levels decreased, and cardiac function was improved compared with before treatment, which was the most significant in the routine + atorvastatin + folic acid group, followed by the routine + atorvastatin group, then the routine + folic acid group, and lastly, the routine group. CONCLUSIONS The results indicated that the combination of atorvastatin and folic acid improved the cardiac function and inhibited ventricular remodeling of elderly CHF patients with HHcy.


PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=29884547

ABSTRACT

OBJECTIVE: The incretin hormones GLP-1 (glucagon-like peptide-1) and GIP (glucose-dependent insulinotropic peptide) are secreted by the gut after food intake leading to pancreatic insulin secretion and glucose lowering. Beyond its role in glucose control, GLP-1 was found in mice and men to beneficially modulate the process of atherosclerosis, which has been linked to improved cardiovascular outcome of patients with diabetes at high cardiovascular risk treated with GLP-1 receptor agonists. However, little is known on the role of the other main incretin in the cardiovascular system. The aim of this study was to characterize GIP in atherosclerotic cardiovascular disease. METHODS AND RESULTS: Serum concentrations of GIP were assessed in 731 patients who presented for elective coronary angiography at the University Hospital Aachen. While GIP concentrations were not associated with coronary artery disease (CAD), we found 97 patients with PAD (peripheral artery disease) vs. 634 without PAD to have higher circulating GIP levels (413.0 +/- 315.3 vs. 332.7 +/- 292.5 pg/mL, p = 0.0165). GIP levels were independently related to PAD after multivariable adjustment for CAD, age, sex, BMI, hypertension, diabetes, CRP, WBC, and smoking. To investigate the functional relevance of elevated GIP levels in human atherosclerotic disease, we overexpressed GIP (1-42) in ApoE(-/-) mice fed a Western diet for 12 weeks using an adeno-associated viral vector system. GIP overexpression led to reduced atherosclerotic plaque macrophage infiltration and increased collagen content compared to control (LacZ) with no change in overall lesion size, suggesting improved plaque stability. Mechanistically, we found GIP treatment to reduce MCP-1-induced
monocyte migration under in vitro conditions. Additionally, GIP prevented proinflammatory macrophage activation leading to reduced LPS-induced IL-6 secretion and inhibition of MMP-9 activity, which was attributable to GIP dependent inhibition of NfκB, JNK-, ERK, and p38 in endotoxin activated macrophages. CONCLUSION: Elevated concentrations of the incretin hormone GIP are found in patients with atherosclerotic cardiovascular disease, while GIP treatment attenuates atherosclerotic plaque inflammation in mice and abrogates inflammatory macrophage activation in vitro. These observations identified GIP as a counterregulatory vasoprotective peptide, which might open new therapeutic avenues for the treatment of patients with high cardiovascular risk.


ABSTRACT

BACKGROUND: Patients with primary biliary cholangitis who have an inadequate response to therapy with ursodeoxycholic acid are at high risk for disease progression. Fibrates, which are agonists of peroxisome proliferator-activated receptors, in combination with ursodeoxycholic acid, have shown potential benefit in patients with this condition. METHODS: In this 24-month, double-blind, placebo-controlled, phase 3 trial, we randomly assigned 100 patients who had had an inadequate response to ursodeoxycholic acid according to the Paris 2 criteria to receive bezafibrate at a daily dose of 400 mg (50 patients), or placebo (50 patients), in addition to continued treatment with ursodeoxycholic acid. The primary outcome was a complete biochemical response, which was defined as normal levels of total bilirubin, alkaline phosphatase, aminotransferases, and albumin, as well as a normal prothrombin index (a derived measure of prothrombin time), at 24 months. RESULTS: The primary outcome occurred in 31% of the patients assigned to bezafibrate and in 0% assigned to placebo (difference, 31 percentage points; 95% confidence interval, 10 to 50; P<0.001). Normal levels of alkaline phosphatase were observed in 67% of the patients in the bezafibrate group and in 2% in the placebo group. Results regarding changes in pruritus, fatigue, and noninvasive measures of liver fibrosis, including liver stiffness and Enhanced Liver Fibrosis score, were consistent with the results of the primary outcome. Two patients in each group had complications from end-stage liver disease. The creatinine level increased 5% from baseline in the bezafibrate group and decreased 3% in the placebo group. Myalgia occurred in 20% of the patients in the bezafibrate group and in 10% in the placebo group. CONCLUSIONS: Among patients with primary biliary cholangitis who had had an inadequate response to ursodeoxycholic acid alone, treatment with bezafibrate in addition to ursodeoxycholic acid resulted in a rate of complete biochemical response that was significantly higher than the rate with placebo and ursodeoxycholic acid therapy. (Funded by Programme Hospitalier de Recherche Clinique and Arrow Generiques; BEZURSO ClinicalTrials.gov number, NCT01654731 ).


ABSTRACT
Nutrient intake during infancy is critical for healthy growth and development. The present study examined egg consumption and associations with nutrient intakes, markers of growth and weight-related measures in infants 6(-)24 months of age (N = 561) compared to infant egg non-consumers (N = 2129). Egg consumers were defined as those infants consuming eggs (i.e., with the exclusion of mixed dishes) during a 24-h dietary recall. Associations with nutrient intakes and markers of growth variables were evaluated using data from What We Eat in America, the dietary component of the National Health and Nutrition Examination Survey, 2001(-)2012.

Mean energy and nutrient intakes were adjusted for the sample design using appropriate survey parameters and sample weights. Egg consumption was associated with greater energy intake compared to infants not consuming eggs (1265 +/- 27 vs. 1190 +/- 14 kcal/day; \( p = 0.01 \)). Infant consumers of eggs also had greater protein (48 +/- 0.7 vs. 41 +/- 0.4 g/day), total choline (281 +/- 6 vs. 163 +/- 2 mg/day), lutein + zeaxanthin (788 +/- 64 vs. 533 +/- 23 mcg/day), alphalinolenic acid (0.87 +/- 0.02 vs. 0.82 +/- 0.01 g/day), docosahexaenoic acid (DHA) (0.04 +/- 0.02 vs. 0.02 +/- 0.001 g/day), vitamin B12 (4.2 +/- 0.1 vs. 3.7 +/- 0.1 mcg/day), phosphorus (977 +/- 15 vs. 903 +/- 8 mg/day), and selenium (67 +/- 1 vs. 52 +/- 0.6 mcg/day; all p-values < 0.05). Egg consumers also had greater consumption of total fat (50 +/- 0.7 vs. 45 +/- 0.3 g/day), monounsaturated fat (17 +/- 0.3 vs. 15 +/- 0.1 g/day), saturated fat (20 +/- 0.4 vs. 18 +/- 0.2 g/day), and sodium (1663 +/- 36 vs. 1418 +/- 19 mg/day), with lower added sugar (4.7 +/- 0.3 vs. 6.1 +/- 0.2 tsp eq/day), and total sugar (87 +/- 2 vs. 99 +/- 1 g/day; all p-values < 0.05) vs. non-consumers of eggs. Egg consumption was also associated with lower intake of dietary folate, iron, magnesium and niacin relative to non-consumers of eggs. Egg consumption in infants was associated with longer recumbent length when compared to non-consumers of eggs (79.2 +/- 0.2 vs. 78.7 +/- 0.1 cm; \( p = 0.03 \)). No associations were observed when comparing body weight. When compared to non-consumers of eggs and regardless of food security, poverty-income-ratio and Women, Infants and Children (WIC) supplemental nutrition status, egg consumption was associated with greater lutein + zeaxanthin intake per day. The current analyzes show that consumption of eggs in infant 6(-)24 months of age is linked with several nutrient intakes, including higher protein, lutein + zeaxanthin, choline, B12, selenium and phosphorus; and lower added and total sugars relative to non-consumers. Egg consumers also have less of several nutrients to be encouraged and a higher intake of nutrients to limit, thus presenting opportunities for educational strategies to potentially increase consumption of nutrient-dense foods in combination with eggs.


ABSTRACT
Patients with acute coronary syndrome (ACS) with normal or near-normal (non-obstructive) coronary arteries (ACSNNOCA) constitute an important, albeit heterogeneous, patient subset of younger patients, more commonly females, who may have lower risk of cardiovascular events compared to patients with obstructive coronary artery disease; however this risk remains substantial, hence needing further investigation to identify the underlying cause and devise a
proper therapeutic strategy. A diagnostic algorithm starts during coronary angiography with some essential additional diagnostic steps, such as a left ventricular angiogram that may readily identify the underlying cause, e.g. Takotsubo syndrome, while intravascular imaging and vascular reactivity testing may need to be considered for assessing other diagnostic possibilities (e.g. occult atherosclerotic plaque rupture, spontaneous coronary dissection or microvascular dysfunction). Nevertheless, pursuing further investigation with less risky noninvasive tests, such as echocardiography and cardiac magnetic resonance imaging, may effectively identify the cause of ACSNNOCA (e.g. myocarditis or Takotsubo syndrome), and guide management.


ABSTRACT
The increase in fetal and neonatal morbidity and mortality associated with twin pregnancies correlates with an increased risk of preterm delivery, low birth weight, and intrauterine growth restriction (IUGR). Although the pathogenesis of IUGR is unclear and thus management remains a major challenge, feto-placental blood vessels are compromised, and altered umbilical blood flow is observed. In this pilot observational study we investigated the effects of pravastatin plus l-arginine on umbilical artery (umb art) blood flow. Between 2013 and 2016, five women received daily doses l-arginine and pravastatin when an umb art pulsatility index above limits for gestational age was observed and concerns about selective growth restrictions arose. All patients showed selective absent or reversed end-diastolic umbilical artery Doppler flow (AREDV) associated with increased perinatal mortality. Pravastatin (PRAV) plus l-arginine (l-Arg) treatment diminished umb art resistance significantly and allowed pregnancy to continue. No signs of acidosis or hypoxia, normal cardiotocography tracing, normal fetal movement and fetal weight gain were observed in the twins that showed abnormal umb art Dopplers. All neonates were born around 33weeks (median 33weeks, IQR [31.4-33.0]), thus diminishing substantially the chances for any prematurity-associated adverse neonatal outcomes. The infants now show normal growth and development. In in vitro studies, pravastatin induced relaxation of aortic rings. Murine studies identified were performed to investigate the mechanism behind PRAV+l-Arg beneficial effects. A nitric oxide (NO)-dependent synergistic vasorelaxant effect of PRAV+l-Arg was demonstrated using aortic rings. Increased levels of placental NO and increased synthesis of eNOS in placental endothelial cells were observed in mice treated with PRAV+l-Arg compared to untreated mice and mice treated with PRAV- or L-Arg alone. This study suggests that PRAV plus L-Arg might be a good therapeutic option to improve blood flow in umbilical arteries prolonging pregnancy and improving pregnancy outcomes in twins. A RCT should be organized to confirm these results.