ABSTRACT

INTRODUCTION: Switching from any statin to another non-equipotent lipid lowering treatment (LLT) may cause a low-density lipoprotein cholesterol increase and has been associated with a higher probability of negative cardiovascular outcomes. The aim of the study was to assess the impact of switching from rosuvastatin to any other LLT on clinical outcomes in primary care.

METHODS: This was a retrospective analysis based on data from IMS Health Longitudinal Patient Database, which is a general practice database including information of more than 1.0 million patients representative of the Italian population by age, and medical conditions. Patients that started on rosuvastatin (10-40 mg/day) between January 2011 and December 2013 were considered. The date of the first prescription was defined as the index date (ID). The observation period lasted from the ID to September 2015 or until LLT discontinuation, or the occurrence of an acute myocardial infarction (AMI), or death. RESULTS: The primary end point of the study was the occurrence of an AMI during the observation period. The final study population included 10,368 patients. During the observation period, 2452 (23.6%) patients were switched from rosuvastatin to another LLT. The majority of patients (55.6%) were switched to atorvastatin, followed by simvastatin (24.9%), simvastatin/ezetimibe combination (10.0%) and other statins (9.5%). Female gender (HR, hazard ratio, 1.10, 95% CI, confidence interval, 1.02-1.19, p = 0.04) and the presence of chronic kidney disease (HR 1.47, 95% CI 1.16-1.86, p = 0.05) were associated with a higher probability of switch. During the observation period, 113 patients experienced an AMI (incidence of 6.7 AMI/1000 patient-years). Multivariate analysis with Cox proportional hazards method, including switching as a time-dependent covariate, demonstrated that changing from rosuvastatin to another LLT was an independent predictor of AMI (HR 2.2, 95% CI 1.4-3.5, p = 0.001).

CONCLUSION: We conclude that switching from rosuvastatin to another non-equipotent LLT may impart an increased risk of AMI and should be avoided. FUNDING: AstraZeneca SpA.


ABSTRACT

BACKGROUND AND AIMS: There is an inconsistency between international guidelines on lipid-lowering treatment regarding whether to pursue LDL-C treatment targets or to focus on the intensity of treatment. While either approach is attractive, there is no recent global data on actual LDL-C values, treatment targets attained, and the intensity of treatment in statin-treated patients. We aimed to determine and compare the extent of treatment target attainment globally using standardized data collection.

METHODS: Analyses were based on the Dyslipidemia International Study (DYSIS), a cross-sectional study documenting statin-treated outpatients throughout 30 countries worldwide (across Europe, the Middle East, Canada, Africa, and Asia). Patients were classified as being at very high, high, or non-high cardiovascular risk based on the 2011 European Society of Cardiology (ESC)/European Atherosclerosis Society (EAS) guidelines. RESULTS: Data were available for a total of 57,885 patients with a median LDL-C value of 98.2 mg/dl (IQR: 76.6, 125.7 mg/dl). Overall, only 26.8% of patients were documented to have attained their risk-based target LDL-C level. Of the 76% of patients who were classified as being at very high risk, only 21.7% attained their LDL-C goal. Globally, the median distance to target was 33.0 mg/dl, ranging from 18.8 to 42.1 mg/dl across countries. We calculated that a further LDL-C reduction of just 10 mg/dl would result in an 11% increase in the proportion of very-high-risk and high-risk patients attaining their target level (9% for non-high risk patients).

CONCLUSIONS: In spite of statin therapy, LDL-C values were high, with a substantial distance to target that was even more pronounced in (very) high risk patients. These results call for the optimization of existing treatment strategies and a collaborative effort to improve the impact of treatment guidance on clinical practice.
BACKGROUND AND AIMS: Early detection and evaluation of vulnerable atherosclerotic plaque are important for risk stratification and timely intervention, and vascular cell adhesion molecule 1 (VCAM1) assists in adhesion and recruitment of inflammatory cells to vulnerable lesions. We labeled a single-chain variable fragment (scFv) of VCAM1 with 99mtechnetium (99mTc) and fluorescent markers to investigate its potential utility in detecting vulnerable plaques in animal models of atherosclerosis. METHODS: We labeled VCAM1 scFv with 99mTc and cyanine5 (CY5) and evaluated the probes on apolipoprotein E gene-deficient mice and New Zealand White rabbits with induced atherosclerosis. Histopathology and Western blot examinations confirmed atherosclerotic plaque and VCAM1 expression in the aortas. In vivo biodistribution of 99mTc-scFv-VCAM1 was studied. Abdominal organs of mice were removed after CY5-scFv-VCAM1 administration for aortic fluorescence imaging. Rabbits SPECT imaging of 99mTc-scFv-VCAM1 was performed and autoradiography (ARG) of the aortas was checked to confirm the tracer uptake. RESULTS: The radiochemical purity of 99mTc-scFv-VCAM1 was 98.72 +/- 1.04% (n = 5) and its specific activity was 7.8 MBq/mug. Biodistribution study indicated predominant probe clearance by kidneys. In fluorescence imaging, stronger signal from CY5-scFv-VCAM1 in the aorta was observed in atherosclerotic mice than that in controls. SPECT imaging with 99mTc-scFv-VCAM1 showed tracer uptake in the abdominal aorta and the aortic arch of atherosclerotic animals. ARG confirmed tracer uptake in the aortas of atherosclerotic rabbits, with higher uptake ratios of aortic arch/descending aorta in experimental animals (4.45 +/- 0.63, n = 5) than controls (1.12 +/- 0.15, n = 5; p < 0.05). CONCLUSIONS: SPECT and fluorescence imaging results showed the feasibility and effectiveness of detecting vulnerable plaque with scFv of VCAM1, indicating its potential for early diagnosis and evaluation of atherosclerosis.


ABSTRACT

BACKGROUND AND AIMS: Familial hypercholesterolaemia (FH) leads to a lifelong increase in plasma LDL levels with subsequent increase in premature vascular disease. Early diagnosis and treatment is the key to effective management of this condition. This research aims to produce a simple and cost effective genetic test which could identify the majority (71%) of mutations causing FH in the UK and Ireland. METHODS: The Randox Biochip Array Technology was used to detect 40 point mutations in LDLR, APOB and PCSK9 genes, over two 5 x 5 arrays. This technology uses multiplex allele specific PCR and biochip array hybridisation, followed by a chemiluminescence detection system and software for automated mutation calling. RESULTS: The FH biochip array assay was validated in the Belfast Genetics Laboratory using 199 cascade screening samples previously sequenced for known FH causing family mutations, the overall
sensitivity was 98%. The assay was then used for routine testing of 663 patients with possible FH, from clinics across the UK and Ireland. A total of 49 (7.4%) mutation positive individuals were identified, however, for the clinics in England the detection rate was 12.9%. Further analysis of 120 biochip negative patients, using DNA sequencing, did not identify any false negatives. CONCLUSIONS: The FH biochip array provides a rapid and reliable genetic test for the majority of FH causing point mutations in the UK and Ireland. A total of 32 samples can be run in 3 h. This allows clinics to evaluate additional patients for a possible diagnosis of FH such as patients with high LDL, patients with early onset coronary disease, and patients with relatives known to have FH.


ABSTRACT

Sterols, which are isoprenoid derivatives, are structural components of biological membranes. Special attention is now being given not only to their structure and function, but also to their regulatory roles in plants. Plant sterols have diverse composition; they exist as free sterols, sterol esters with higher fatty acids, sterol glycosides, and acylsterol glycosides, which are absent in animal cells. This diversity of types of phytosterols determines a wide spectrum of functions they play in plant life. Sterols are precursors of a group of plant hormones, the brassinosteroids, which regulate plant growth and development. Furthermore, sterols participate in transmembrane signal transduction by forming lipid microdomains. The predominant sterols in plants are beta-sitosterol, campesterol, and stigmasterol. These sterols differ in the presence of a methyl or an ethyl group in the side chain at the 24th carbon atom and are named methylsterols or ethylsterols, respectively. The balance between 24-methylsterols and 24-ethylsterols is specific for individual plant species. The present review focuses on the key stages of plant sterol biosynthesis that determine the ratios between the different types of sterols, and the crosstalk between the sterol and sphingolipid pathways. The main enzymes involved in plant sterol biosynthesis are 3-hydroxy-3-methylglutaryl-CoA reductase, C24-sterol methyltransferase, and C22-sterol desaturase. These enzymes are responsible for maintaining the optimal balance between sterols. Regulation of the ratios between the different types of sterols and sterols/sphingolipids can be of crucial importance in the responses of plants to stresses.

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ABSTRACT

ATP-binding cassette transporter A1 (ABCA1) mediates formation of disc-shaped high-density lipoprotein (HDL) from cell lipid and lipid-free apolipoprotein A-I (apo A-I). Discoidal HDL particles are heterogeneous in physicochemical characteristics for reasons that are understood incompletely. Discoidal lipoprotein particles similar in characteristics and heterogeneity to cell-formed discoidal HDL can be reconstituted from purified lipids and apo A-I by cell-free, physicochemical methods. The heterogeneity of reconstituted HDL (rHDL) is sensitive to the lipid composition of the starting lipid/apo A-I mixture. To determine whether the heterogeneity of cell-formed HDL is similarly sensitive to changes in cell lipids, we investigated four compounds that have well-established effects on cell lipid metabolism and ABCA1-mediated cell cholesterol efflux. 2-Bromopalmitate, D609, monensin and U18666A decreased formation of the larger-sized, but dramatically increased formation of the smaller-sized HDL. 2-Bromopalmitate did not appear to affect ABCA1 activity, subcellular localization or oligomerization, but induced dissolution of the cholesterol-phospholipid complexes in the plasma membrane. Arachidonic and linoleic acids shifted HDL formation to the smaller-sized species. Tangier disease mutations and inhibitors of ABCA1 activity wheat germ agglutinin and AG 490 reduced formation of both larger-sized and smaller-sized HDL. The effect of probucol was similar to the effect of 2-bromopalmitate. Taking rHDL formation as a paradigm, we propose that ABCA1 mutations and activity inhibitors reduce the amount of cell lipid available for HDL formation, and the compounds in the 2-bromopalmitate group and the polyunsaturated fatty acids change cell lipid composition from one that favors formation of the larger-sized HDL particles to one that favors formation of the smaller-sized species.


ABSTRACT

BACKGROUND: Before our study, there were no data concerning complex evaluation of: plasma PCSK9 concentrations, transcript LDL receptor (LDLR), as well as the total amount of monocytes' LDLR in acute coronary syndrome (ACS) patients. PCSK9 levels in a few cohort studies were found to correlate with the number of white blood cells or platelets. The study aims to evaluate PCSK9-LDLR concentrations, as well as to find any association between PCSK9 and white blood cells (WBC) or platelets (PLT). METHODS: The study group included 95 consecutive patients with acute myocardial infarction, in whom angiography/angioplasty of the culprit vessel was performed. The control group consisted of 10 healthy young volunteers. Thirty patients from
the studied group were qualified for further percutaneous revascularization after 3 months. Laboratory tests were performed using commercially available kits. LDLR expression on monocyte surface was measured by flow cytometry, but the mRNA level for LDLR was established by real time PCR. The PCSK9 plasma concentration was measured by ELISA kits.

RESULTS: Study results and conclusions. Higher concentration of PCSK9 and amount of LDLR on monocytes surface were observed in patients with ACS compared with healthy young volunteers (number of LDLRs on monocytes 10.8 +/- 9.6 vs. 41.8 +/- 11.8, p < 0.001, PCSK9 [ng/mL] 295.4 +/- 76.4 vs. 213 +/- 63.2, p < 0.001). A similar relationship was observed after application of 3-month intensive lipid-lowering therapy in patients with ACS (n = 30, PCSK9 [ng/mL] 281.1 +/- 59.5 vs. 358.5 +/- 74.7, p < 0.001, LDLR transcript 0.6 +/- 0.32 vs. 1.87 +/- 0.24, p < 0.001, number of LDLRs on monocytes 5.9 +/- 3.1 vs. 22.3 +/- 3.8, p < 0.001). There were no significant differences in levels of PCSK9, LDLR between patients with ST-segment elevation myocardial infarction (STEMI) and non-ST-segment elevation myocardial infarction (NSTEMI). There was no relation of the PCSK9 with WBC as well as with PLT. CONCLUSIONS: We observed significantly higher concentration of PCSK9, and significantly higher levels of mRNA LDLR transcript in patients with ACS compared with healthy young volunteers. A similar pattern was observed after 3 months of intensive statin therapy among patients with ACS. There were no differences in these parameters between patients with STEMI vs. NSTEMI. The results of the study require confirmation in a larger population of patients.


ABSTRACT


ABSTRACT
ABSTRACT

BACKGROUND: Type 2 diabetes (T2DM) is associated with an increased risk of cardiovascular disease (CVD). This can be partly explained by large artery dysfunction, which already occurs in prediabetes ('ticking clock hypothesis'). Whether a similar phenomenon also applies to microvascular dysfunction is not known. We therefore tested the hypothesis that microvascular dysfunction is already present in prediabetes and is more severe in T2DM. To do so, we investigated the associations of prediabetes, T2DM, and measures of hyperglycemia with microvascular function measured as flicker light-induced retinal arteriolar dilation and heat-induced skin hyperemia. METHODS: In The Maastricht Study, a T2DM-enriched population-based cohort study (N=2213, 51% men, aged ((mean+/−standard deviation (SD)) 59.7+/−8.2 years), we determined flicker light-induced retinal arteriolar % dilation (Dynamic Vessel Analyzer), heat-induced skin %–hyperemia (laser-Doppler flowmetry) and glucose metabolism status (OGTT; normal glucose metabolism (NGM), (N=1269), prediabetes (N=335) or T2DM (N=609)). Differences were assessed with multivariable regression analyses adjusted for age, sex, body mass index, smoking, physical activity, systolic blood pressure, lipid profile, retinopathy, estimated glomerular filtration rate, (micro)albuminuria, the use of lipid-modifying and/or blood pressure-lowering medication, and prior CVD. RESULTS: Retinal arteriolar % dilation was (mean+/−SD) 3.4+/−2.8 in NGM, 3.0+/−2.7 in prediabetes, and 2.3+/−2.6 in T2DM. Adjusted analyses showed a lower arteriolar %–dilation in prediabetes (B=−0.20,95%CI [-0.56;0.15]), with further deterioration in T2DM (B=−0.61, [-0.97;−0.25]) vs NGM, p for trend=0.001. Skin %–hyperemia was (mean+/−SD) 1235+/−810 in NGM, 1109+/−748 in prediabetes, and 937+/−683 in T2DM. Adjusted analyses showed a lower %–hyperemia in prediabetes (B=−46, [-163;72]), with further deterioration in T2DM (B=−184, [-297;−71]) vs NGM, p for trend=0.001. In addition, higher HbA1c and fasting plasma glucose (FPG) were associated with lower retinal arteriolar %–dilation and skin %–hyperemia in fully adjusted models (for HbA1c, standardized B (stB)=−0.10, [-0.15;−0.05], p<0.001 and stB=−0.13, [-0.19;−0.07], p<0.001, respectively; for FPG, stB=−0.09, [-0.15;−0.04], p<0.001 and stB=−0.10, [-0.15;−0.04], p=0.002, respectively). CONCLUSIONS: Prediabetes, T2DM and measures of hyperglycemia are independently associated with impaired microvascular function in the retina and skin. These findings support the concept that microvascular dysfunction precedes and thus may contribute to T2DM-associated CVD and other complications which may in part have a microvascular origin, such as impaired cognition and heart failure.


ABSTRACT

INTRODUCTION: Although the role of inflammation in DVT has been investigated in different studies, there is no definite answer as to whether increased systemic inflammation is the cause or the consequence of DVT. AIM: To follow inflammatory parameters in a cohort of patients with idiopathic DVT. METHODS: Out of 49 patients with an acute idiopathic DVT, which were investigated four months after an acute episode (DEVTA 1), 43 patients were included in the follow-up study investigating inflammatory markers and hemostatic markers of endothelial damage five years after an acute DVT (DEVTA 2). A control group consisted of 43 sex and age matched healthy subjects (CONTROLS). RESULTS: The levels of inflammatory markers were significantly higher in DEVTA 2 in comparison to CONTROLS: tumor necrosis factor alpha 2.0 pg/mL (1.1-2.3) vs 1.3 pg/mL (0.8-1.9), p < .001, high sensitivity C-reactive protein 3.2 mg/L (1.5-5.2) vs 1.7 mg/L (0.9-3.0), p = .008, interleukin-6 (IL-6) 2.7 pg/mL (2.0-3.5) vs 2.1 pg/mL (1.5-2.6), p = .025, IL-8 5.0 pg/mL (3.6-7.3) vs 2.4 pg/mL (1.8-2.8), p < .001. IL-10 was significantly decreased (0.9 pg/mL (0.7-1.8) vs 1.8 (1.5-2.2), p < .001. Most of the proinflammatory markers remained elevated in the DEVTA 2 in comparison to DEVTA 1. Markers of endothelial damage were higher in DEVTA 2 in comparison to CONTROLS and higher than in DEVTA 1. CONCLUSION: Patients with idiopathic DVT have long-term increased inflammatory markers and markers of endothelial damage. These findings favor the hypothesis that inflammation is a cause and not merely a consequence of acute DVT.


ABSTRACT

Bempedoic acid (ETC-1002), a novel therapeutic approach for low-density lipoprotein cholesterol (LDL-C) lowering, inhibits ATP citrate lyase (ACL), an enzyme involved in fatty acid and cholesterol synthesis. Although rodent studies suggested potential effects of ACL inhibition on both fatty acid and cholesterol synthesis, studies in humans show an effect only on cholesterol synthesis. In phase 2 studies, ETC-1002 reduced LDL-C as monotherapy, combined with ezetimibe, and added to statin therapy, with LDL-C lowering most pronounced when ETC-1002 was combined with ezetimibe in patients who cannot tolerate statins. Whether clinically relevant favorable effects on other cardiometabolic risk factors such as hyperglycemia and
insulin resistance occur in humans is unknown and requires further investigation. Promising phase 2 results have led to the design of a large phase 3 program to gain more information on efficacy and safety of ETC-1002 in combination with statins and when added to ezetimibe in statin-intolerant patients.


ABSTRACT

PURPOSE OF REVIEW: Randomized clinical outcome trials are costly, long, and often yield neutral or modestly positive results, and these issues have impeded cardiovascular drug development in the past decade. Despite the significant reduction of cardiovascular morbidity and mortality with statins, substantial residual risk of major cardiovascular events remains. This could be because of the difficulty of demonstrating benefits of new drugs in addition to the current standard of care in unselected populations as well as the interindividual variability in drug response. Pharmacogenomics is a promising avenue for the development of novel or failed drugs and for the repurposing of other medications. RECENT FINDINGS: Several variants were identified in genes that were associated with the effects of statins on plasma lipids. Genomic studies of mutations in genes that encode drug targets have the potential to inform on the link between drug therapy acting on those targets and clinical outcomes. Recently, ADCY9 gene variants were shown to be significantly associated with responses to dalcetrapib in terms of clinical outcomes, atherosclerosis imaging, cholesterol efflux, and inflammation, which provided support for the conduct of a new prospective clinical trial in a genetically determined population. SUMMARY: Pharmacogenomics hold great potential in future lipid trials to decrease failure rates in drug development and to identify patients who will respond with greater benefits and smaller risk.


ABSTRACT

PURPOSE OF REVIEW: Inhibition of cholesteryl ester transfer protein (CETP) has received considerable interest by virtue of its favorable effects on atherogenic and protective lipid parameters. The impact of CETP inhibitors in large clinical outcome trials will be reviewed. RECENT FINDINGS: Population and genetic studies demonstrate that low CETP activity associates with lower rates of cardiovascular events. Inhibiting CETP activity in animal models
has a favorable impact on experimental atherosclerosis. Although the first CETP inhibitor to advance to an outcome trial proved to have adverse clinical effects and the next agent, a more modest inhibitor, was clinically futile, there continues to be immense interest in the potential to develop nontoxic, potent CETP inhibitors to reduce cardiovascular risk. SUMMARY: The current status of CETP inhibitors in the context of large outcomes trials will be reviewed.


**ABSTRACT**

PURPOSE OF REVIEW: We provide an overview of orally administered lipid-lowering therapies under development. RECENT FINDINGS: Recent data support statins for intermediate risk primary prevention, and ezetimibe for high-risk secondary prevention. Novel agents in development include bempedoic acid and gemcabene, and work continues on one remaining cholesteryl ester transfer protein inhibitor, anacetrapib, to determine whether this class can reduce cardiovascular risk. Selective peroxisome proliferator-activated receptor modulators such as K-877 are under study to determine whether they have an advantage over older fibrates. Diacylglycerol transferase inhibitors such as pradigastat appear to have potent triglyceride-lowering effects, even for patients with familial chylomicronemia syndrome. Finally, novel omega-3 preparations are available with significant triglyceride lowering, although their role in therapy remains unclear. SUMMARY: Statins will remain the backbone of lipid-lowering therapy, although several novel oral agents are promising. The common theme across drugs in development is the demonstration of good lipid-lowering effect, although lacking cardiovascular outcomes data, which will likely be necessary before any of them, can be recommended or approved for widespread use.


**ABSTRACT**

In humans low levels of growth hormone (GH) and its mediator, insulin-like growth factor-1 (IGF-1), associate with hepatic lipid accumulation. In mice, congenital liver-specific ablation of the GH receptor (GHR) results in reductions in circulating IGF-1 and hepatic steatosis, associated with systemic insulin-resistance. Due to the intricate relationship between GH and IGF-1, the relative contribution of each hormone to the development of hepatic steatosis is unclear. Our goal was to dissect the mechanisms by which hepatic GH resistance leads to
steatosis and overall insulin resistance, independent of IGF-1. We have generated a combined mouse model with liver-specific ablation of GHR in which we restored liver IGF-1 expression via hepatic IGF-1 transgene. We found that liver-GHR ablation leads to increases in lipid uptake, de novo lipogenesis, hyperinsulinemia and hyperglycemia accompanied with severe insulin resistance, and increased body adiposity and serum lipids. Restoration of IGF-1 improved overall insulin sensitivity, lipid profile in serum, reduced body adiposity, but was insufficient to protect against steatosis-induced hepatic inflammation or oxidative stress. We conclude that the impaired metabolism in states of GH resistance results from direct actions of GH on lipid uptake and de novo lipogenesis, while its actions on extrahepatic tissues are mediated by IGF-1.


ABSTRACT

Heart disease and type 2 diabetes are commonly believed to be rare among contemporary subsistence-level human populations, and by extension prehistoric populations. Although some caveats remain, evidence shows these diseases to be unusual among well-studied hunter-gatherers and other subsistence populations with minimal access to healthcare. Here we expand on a relatively new proposal for why these and other populations may not show major signs of these diseases. Chronic infections, especially helminths, may offer protection against heart disease and diabetes through direct and indirect pathways. As part of a strategy to insure their own survival and reproduction, helminths exert multiple cardio-protective effects on their host through their effects on immune function and blood lipid metabolism. Helminths consume blood lipids and glucose, alter lipid metabolism, and modulate immune function towards Th-2 polarization - which combined can lower blood cholesterol, reduce obesity, increase insulin sensitivity, decrease atheroma progression, and reduce likelihood of atherosclerotic plaque rupture. Traditional cardiometabolic risk factors, coupled with the mismatch between our evolved immune systems and modern, hygienic environments may interact in complex ways. In this review, we survey existing studies in the non-human animal and human literature, highlight unresolved questions and suggest future directions to explore the role of helminths in the etiology of cardio-metabolic disease.


ABSTRACT

OBJECTIVES: Using claims data from the Helsana Group, a large Swiss health insurance provider, we examined the association between statin use and the risk of cholecystectomy in a case-control analysis. METHODS: We identified 2,200 cholecystectomy cases between 2013 and 2014 and matched 4 controls to each case on age, sex, index date and canton. We categorised statin users into current or past users (last prescription ≤ 180 or > 180 days before the index date, respectively) and classified medication use by duration based on number of prescriptions before the index date. We applied conditional logistic regression analyses to calculate odds ratios (ORs) with 95% confidence intervals (CIs) and adjusted the analyses for history of cardiovascular diseases and for use of oestrogens, fibrates and other lipid-lowering agents. RESULTS: The adjusted OR (aOR) for cholecystectomy was 0.85 (95% CI: 0.74, 0.99) for current statin users compared to non-users. Long-term current statin use (5-19 prescriptions) was associated with a reduced OR (aOR 0.77, 95% CI: 0.65, 0.92). However, neither short-term current use nor past statin use affected the risk of cholecystectomy. CONCLUSIONS: The study supports the previously raised hypothesis that long-term statin use reduces the risk of cholecystectomy.


ABSTRACT

INTRODUCTION: Acute coronary syndromes (ACS) are one of the leading causes of death worldwide. Several landmark trials, followed by a widespread introduction of new agents, have significantly improved ACS outcomes in recent years. However, despite the use of contemporary therapy, a substantial number of ACS patients continue to suffer from cardiovascular events. AREAS COVERED: The aim of this review was to summarize available data on innovative drugs and pharmacological strategies that have potential to amend the current ACS therapy. We present the results of recent large clinical trials, as well as insights from ongoing phase III and phase IV studies, exploring the value of new strategies for the improvement of outcomes in ACS. EXPERT OPINION: More potent platelet inhibition, more profound lipid reduction and possibly anti-inflammatory action are considered to have potential to further reduce the rates of adverse cardiovascular and thrombotic events in ACS patients. "Hit fast, hit hard" approach regarding novel antiplatelet and lipid-lowering therapy seems attractive, but it has to be considered that these strategies may be associated with increased adverse events rate. Introduction of cangrelor and ezetimibe, and potentially future recognition of proprotein convertase subtilisin/kexin type 9 antibodies, are likely to alter the landscape of ACS pharmacotherapy.
[22] Ahmed AM. Inhibition of Inducible Nitric Oxide Synthase (iNOS) by Simvastatin Attenuates Cardiac Hypertrophy in Rats. Folia morphologica 2016.


ABSTRACT

The left ventricular hypertrophy (LVH) occurs in response to the hemodynamic overload in some physiological and pathological conditions. This study was designed to investigate the possible cardioprotective effect of simvastatin (SIM) treatment against isoproterenol (ISO)-induced LVH and the probable underlying mechanism in adult male Wistar rats. Animals were allocated into 4 groups. Rats of control group received normal saline orally for 30 days and intraperitoneally for the last 7 days. Rats of SIM group received SIM orally (10 mg/kg/day in saline) for 30 days. Rats of ISO group received normal saline orally for 30 days and ISO intraperitoneally (5 mg/kg) for the last 7 days to induce LVH. Rats of ISO/SIM group received SIM for 30 days and ISO intraperitoneally for the last 7 days. At the end of the experiment, all animals were sacrificed by cervical decapitation under anesthesia. Truncal blood was collected and serum was separated and used for biochemical assay. The heart was dissected and processed for histological and immunohistochemical studies. The results of the present study confirmed the ISO-induced myocardial lesions including significant increase of heart weight (HW), heart weight/body weight (HW/BW) ratio, LVH, interstitial myocardial fibrosis (increased collagen types I and III), inflammatory cellular infiltration, necrosis of cardiomyocytes, and increased expression of inducible nitric oxide synthase (iNOS) and thioredoxin in cardiomyocytes. These changes were accompanied by significant increase of serum levels of troponin-T, creatine phosphokinase-MB (CPK-MB), tumor necrosis factor-alpha (TNF-alpha) and interleukin-6 (IL-6). Co-administration of SIM to ISO-injected rats significantly reduced all these cardiac changes and serum biochemical markers in addition to marked depletion of iNOS and thioredoxin expression in cardiomyocytes. It is concluded that SIM co-administration attenuated ISO-induced cardiac lesions including LVH by inhibiting iNOS expression in cardiomyocytes.


ABSTRACT

Statin treatment reduces the risk of cardiovascular mortality in the general population, but it has little or no benefit in hemodialyzed patients (HD). This may reflect different underlying
pathophysiology of CVD in patients treated with HD, maybe involving the oxidative stress. Our aim was to assess the association of oxidized LDL (oxLDL), determined by Mercodia oxLDL ELISA Kit, with major adverse cardiac events (MACE) and all-cause mortality in HD patients based on the AURORA trial (rosuvastatin vs placebo), and patients not on HD from the LURIC study. We also assessed whether its decrease due to statin use improves these outcomes using Cox proportional hazard models. Baseline oxLDL level was 34.2 +/- 13.8 U/L in AURORA, and did not differ between treatment groups, and 74.6+/−28.1 U/L in LURIC. Lower baseline oxLDL levels were associated with higher HRs for outcomes, but not anymore after adjusting for apolipoprotein B level in AURORA and was not related to mortality in LURIC. OxLDL levels decreased by 30.9% between baseline and 3 months in the statin-treated group, and increased by 10.5% between 3 and 12 months. Nevertheless, oxLDL reduction was not significantly associated with adjusted HRs for MACE and for all-cause mortality. These results showed no association between oxLDL and MACE after adjustment on apolipoprotein B probably related to the technical limitation of the Mercodia method. Our results also showed no benefit for oxLDL reduction by rosuvastatin on outcomes. Future clinical trials are needed to define the relative CVD risks and benefits of other modalities of oxidative stress modification in this population.


**PM:** http://www.ncbi.nlm.nih.gov/pubmed/?term=27688698

**ABSTRACT**

BACKGROUND: Proton pump inhibitors (PPIs) might influence the metabolism of cholesterol and statins in the liver. AIM: The impact of PPIs on low-density lipoprotein cholesterol (LDL-C) levels in statin-treated patients. METHODS: Retrospective observational study including consecutive statin-treated individuals followed for >/=3 years in a university hospital lipid clinic. Demographic characteristics as well as clinical and laboratory data were recorded at baseline and the most recent visit. High, moderate and low-intensity statin therapy was defined according to the expected LDL-C reduction (>/=50%, 30-50%, and <30%, respectively). We compared the LDL-C reduction in subjects receiving statin + PPI with those on statin alone and assessed the overall effect of PPI administration on LDL-C lowering. RESULTS: Of 648 statin-treated subjects, 7% were also taking a PPI. There was no difference between PPI vs. non-PPI group regarding baseline characteristics and intensity of lipid-lowering therapy. Stepwise linear regression analysis showed that PPI use was significantly associated with LDL-C reduction (b =0.104, p =0.005) along with baseline LDL-C levels (b =0.482, p <0.001), treatment with ezetimibe (b =0.198, p <0.001), presence of diabetes (b =0.168, p <0.001), compliance with treatment (b =0.205, p <0.001), intensity of statin treatment (b =0.101, p =0.005) and cardiovascular risk (b =0.082, p =0.049). Subjects receiving statin + PPI had a higher LDL-C
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reduction by 6.4% compared with those taking a statin alone (fully adjusted p =0.005).
CONCLUSIONS: PPIs may modestly boost the statin-mediated LDL-C reduction. This effect should be confirmed by prospective clinical studies. Hippokratia 2015; 19 (4): 332-337.


ABSTRACT

OBJECTIVE: This study evaluated the possible pharmacokinetic interactions between rosuvastatin and fimasartan, an angiotensin II type 1 (AT1) receptor blocker (ARB), approved in Korea for the treatment of mild to moderate hypertension. METHODS: In this open-label, multiple-dose, two-period, single-sequence study, the enrolled subjects were randomized into two separate parts (A and B). In part A, subjects received 120 mg of fimasartan alone for 7 days during period I, and 120 mg fimasartan with 20 mg rosuvastatin for 7 days during period II. In Part B, subjects received rosuvastatin alone, followed by concomitant administration of fimasartan, with the same doses used as in Part A. There was a 7-day washout between periods I and II. Serial blood samples were collected for up to 48 hours for fimasartan and for up to 72 hours for rosuvastatin after the last dose of each period to determine the steady-state pharmacokinetics of both drugs. RESULTS: The mean Cmax,ss and AUCtau,ss values of fimasartan were 258.03 +/- 176.75 ng/mL and 746.52 +/- 273.49 ngxh/mL for fimasartan alone, and 289.40 +/- 231.44 ng/mL and 848.43 +/- 267.45 ngxh/mL for fimasartan and rosuvastatin coadministration, respectively (p-values for Cmax,ss and AUCtau,ss, 0.513 and 0.006, respectively). The mean Cmax,ss and AUCtau,ss values of rosuvastatin were 9.94 +/- 4.48 ng/mL and 85.29 +/- 36.25 ngxh/mL for rosuvastatin alone and 11.94 +/- 8.47 ng/mL and 77.33 +/- 38.71 ngxh/mL for fimasartan and rosuvastatin coadministration, respectively (p-values for Cmax,ss and AUCtau,ss, 0.066 and 0.009, respectively). The geometric mean ratio (GMR) and 90% confidence intervals (CI) for the Cmax,ss and AUCtau,ss of fimasartan (with/without rosuvastatin) were 1.109 (0.813 - 1.511) and 1.159 (1.061 - 1.265), respectively. The GMR and 90% CI for the Cmax,ss and AUCtau,ss of rosuvastatin (with/without fimasartan) were 1.090 (0.979 - 1.213) and 0.870 (0.804 - 0.940), respectively. CONCLUSIONS: These results suggest that fimasartan and rosuvastatin have no relevant pharmacokinetic drug-drug interactions. All treatments were well tolerated during this study, with no serious adverse effects..


ABSTRACT

Lipid nanoparticles and their multiple designs have been considered appealing nanocarrier systems. Bringing the benefits of these nanosystems together with conventional coating technology clearly results in product differentiation. This work aimed at developing an innovative solid dosage form for oral administration based on tableting nanostructured lipid carriers (NLC), coated with conventional polymer agents. NLC dispersions co-encapsulating olanzapine and simvastatin (Combo-NLC) were produced by high pressure homogenization, and evaluated in terms of scalability, drying procedure, tableting and performance from in vitro release, cytotoxicity and intestinal permeability stand points. Factorial design indicated that the scaling-up of the NLC production is clearly feasible. Spray-drying was the method selected to obtain dry particles, not only because it consists of a single step procedure, but also because it facilitates the coating process of NLC with different polymers. Modified NLC formulations with the polymers allowed obtaining distinct release mechanisms, comprising immediate, delayed and prolonged release. Sureteric:Combo-NLC provided a low cytotoxicity profile, along with a 11-fold OL/2-fold SV higher intestinal permeability, compared to those obtained with commercial tablets. Such findings can be ascribed to drug protection and control over release promoted by NLC, supporting them as a versatile platform able to be modified according to the intended needs.


ABSTRACT


ABSTRACT


ABSTRACT

Purpose: Retinopathy of prematurity (ROP) is a vision-threatening disease associated with abnormal retinal vascular development. Proteins from the insulin-like growth factor pathway are related to ROP. However, there is a paucity of research on the role of other proteins in ROP. The aim of this study was to identify plasma proteins related to clinically significant ROP.

Methods: We measured 1121 plasma proteins in the early neonatal period in infants at risk for ROP using an aptamer-based proteomic technology. The primary aim of the study was to compare plasma protein concentrations in infants who did (n = 12) and did not (n = 23) subsequently develop clinically significant ROP using logistic regression. As a secondary aim, we examined patterns in the proteins across categories of clinically significant, low-grade, and no ROP groups. Results: Lower levels of 16 proteins were associated with an increased risk of clinically significant ROP. In this group, superoxide dismutase (Mn), mitochondrial (MnSOD), and chordin-like protein 1 (CRDL1) were highly ranked. Other proteins in this group included: C-C motif chemokine 14 (HCC-1), prolactin, insulin-like growth factor-binding protein 7 (IGFBP-7), and eotaxin. Higher levels of 12 proteins were associated with a higher risk for ROP. Fibroblast growth factor 19 (FGF-19) was the top-ranked protein target followed by hepatocyte growth factor-like protein (MSP), luteinizing hormone (LH), cystatin M, plasminogen, and proprotein convertase subtilisin/kexin type 9 (PCSK9). We also noted different patterns in the trend of concentrations of proteins across the clinically significant, low-grade, and no ROP groups.

Conclusions: We discovered plasma proteins with novel associations with clinically significant ROP (MnSOD, CRDL1, PCSK9), proteins with links to established ROP signaling pathways (IGFBP-7), and proteins such as MnSOD that may be a target for future therapeutic interventions.


ABSTRACT

High-fat diet reduces the expression of the carcinoembryonic antigen-related cell adhesion molecule 1 (CEACAM1), a transmembrane glycoprotein that promotes insulin clearance and downregulates fatty acid synthase activity in the liver upon its phosphorylation by the insulin receptor. Because peroxisome proliferator-activated receptoralpha (PPARalpha) transcriptionally suppresses CEACAM1 expression, we herein examined whether high-fat downregulates CEACAM1 expression in a PPARalpha-dependent mechanism. By activating PPARalpha, the lipid-lowering drug fenofibrate reverses dyslipidemia and improves insulin sensitivity in type 2 diabetes in part by promoting fatty acid oxidation. Despite reducing glucose-stimulated insulin secretion, fenofibrate treatment does not result in insulin insufficiency. To examine whether this is mediated by a parallel decrease in CEACAM1-dependent hepatic insulin clearance pathways, we fed wild-type and Pparalpha null mice a
high-fat diet supplemented with either fenofibrate or Wy14,643, a selective PPARalpha agonist, and examined their effect on insulin metabolism and action. We demonstrated that the decrease in insulin secretion by fenofibrate and Wy14,643 is accompanied by reduction in insulin clearance in wild-type, but not Pparalpha null mice, thereby maintaining normoinsulinemia and insulin sensitivity despite continuous high-fat intake. Intact insulin secretion in L-CC1 mice with protected hepatic insulin clearance and CEACAM1 levels provide an in vivo evidence that insulin secretion responds to changes in insulin clearance to maintain physiologic insulin and glucose homeostasis. They also emphasize the relevant role of hepatic insulin extraction in regulating insulin sensitivity.


ABSTRACT

Familial hypercholesterolaemia (FH) is a major risk for premature coronary heart disease due to severe long-life exposure to high LDL levels. Accumulation of LDL in the vascular wall triggers atherosclerosis with activation of the innate immunity system. Here, we have investigated (i) gene expression of LDLR and LRPs in peripheral blood cells (PBLs) and in differentiated macrophages of young FH-patients; and (ii) whether macrophage from FH patients have a differential response when exposed to high levels of atherogenic LDL. PBLs in young heterozygous genetically characterized FH patients have higher expression of LRP5 and LRP6 than age-matched healthy controls or patients with secondary hypercholesterolaemia. LRP1 levels were similar among groups. In monocyte-derived macrophages (MACs), LRP5 and LRP1 transcript levels did not differ between FHs and controls in resting conditions, but when exposed to agLDL, FH-MAC showed a highly significant up-regulation of LRP5, while LRP1 was unaffected. PBL and MAC cells from FH patients had significantly lower LDLR expression than control cells, independently of the lipid-lowering therapy. Furthermore, exposure of FH-MAC to agLDL resulted in a reduced expression of CD163, scavenger receptor with anti-inflammatory and atheroprotective properties. In summary, our results show for first time that LRPs, active lipid-internalizing receptors, are up-regulated in innate immunity cells of young FH patients that have functional LDLR mutations. Additionally, their reduced CD163 expression indicates less atheroprotection. Both mechanisms may play a synergic effect on the onset of premature atherosclerosis in FH patients.
BACKGROUND: Heterozygous familial hypercholesterolemia (heFH) is a genetic disease causing high levels of low-density lipoprotein cholesterol (LDL-C). Although this population is at high cardiovascular (CV) risk, the risk is variable within patients depending on additional risk factors. CV disease risk groups have been defined by the Nouvelle Societe Francophone d'Atherosclerose (NSFA) and by the National Lipid Association recommendations. OBJECTIVES: The study aimed to describe a sample of French heFH patients, comparing patients at very high risk (VHR) and patients at high risk in terms of demographic and clinical characteristics as well as biological measurements and disease management. METHODS: Cross-sectional retrospective analysis on 734 patients hospitalized after 2005 in 5 academic centers. RESULTS: When considering NSFA classification, 550 (74.9%) patients belonged to the VHR group. Most patients in the VHR group presented more than 1 risk factor, the most prevalent ones being Lp(a) > 50 mg/dL and smoking. Patients in the VHR group were older (50.6 vs 45.0 years old, P = .0002), and presented a higher body mass index (25.5 kg/m(2) vs 23.3 kg/m(2), P < .0001). The proportion of patients with carotid arterial plaque was higher in the VHR group (59.8% vs 48.6%, P = .06). Total cholesterol (2.41 g/L on average) and LDL-C (1.65 g/L on average) were not found to be significantly different. Maximum level of lipid-lowering treatments were used in 34% of cases in the VHR group, significantly higher than 16% in the high-risk group (P = .001). Very similar results were found when using the National Lipid Association recommendations. CONCLUSION: This study provides a detailed description of French heFH patients according to their CV risk. Patients with very high CV risk had usually more advanced carotid plaques and were treated with heavier lipid-lowering drugs although their LDL-C level remained similar. This highlights the significant burden of this population.


ABSTRACT

The roundtable discussion in this issue will focus on the problems faced by young women with lipid disorders. This is often the source of confusion for the patient and physician because the myth continues that young women do not have complications of atherosclerosis as a result of elevated blood cholesterol. The essential role of women in bearing children during the early years of adulthood also produces difficult decisions because the mother and fetus are usually
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experiencing similar exposure to therapeutic regimens. We are joined in this discussion by Drs. Pamela Morris of the Medical University of South Carolina and Robert Wild of the University of Oklahoma Health Sciences Center. Dr Morris is an Internist, and Dr Wild is an Obstetrician and Gynecologist. Both are board certified in clinical lipidology and are actively publishing in this field. We have recorded this roundtable discussion during the National Lipid Association Scientific Sessions held in New Orleans during May 2016.


ABSTRACT
Xanthelasmas are superficial fat deposits around the eyelids commonly present in different hyperlipidemias and associated with increased cardiovascular risk. Statins or other lipid-lowering treatments do not usually modify them. We present the case of a middle-age man with severe high levels of LDL cholesterol from youth due to a genetically defined heterozygous familiar hypercholesterolemia (HeFH). He presented large xanthelasmas of both inner eyelids in spite of long term treatment with statins and ezetimibe that disappeared after treatment with alirocumab75 mg every 2 weeks for 26 months. His LDL cholesterol went from 164 mg/dL to 47 mg/dL with alirocumab. Xanthelasma regression was not previously reported with lipid-lowering drugs in HeFH. This case demonstrates that regression of skin lipid lesions can be achieved with very low LDL cholesterol concentrations.


ABSTRACT
Proprotein convertase subtilisin/kexin type 9 (PCSK9) plays an integral role in the degradation of low-density lipoprotein receptors (LDL-R), making it an intriguing target for emerging pharmacotherapy. Two PCSK9 inhibitors, alirocumab and evolocumab, have been approved and are available in the United States and European Union. However, much of the PCSK9 story remains to be told. The pipeline for additional pharmacotherapy options is rich with several compounds under development, using alternative strategies for inhibiting PCSK9. Perhaps, more intriguing is the interaction between PCSK9 and non-LDL-R targets, including mediators of inflammation and immunological processes, which remain under intense investigation. This review will discuss the currently available PCSK9 inhibitors, the development of novel
approaches to PCSK9 modulation, and the potential non-LDL-R-mediated effects of PCSK9 inhibition.


ABSTRACT

BACKGROUND: Metabolic syndrome (MetS) is associated with altered lipoprotein metabolism and impairment in the functionality of small, dense high-density lipoprotein (HDL) particles secondary to compositional alterations. OBJECTIVE: The objective of this study was to investigate the capacity of a lifestyle program to improve the composition and antioxidative function (AOX) of small dense HDL3c in MetS. METHODS: Patients with MetS (n = 33) not taking lipid-lowering drugs were recruited to follow a 12-week educational program to reduce caloric intake and to increase physical activity. HDL subfractions were preparatively isolated by isopycnic density-gradient ultracentrifugation. AOX of HDL3c was assessed as its capacity to inhibit low-density lipoprotein oxidation induced by an azoinitiator. RESULTS: AOX of HDL3c was significantly improved (mean reduction in the propagation rate of low-density lipoprotein oxidation by HDL3c, -6.8%, P = .03) and systemic oxidative stress, assessed as plasma levels of 8-isoprostanes, tended to decrease in normocholesterolemic MetS patients (low-density lipoprotein cholesterol [LDL-C] < 130 mg/dL) but not in patients with elevated LDL-C levels and in the whole study population. In both the whole study population and the normocholesterolemic subgroup, lifestyle intervention resulted in a significant degree of normalization of HDL3c composition, (enrichment in apolipoprotein A-I and cholesteryl esters, depletion in triglycerides), which was more pronounced at LDL-C < 130 mg/dL. CONCLUSION: In patients with MetS, a lifestyle program improves AOX of small, dense HDL in subjects with normal LDL-C levels. Correction of HDL composition, involving partial normalization of apoA-I content and core lipid composition, 2 central features of the lipid hydroperoxide-inactivating capacity of HDL, may account for this effect.


ABSTRACT
BACKGROUND: Familial hypercholesterolemia (FH) leads to premature coronary artery disease and aortic stenosis, with undertreated severe forms causing death at a young age. Lipoprotein apheresis (LA) is often required for lowering low-density lipoprotein cholesterol levels in severe FH. OBJECTIVES: The objective of this study was to present the first experiences with LA in Malaysia, between 2004 and 2014. METHODS: We retrospectively collected data from patient records to assess the effectiveness, adverse effects, patient quality of life, and costs associated with an LA service for genetically confirmed homozygous and heterozygous FH. RESULTS: We treated 13 women and 2 men aged 6 to 59 years, 10 with homozygous and 5 with heterozygous FH, all on maximally tolerated cholesterol-lowering drug therapy, for a total of 65 patient-years. Acute lowering of low-density lipoprotein cholesterol post apheresis was 56.3 +/- 7.2%, with time-averaged mean lowering of 34.9 +/- 13.9%. No patients experienced any cardiovascular events during the period of receiving LA. Patients receiving LA experienced few side effects and enjoyed reasonable quality of life, but inability to continue treatment was frequent because of cost. CONCLUSION: LA for severe FH can be delivered effectively in the short term in developing nations, but costs are a major barrier to sustaining this mode of treatment for this high-risk group of patients. New drug therapies for FH, such as the proprotein convertase subtilisin/kexin type 9 inhibitors, microsomal triglyceride transfer protein inhibitors, and apolipoprotein-B100 antisense oligonucleotides may allow improved care for these patients, but costs and long-term safety remain as issues to be addressed.


ABSTRACT

BACKGROUND: Familial hypercholesterolemia (FH) is an autosomal dominant genetic disease resulting in elevated serum low-density lipoprotein cholesterol (LDL-C) levels. Patients with FH have a very high lifetime risk of cardiovascular disease, but FH often goes unrecognized in clinical care. New treatments including PCSK9 inhibitors are now available for this population, and the use of the electronic record may be able to help identify potential patients for therapy. OBJECTIVES: The goal of this study was to determine the period prevalence of FH in a large ambulatory care population, including the homozygous form. In addition, use of cholesterol lowering therapy in individuals with FH was characterized. METHODS: A retrospective analysis was carried out among patients seen in an upper Midwest health care system between 2009 and 2012. In a search of electronic health records (EHR) and using the current National Lipid Association guidelines, FH patients (including homozygous cases) were identified based on age and highest LDL-C. Statin therapy was characterized according to current FH treatment guidelines. RESULTS: There were 391,166 individuals with available measures during the study
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timeframe. Of these, 841 were identified as having probable HeFH, representing a prevalence of 0.21% (about 1 in 470 patients) in this population. HoFH was identified as probable in 6 patients. For the total group, two-thirds of FH patients were on a statin, but only half were treated adequately. The remaining one-third of FH patients were not on statin therapy, with only 27% of those not on statin therapy having a documented statin intolerance.

CONCLUSIONS: FH is often underdiagnosed and suboptimally treated in clinical practice. Statin therapy in this population rarely went beyond low-moderate doses. These findings support EHR-based population health efforts to initiate an FH cascade-screening model and ensure higher quality care for this high-risk population and identify those who may benefit from advanced therapy.


ABSTRACT

Lipoprotein(a) [Lp(a)] is an apolipoprotein(a) molecule bound to 1 apolipoprotein B-100. Elevated levels of Lp(a) are thought to be an independent risk factor for atherosclerosis and to promote thrombosis through incompletely understood mechanisms. We report a 34-year-old man with an ischemic stroke in the setting of an extremely high Lp(a) level-212 mg/dL. He developed severe carotid artery stenosis over a 6-year period and had thrombus formation post-carotid endarterectomy. To our knowledge, this case is unique because the Lp(a) is the highest reported level in a patient without renal disease. Moreover, this is the first reported case of the youngest individual with a stroke presumably related to development of carotid plaque over a 6-year period. The thrombotic complication after endarterectomy may have been related to the prothrombotic properties of Lp(a). Of note, the Lp(a) level did not respond to atorvastatin but did decrease 15% after aspirin 325 mg was added although his Lp(a) levels were variable, and it is not clear that this was cause and effect. This case highlights the need to better understand the relation between Lp(a) and vascular disease and the need to screen family members for elevated Lp(a). We also review treatment options to lower Lp(a) and ongoing clinical trials of newer lipid-lowering drugs that can also lower Lp(a).


ABSTRACT

BACKGROUND: The efficacy and safety of atorvastatin in children/adolescents aged 10-17 years with heterozygous familial hypercholesterolemia (HeFH) have been demonstrated in trials of up to 1 year in duration. However, the efficacy/safety of >1 year use of atorvastatin in children/adolescents with HeFH, including children from 6 years of age, has not been assessed. OBJECTIVE: To characterize the efficacy and safety of atorvastatin over 3 years and to assess the impact on growth and development in children aged 6-15 years with HeFH. METHODS: A total of 272 subjects aged 6-15 years with HeFH and low-density lipoprotein cholesterol (LDL-C) >/=4.0 mmol/L (154 mg/dL) were enrolled in a 3-year study (NCT00827606). Subjects were initiated on atorvastatin (5 mg or 10 mg) with doses increased to up to 80 mg based on LDL-C levels. RESULTS: Mean percentage reductions from baseline in LDL-C at 36 months/early termination were 43.8% for subjects at Tanner stage (TS) 1 and 39.9% for TS >/=2. There was no evidence of variations in the lipid-lowering efficacy of atorvastatin between the TS groups analyzed (1 vs >/=2) or in subjects aged <10 vs >/=10 years, and the treatment had no adverse effect on growth or maturation. Atorvastatin had a favorable safety and tolerability profile, and only 6 (2.2%) subjects discontinued because of adverse events. CONCLUSIONS: Atorvastatin over 3 years was efficacious, had no impact on growth/maturation, and was well tolerated in children and adolescents with HeFH aged 6-15 years.


ABSTRACT

BACKGROUND: Little is known about prevalence, awareness, and control of familial hypercholesterolemia (FH) in the United States. OBJECTIVE: To address these knowledge gaps, we developed an ePhenotyping algorithm for rapid identification of FH in electronic health records (EHRs) and deployed it in the Screening Employees And Residents in the Community for Hypercholesterolemia (SEARCH) study. METHODS: We queried a database of 131,000 individuals seen between 1993 and 2014 in primary care practice to identify 5992 (mean age 52 +/- 13 years, 42% men) patients with low-density lipoprotein cholesterol (LDL-C) >/=190 mg/dL, triglycerides <400 mg/dL and without secondary causes of hyperlipidemia. RESULTS: Our EHR-based algorithm ascertained the Dutch Lipid Clinic Network criteria for FH using structured data sets and natural language processing for family history and presence of FH stigmata on physical examination. Blinded expert review revealed positive and negative predictive values for the SEARCH algorithm at 94% and 97%, respectively. The algorithm identified 32 definite and 391 probable cases with an overall FH prevalence of 0.32% (1:310). Only 55% of the FH cases had a diagnosis code relevant to FH. Mean LDL-C at the time of FH ascertainment was 237 mg/dL; at follow-up, 70% (298 of 423) of patients were on lipid-lowering treatment with 80% achieving an
LDL-C ≤100 mg/dL. Of treated FH patients with premature CHD, only 22% (48 of 221) achieved an LDL-C ≤70 mg/dL. CONCLUSIONS: In a primary care setting, we found the prevalence of FH to be 1:310 with low awareness and control. Further studies are needed to assess whether automated detection of FH in EHR improves patient outcomes.


**ABSTRACT**

BACKGROUND: Ezetimibe added to statin therapy further reduces LDL-C and clinical atherosclerotic cardiovascular disease compared to statin alone. However, the number of effective and safe oral agents for patients not at LDL-C goal is limited. In prior clinical trials, gemcabene reduced LDL-C and was generally well-tolerated in nearly 900 patients treated for up to 12 weeks. OBJECTIVE: To evaluate the LDL-C lowering and safety of gemcabene as add-on to stable statin therapy in hypercholesterolemic patients. METHODS: This was an 8-week, double-blind, placebo-controlled, randomized, phase 2 study in men and postmenopausal women ≥18 and ≤65 years of age with LDL-C ≥130 mg/dL (3.4 mmol/L) while on low-intensity to high-intensity stable statin (the majority on moderate intensity) therapy. Sixty-six patients were randomized 1:1:1 to gemcabene 300 mg, 900 mg, or placebo QD. RESULTS: Gemcabene 300 mg and 900 mg produced a mean percent change in LDL-C of -23.4 +/- 4.7% (P = .005) and -27.7 +/- 4.3% (P < .001), respectively, vs -6.2 +/- 4.3% for placebo. The median percent change in CRP was -26.1% (P = .196) and -53.9% (P < .001) for gemcabene 300 mg and 900 mg, respectively, vs -11.1% for placebo. Gemcabene 300 mg and 900 mg were well-tolerated with no significant difference in AEs compared to placebo. CONCLUSIONS: Gemcabene as add-on to stable statin therapy demonstrated additional dose-dependent and statistically significant reductions in LDL-C of >20% and CRP >40% compared to placebo. The results support gemcabene-continued development for patients requiring LDL-C lowering beyond that provided by background statin therapy.


**ABSTRACT**

BACKGROUND: TA-8995 is a potent inhibitor of cholesteryl ester transfer protein (CETP) with beneficial effects on lipids and lipoproteins. The effect of TA-8995 on cholesterol efflux capacity
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(CEC), a measure of high-density lipoprotein (HDL) function, and HDL subparticle distribution is largely unknown. OBJECTIVE: To assess the effect of the CETP inhibitor TA-8995 on ABCA1- and non-ABCA1-driven CEC and on HDL particle distribution. METHODS: Total, non-ABCA1-, and ABCA1-specific CEC from J774 cells and HDL subclass distribution assessed by two-dimensional gel electrophoresis were measured at baseline and after 12-week treatment in 187 mild-dyslipidemic patients randomized to placebo, 1 mg, 5 mg, 10 mg TA-8995, or 10 mg TA-8995 combined with 10 mg rosuvastatin (NCT01970215). RESULTS: Compared with placebo, total, non-ABCA1-, and ABCA1-specific CEC were increased dose dependently by up to 38%, 72%, and 28%, respectively, in patients randomized to 10 mg of TA-8995. PreBeta-1 HDL, the primary acceptor for ABCA1-driven cholesterol efflux, was increased by 36%. This increase in preBeta-1 HDL correlated significantly with the total and the ABCA1-driven CEC increase, whereas the high-density lipoprotein cholesterol (HDL-C) increase did not. CONCLUSION: TA-8995 dose dependently increased not only total and non-ABCA1-specific CEC but also ABCA1-specific CEC and preBeta-1 HDL particle levels. These findings suggest that TA-8995 not only increases HDL-C levels but also promotes functional properties of HDL particles. This CETP inhibitor-driven preBeta-1 HDL increase is an important predictor of both ABCA1 and total CEC increase, independent of HDL-C increase. Whether these changes in HDL particle composition and functionality have a beneficial effect on cardiovascular outcome requires formal testing in a cardiovascular outcome trial.


ABSTRACT


ABSTRACT

BACKGROUND: Low-density lipoprotein particle (LDL-P) has recently been found to be a stronger predictor of cardiovascular disease (CVD) than LDL-cholesterol (LDL-C). OBJECTIVES: Whether LDL-P is associated with subclinical atherosclerosis, independent of LDL-C, as well as other lipid measures has not been fully examined. We aimed to analyze LDL-P associations with measures of subclinical atherosclerosis. METHODS: We examined 870 Japanese men randomly
selected from Kusatsu City, Shiga, Japan, aged 40-79 years from 2006-2008, free of clinical CVD and not using lipid-lowering medication. Cross-sectional associations of lipid measures with carotid intima-media thickness (cIMT) and coronary artery calcification (CAC; >0 Agatston score) were examined. RESULTS: LDL-P was significantly positively associated with cIMT and maintained this association after adjustments for LDL-C and other lipid measures. Although these lipid measures were positively associated with cIMT, model adjustment for LDL-P removed any significant relationships. Higher LDL-P was associated with a significantly higher odds ratio of CAC and further adjustment for LDL-C did not affect this relationship. In contrast, the LDL-C association with CAC was no longer significant after adjustment for LDL-P. Other lipid measures attenuated associations of LDL-P with CAC. Likewise, associations of these measures with CAC were attenuated when model adjustments for LDL-P were made. CONCLUSIONS: In a community-based sample of Japanese men, free of clinical CVD, LDL-P was a robust marker for subclinical atherosclerosis, independent of LDL-C and other lipid measures. Associations of LDL-C and other lipid measures with either cIMT or CAC were generally not independent of LDL-P.


**ABSTRACT**

BACKGROUND: Cardiovascular disease (CVD) begins early in life and is associated with both the number of risk factors present and length of exposure to these risk factors including hyperlipidemia. OBJECTIVES: The clinical benefit of intensive lipid therapy over 25 years was investigated in the Familial Atherosclerosis Treatment Study-Observational Study. METHODS: Of 175 coronary artery disease subjects with mean low-density lipoprotein cholesterol (LDL-C) of 191 mg/dL and mean age of 50 years, who completed the randomized and placebo-controlled Familial Atherosclerosis Treatment Study, 100 chose receiving lipid management by their physicians (usual care [UC]) and 75 elected to receive an intensive treatment [IT] for lipid management with lovastatin (40 mg/d), niacin (2.5 g/d), and colestipol (20 g/d) from 1989 to 2004, followed by double therapy with simvastatin (40-80 mg/d) and niacin from 2005 to 2006 and by triple therapy of ezetimibe 10 mg and simvastatin 40 to 80 mg/d plus niacin during 2007 to 2012. Deaths from CVD, non-CVD, and any cause were compared between UC and IT using Cox proportional hazards model. RESULTS: UC and IT groups were similar in risk factors with the exception that IT had more severe coronary artery disease. Mean LDL-C levels were 167 mg/dL from 1988 to 2004, 97 from 2005 to 2006, and 96 from 2007 to 2012 in surviving subjects receiving UC. IT lowered LDL-C to 119, 97, and 83 mg/dL in the 3 periods, respectively. Compared with UC, IT significantly reduced total mortality (11.1 vs 26.3 per 1000 person years [PY], hazard ratio [HR] = 0.45, 95% confidence interval [CI]: 0.26-0.77, P = .003) and CVD
mortality (10.6 vs 27.7 per 1000 PY, HR = 0.34, 95% CI: 0.15-0.80, P = .009). The non-CVD mortality was also reduced but was not of statistical significance (6.8 vs 12.7 per 1000 PY, HR = 0.55, 95% CI: 0.27-1.14, P = .11). CONCLUSIONS: Long-term intensive lipid therapy significantly reduced total and cardiovascular mortality in Familial Atherosclerosis Treatment Study-Observational Study. These results support the importance of lifetime risk management to improve long-term outcome.


ABSTRACT

Evolocumab binds PCSK9, increasing low-density lipoprotein cholesterol (LDL-C) receptors and lowering LDL-C. Target-mediated evolocumab elimination is attributable to PCSK9 binding. As circulating PCSK9 and LDL-C levels are primarily regulated by the liver, we compared evolocumab pharmacokinetics, pharmacodynamics, and safety in individuals with and without hepatic impairment. Open-label, parallel-group study evaluating the pharmacokinetics of evolocumab in hepatic-impaired (Child-Pugh Class A or B) or healthy adults. Participants were classified as having no, mild, or moderate hepatic impairment (n = 8/group), and received a single 140-mg evolocumab dose. Assessments of unbound evolocumab and PCSK9 were made pre- and post-dose. Adverse events were monitored throughout the study. No significant association was observed between baseline PCSK9 and increasing level of hepatic impairment. No difference in extent and time-course of PCSK9 or LDL-C reduction was observed, despite an apparent decrease in mean unbound evolocumab exposure with increasing hepatic impairment (Jonckheere-Terpstra trend test; maximum serum concentration: P = .18; area under the curve: P = .09). Maximum reductions were observed in moderately impaired subjects versus healthy individuals: mean maximum serum concentration, -34%; mean area under the concentration-time curve (AUC), -47%. On average, unbound PCSK9 serum concentrations fell by >80% at 4 hours after a single evolocumab dose. Mean (95% confidence interval) maximum LDL-C reductions in the healthy, mild, and moderate groups were -57% (-64%, -48%), -70% (-75%, -63%), and -53% (-61%, -43%), respectively. No safety risks were identified. These results support evolocumab use without dose adjustment in patients with active liver disease and mild or moderate hepatic impairment. This article is protected by copyright. All rights reserved.


ABSTRACT

Coronary heart disease is the main cause of mortality in patients with rheumatoid arthritis (RA), a disease known to be associated with accelerated atherosclerosis. The role of inflammation and immunity in atherosclerotic process offers possible explanations for the increased cardiovascular risk in patients with RA. The immune response to citrullinated peptides has been extensively studied in RA; antibodies directed to citrullinated peptides are now a cornerstone for RA diagnosis. However, few studies have investigated the response to citrullinated peptides and the development of atherosclerotic plaque. Antibodies to carbamylated proteins can be detected before the clinical onset of RA, suggesting a potential predictive role for these antibodies; on the other hand, carbamylation of lipoproteins has been described in patients with cardiovascular disease. This review examines the role of citrullination and carbamylation, two post-translational protein modifications that appear to be involved in the pathogenesis of both RA and atherosclerosis, expanding the similarities between these two diseases. Further investigation on the role of the immune response to modified proteins may contribute to a better comprehension of cardiovascular disease in patients with RA.


ABSTRACT

Human epidemiologic and genetic evidence using the Mendelian randomization approach in large-scale studies now strongly support that elevated lipoprotein(a) (Lp(a)) is a causal risk factor for cardiovascular disease, that is, for myocardial infarction, atherosclerotic stenosis, and aortic valve stenosis. The Mendelian randomization approach used to infer causality is generally not affected by confounding and reverse causation, the major problems of observational epidemiology. This approach is particularly valuable to study causality of Lp(a), as single genetic variants exist that explain 27-28% of all variation in plasma Lp(a). The most important genetic variant likely is the kringle IV type 2(KIV-2) copy number variant, as the apolipoprotein(a)(apo(a)) product of this variant influences fibrinolysis and thereby thrombosis, as opposed to the Lp(a) particle per se. We speculate that the physiological role of KIV-2 in Lp(a) could be through wound healing during childbirth, infections and injury, a role that in addition could lead to more blood clots promoting stenosis of arteries and the aortic valve, and myocardial infarction. Randomized placebo-controlled trials of Lp(a) reduction in individuals with very high concentrations to reduce cardiovascular disease are awaited. Recent genetic evidence document elevated Lp(a) as a cause of myocardial infarction, atherosclerotic stenosis, and aortic valve stenosis.


ABSTRACT

OBJECTIVE: To study the effect of hypertension on lipid levels in patients with type 2 diabetes mellitus. METHODS: This prospective, observational study was conducted at 1 Mountain Medical Battalion, Bagh, Azad Kashmir, from May 2012 to April 2015, and comprised adult type 2 diabetics. Patients already on lipid-lowering agents, hypothyroidism, nephrotic syndrome, unwilling patients and those who had serum triglycerides>4.5mmol/l were excluded. Blood pressure was measured twice in sitting position. Amongst hypertensive patients, blood pressure <140/90mmHg reflected good control. Serum total cholesterol, triglyceride and high-density lipoproteins were measured using enzymatic calorimetric method. Friedewald equation was used to calculate low-density lipoprotein levels. Subjects were divided into three groups: those without hypertension; those with hypertension but good blood pressure control; and hypertensives with poor blood pressure control. SPSS 20 was used for data analysis. RESULTS: Of the 322 patients, 129(40.06%) were women and 193(59.94%) were men. The overall mean age was 51.42+/10.93 years. Hypertension was seen in 144(44.72%) patients. Blood pressure was well controlled in 46(31.94%) hypertensive patients. Among patients without hypertension and those with good or poorly controlled blood pressure, the mean values for serum total cholesterol were 181.08+/32.05, 186.87+/39.00, 185.33+/35.55 mg/dl, triglycerides were 172.57+/38.53, 187.61+/41.42, 183.19+/34.34 mg/dl, high-density lipoproteins were 40.54+/12.36, 37.06+/8.80, 40.15+/12.35 mg/dl and low-density lipoproteins were 105.79+/39.73, 110.81+/31.66, 106.56+/35.16 mg/dl. The number of patients with abnormalities of total cholesterol was 44(26.83%), 13(28.26%), 33(29.46%), triglycerides was 83(50.61%), 30(65.22%), 66(58.93%), high-density lipoproteins was 119(72.56%), 39(84.78%), 93(83.04%) and low-density lipoproteins was 90(54.88%), 29(63.04%) and 59(52.68%), respectively. CONCLUSIONS: Hypertension did not worsen diabetic dyslipidaemia.


ABSTRACT

OBJECTIVE: To evaluate the anti-dyslipidaemic effects of pioglitazone in diet-induced non-diabetic hyperlipidaemic rats and to compare them with gemfibrozil. METHODS: This comparative animal study was conducted at the Postgraduate Medical Institute, Lahore, Pakistan, from July to September 2011, and comprised Sprague Dawley albino rats divided into
three equal groups. Initially all three groups were given high-lipid diet containing cholesterol 1.5g, coconut oil 8ml and sodium cholate 1.0g per 100g of rat chow to induce hyperlipidaemia. From 4th to 8th week, Group A (control) was given 0.5ml of distilled water, Group B was given pioglitazone 10mg/kg body weight, and Group C was given gemfibrozil 10mg/kg body weight as single morning dose by oral route for a period of 04 weeks in addition to hyperlipidaemic diet. Serum lipid levels were estimated at zero, 4th and 8th week. Blood sugar level was estimated at 4th week to exclude diabetic rats. SPSS 17 was used for data analysis. RESULTS: Of the 27 rats, each group had 9(33.33%) rats. At the start of the study, the mean weight was 254.44+-14.67g in Group A, 255.11+-14.66g in Group B and 252.22+-14.18g in Group C. It was 352.22+-16.79g, 332.22+-17.19 and 328.11+-12.92 at the 8th week. The mean total cholesterol at 0 week was 71.4+-4.88 mg/dl in Group A, 71.9+-7.03 in Group B and 73.4+-5.27 in Group C. At the 8th week, the values were 161.8+-9.2 mg/dl, 100.8+-7.0 and 95.0+-6.6. The mean low-density lipoproteincholesterol levels in the respective groups were 30.2+-4.9mg/dl, 32.2+-7.0 and 33.6+-6.0 at 0 week; 77.8+-8.4, 85.1+-15.3 and 86.9+-6.3 at the 4th week and 113.9+-10.1, 60.4+-9.2 (p<0.001) and 54.8+-6.6 (p<0.001) at the 8th week. The mean serum high-density lipoprotein cholesterol at the 8th week was 11.4+-1.7 mg/dl, 19.7+-2.4 (p<0.001) and 19.2+-2.5 (p<0.001) in the three groups, respectively. CONCLUSIONS: Treatment with pioglitazone improved serum lipid profile of non-diabetic hyperlipidaemic rats equivalent to that of gemfibrozil.


ABSTRACT

BACKGROUND: Previous studies have suggested that people with obesity showed elevated serum levels of leptin as well as lipid dysfunction and proprotein convertase subtilisin/kexin type 9 (PCSK9) played an important role in the regulation of lipid metabolism recently. The aim of this study was to determine if leptin participated in regulating the uptake of low-density lipoproteins (LDL) in hepatocytes via PCSK9. METHODS: HepG2 cells were treated with human recombinant leptin. The impact of leptin on cellular low density lipoprotein receptor (LDLR) and PCSK9 protein levels was determined by Western blot. Dil-LDL uptake assay was performed to examine the LDLR function. Specific small interfering RNAs (siRNAs) were used to interfere the expressions of target proteins. RESULTS: The expression of LDLR and LDL uptake could be significantly down-regulated by leptin treatment while the expressions of PCSK9 and hepatocyte nuclear factor 1alpha (HNF1alpha) were enhanced in HepG2 cells. Furthermore, inhibition of PCSK9 or HNF1alpha expression by siRNAs rescued the reduction of LDLR expression and LDL uptake by leptin. We found that leptin activated the p38 mitogen-activated
protein kinase (p38MAPK) signaling pathway. Moreover, the changes of the expressions of HNF1alpha, PCSK9, LDLR, and LDL uptake induced by leptin could be blocked by p38MAPK inhibitor (SB203580). Additionally, leptin attenuated the up-regulation of LDLR caused by atorvastatin in HepG2 cells. CONCLUSIONS: These findings indicated firstly that leptin reduced LDLR levels in hepatocyte via PCSK9 pathway, suggesting that PCSK9 might be a alternative target for dyslipidemia in the obesity.


ABSTRACT
OBJECTIVE: Diabetes mellitus (DM) is associated with peripheral arterial disease (PAD) and leads to worse clinical outcome compared with patients without DM. The objective of this study was to determine the impact of DM on iliofemoral artery plaque characteristics and to examine secondary clinical outcomes in patients with DM and PAD undergoing surgical revascularization. METHODS: We analyzed 198 patients with and 453 patients without DM from the Athero-Express biobank, a prospective ongoing biobank study, who underwent endarterectomy of the femoral or iliac artery between 2002 and 2013. Seven histologic plaque characteristics (calcification, collagen, lipid core, intraplaque hemorrhage, macrophages, microvessels, and smooth muscle cells) and secondary clinical outcome were compared. Composite outcome consisted of any of the following secondary manifestations of cardiovascular disease: stroke, myocardial infarction, cardiovascular death, or peripheral intervention. In addition, target vessel revascularization (TVR) was examined. The follow-up period was standardized at 3 years after the procedure. RESULTS: Patients with DM were more likely to have calcified plaques compared with patients without DM (odds ratio, 2.11; 95% confidence interval, 1.43-3.12; P < .01). No other plaque characteristic differed significantly between the two groups. In total, 112 (57.1%) patients with DM and 198 (45.1%) patients without DM reached a composite end point during follow-up, of whom 21 (10.7%) and 27 (6.2%) died of cardiovascular causes, respectively. DM was an independent predictor of composite cardiovascular events (hazard ratio, 1.36; 95% confidence interval, 1.020-1.801; P = .01) during follow-up. No difference in the incidence of TVR was observed between patients with and without DM (31.5% and 30%, respectively; difference in survival time, P = .86) or in longer duration of DM with composite event-free survival (difference in survival time, P = .57). CONCLUSIONS: Patients with DM who undergo surgical revascularization for PAD with the use of thromboendarterectomy or remote endarterectomy have a more calcified atherosclerotic plaque and an increased incidence in composite cardiovascular events but no increase in TVR.
ABSTRACT

OBJECTIVES: The aim of this study was to assess the difference in indication for statin therapy by European Society of Cardiology (ESC) versus American Heart Association/American College of Cardiology (AHA/ACC) guidelines and to quantify the potential additional role of coronary artery calcification (CAC) score over updated guidelines in a primary prevention cohort.

BACKGROUND: Recently, ESC and AHA/ACC updated the guidelines regarding statin therapy in primary prevention. METHODS: In 3,745 subjects (59 +/- 8 years of age, 47% men) from the population based longitudinal Heinz Nixdorf Recall cohort study without cardiovascular disease or lipid-lowering therapy at baseline CAC score was assessed between 2000 and 2003. Subjects remained unaware of their initial CAC score. Statin indication was determined according to 2012 ESC and 2013 AHA/ACC guidelines based on subjects' individual baseline characteristics.

RESULTS: The frequency of statin recommendation was lower according to ESC compared to AHA/ACC guidelines (34% vs. 56%; p < 0.0001), whereas low CAC score (<100) was common in subjects with statin indication by both guidelines (59% for ESC, 62% for AHA/ACC). During 10.4 +/- 2.0 years of follow-up, 131 myocardial infarctions occurred. For ESC recommendations, CAC score differentiated risk for subjects without (1.0 [95% confidence interval (CI): 0.4 to 1.5] vs. 6.5 [95% CI: 4.1 to 8.9] coronary events per 1,000 person-years for CAC 0 vs. >/=100) and with statin indication (2.6 [95% CI: 0.6 to 4.7] vs. 9.9 [95% CI: 7.3 to 12.5] per 1,000 person-years for CAC 0 vs. >/=100). Likewise, CAC score stratified proportions experiencing events subjects with statin indication according to AHA/ACC (2.7 [95% CI: 1.1 to 4.2] vs. 9.1 [95% CI: 7.0 to 11.0] per 1,000 person-years for CAC 0 vs. >/=100), whereas event rate in subjects without statin indication was low (1.1 [95% CI: 0.65 to 1.68] per 1,000 person-years). CONCLUSIONS: Current ESC and AHA/ACC guidelines lead to markedly different recommendation regarding statin therapy in a German primary prevention cohort. Quantification of CAC score in addition to the guidelines improves stratification between subjects at high versus low risk for coronary events, indicating that CAC scoring may help to match intensified risk factor modification to atherosclerotic plaque burden as well as actual risk while avoiding therapy in subjects with low coronary atherosclerosis that have low 10-year event rate.


ABSTRACT

IMPORTANCE: The comparative clinical benefit of nonstatin therapies that reduce low-density lipoprotein cholesterol (LDL-C) remains uncertain. OBJECTIVE: To evaluate the association between lowering LDL-C and relative cardiovascular risk reduction across different statin and nonstatin therapies. DATA SOURCES AND STUDY SELECTION: The MEDLINE and EMBASE databases were searched (1966-July 2016). The key inclusion criteria were that the study was a randomized clinical trial and the reported clinical outcomes included myocardial infarction (MI). Studies were excluded if the duration was less than 6 months or had fewer than 50 clinical events. Studies of 9 different types of LDL-C reduction approaches were included. DATA EXTRACTION AND SYNTHESIS: Two authors independently extracted and entered data into standardized data sheets and data were analyzed using meta-regression. MAIN OUTCOMES AND MEASURES: The relative risk (RR) of major vascular events (a composite of cardiovascular death, acute MI or other acute coronary syndrome, coronary revascularization, or stroke) associated with the absolute reduction in LDL-C level; 5-year rate of major coronary events (coronary death or MI) associated with achieved LDL-C level. RESULTS: A total of 312175 participants (mean age, 62 years; 24% women; mean baseline LDL-C level of 3.16 mmol/L [122.3 mg/dL]) from 49 trials with 39645 major vascular events were included. The RR for major vascular events per 1-mmol/L (38.7-mg/dL) reduction in LDL-C level was 0.77 (95% CI, 0.71-0.84; P < .001) for statins and 0.75 (95% CI, 0.66-0.86; P = .002) for established nonstatin interventions that work primarily via upregulation of LDL receptor expression (ie, diet, bile acid sequestrants, ileal bypass, and ezetimibe) (between-group difference, P = .72). For these 5 therapies combined, the RR was 0.77 (95% CI, 0.75-0.79, P < .001) for major vascular events per 1-mmol/L reduction in LDL-C level. For other interventions, the observed RRs vs the expected RRs based on the degree of LDL-C reduction in the trials were 0.94 (95% CI, 0.89-0.99) vs 0.91 (95% CI, 0.90-0.92) for niacin (P = .24); 0.88 (95% CI, 0.83-0.92) vs 0.94 (95% CI, 0.93-0.94) for fibrates (P = .02), which was lower than expected (ie, greater risk reduction); 1.01 (95% CI, 0.94-1.09) vs 0.90 (95% CI, 0.89-0.91) for cholesteryl ester transfer protein inhibitors (P = .002), which was higher than expected (ie, less risk reduction); and 0.49 (95% CI, 0.34-0.71) vs 0.61 (95% CI, 0.58-0.65) for proprotein convertase subtilisin/kexin type 9 inhibitors (P = .25). The achieved absolute LDL-C level was significantly associated with the absolute rate of major coronary events (11301 events, including coronary death or MI) for primary prevention trials (1.5% lower event rate [95% CI, 0.5%-2.6%] per each 1-mmol/L lower LDL-C level; P = .008) and secondary prevention trials (4.6% lower event rate [95% CI, 2.9%-6.4%] per each 1-mmol/L lower LDL-C level; P < .001). CONCLUSIONS AND RELEVANCE: In this meta-regression analysis, the use of statin and nonstatin therapies that act via upregulation of LDL receptor expression to reduce LDL-C were associated with similar RRs of major vascular events per change in LDL-C. Lower achieved LDL-C levels were associated with lower rates of major coronary events.
Several studies reported the association between total plasma phytosterol concentrations and the parenteral nutrition-associated cholestasis (PNAC). To date, no data are available on phytosterol esterification in animals and in humans during parenteral nutrition (PN). We measured free and esterified sterols (cholesterol, campesterol, stigmasterol, and sitosterol) plasma concentrations during PN in 16 preterm infants (500-1249 g of birth weight; Preterm-PN), in 11 term infants (Term-PN) and in 12 adults (Adult-PN). Gas chromatography-mass spectrometry was used for measurements. Plasma concentrations of free cholesterol (Free-CHO), free phytosterols (Free-PHY) and esterified phytosterols (Ester-PHY) were not different among the three PN groups. Esterified cholesterol (Ester-CHO) was statistically lower in Preterm-PN than Adult-PN. Preterm-PN had significantly higher Free-CHO/Ester-CHO and Free-PHY/Ester-PHY ratios than Adult-PN (Free-CHO/Ester-CHO: 1.1 +/- 0.7 vs. 0.6 +/- 0.2; Free-PHY/Ester-PHY: 4.1 +/- 2.6 vs. 1.3 +/- 0.8; *P < 0.05). Free-CHO/Ester-CHO and Free-PHY/Ester-PHY ratios of Term-PN (Free-CHO/Ester-CHO: 1.1 +/- 0.4; Free-PHY/Ester-PHY: 2.9 +/- 1.7) were not different from either Preterm-PN or from Adult-PN. Plasma Free-CHO/Ester-CHO and Free-PHY/Ester-PHY were unchanged after 24 h on fat-free PN both in Preterm-PN and in Adult-PN. Free-PHY/Ester-PHY did not correlate with phytosterol intake in Preterm-PN. Free-PHY/Ester-PHY of Preterm-PN was positively correlated with the Free-CHO/Ester-CHO and negatively correlated with gestational age and birth weight. In conclusion, PHY were esterified to a lesser extent than CHO in all study groups; the esterification was markedly decreased in Preterm-PN compared to Adult-PN. The clinical consequences of these findings warrant further investigations.

ABSTRACT

BACKGROUND: Type 2 diabetes has become a global epidemic disease. Atorvastatin has become a cornerstone in the prevention and treatment of atherosclerosis. However, increasing evidence showed that statins can dose-dependently increase the risk of diabetes mellitus. The mechanism is not clear. OBJECTIVE: The Ras complex pathway (Ras/Raf/extracellular signal-regulated kinase [ERK]/cAMP response element-binding protein [CREB]) is the major pathway that regulates the gene transcription. Except for the inhibition of cholesterol synthesis by inhibiting the 3-hydroxy-3-methyl glutaryl coenzyme A (HMG-COA) reductase, statins can also
downregulate the phosphorylation of a series of downstream substrates including the key proteins of the Ras complex pathway, therefore may inhibit the insulin syntheses in pancreatic beta cells. In our study, we investigated the inhibitory effect and the underlying mechanism of atorvastatin on insulin synthesis in rat islets. METHODS: Islets were isolated from Wistar rats and cultured in Roswell Park Memorial Institute (RPMI)-1640 medium. The insulin content in the medium was measured by radioimmunoassay before and after the treatment of 50 μM atorvastatin. Effect of atorvastatin on the expression of insulin message Ribonucleic acid (mRNA) in pancreatic islet beta cells was also detected using quantitative real-time polymerase chain reaction. Western blotting was used to explore the possible role of the Ras complex pathway (Ras/Raf/ERK/CREB) in atorvastatin-inhibited insulin synthesis. The effects of atorvastatin on the binding of nuclear transcription factor p-CREB with CRE in INS-1 cells were examined via chromatin immunoprecipitation assay. RESULTS: Compared with the control group, the insulin level decreased by 27.1% at 24 hours after atorvastatin treatment. Atorvastatin inhibited insulin synthesis by decreasing insulin mRNA expression of pancreatic islet beta cells. The activities of Ras, Raf-1, and p-CREB in the Ras complex pathway were inhibited by 50 μM atorvastatin in INS-1 cells in vitro. Moreover, 50 μM atorvastatin reduced the binding of p-CREB with deoxyribonucleic acid (DNA) in INS-1 cells in vitro. CONCLUSION: Atorvastatin inhibits insulin synthesis in beta cells by inhibiting the activation of the Ras complex pathway.

[58] Pan BL, Ma RM. [Correlation of serum omentin-1 and chemerin with gestational diabetes mellitus]. Nan fang yi ke da xue xue bao = Journal of Southern Medical University 2016; 36:1231-1236.


ABSTRACT

OBJECTIVE: To investigate the relationship of serum omentin-1 and chemerin with gestational diabetes mellitus (GDM). METHODS: Serum levels of omentin-1 chemerin, glycolipids biochemical index, inflammation index, fasting insulin (FINS), and insulin resistance indexes (HOMA-IR) were determined in 85 women with GDM and 85 pregnant women with normal glucose tolerance (NGT). RESULTS: BMI, FPG, hs-CRP, blood lipids, blood glucose, FINS, HOMA-IR and serum chemerin level were all significantly higher while serum omentin-1 significantly lower in GDM group than in NGT group (P<0.05). In both groups, serum omentin-1 level was significantly lower and serum chemerin was significantly higher in obese subjects than in the non-obese subjects (P<0.05). Obesity before delivery and/or HOMA-IR >/=2 was associated with a significantly decreased serum omentin-1 level; serum chemerin increased significantly in obese women before delivery but was not associated with HOMA-IR. Serum omentin-1 level was positively correlated with HDL but inversely with BMI (at pregnancy and before delivery), FPG, FINS and HOMA-IR; Chemerin was positively correlated with TC, TG, hs-CRP and FPG;
serum omentin-1 and chemerin levels were not significant correlated (P=0.301). In women with GDM, BMI at pregnancy, TG, FPG, and FINS were all independent factors affecting serum omentin-1; TG, LDL, and hs-CRP were independent factors affecting serum chemerin.

CONCLUSION: An decreased serum omentin-1 can be indicative of glucose and lipid metabolism disorder and insulin resistance, and an increased serum chemerin level indicates hyperlipidemia and chronic inflammation in pregnant women. Both of the adipokines are closed associated with GDM and probably participate in the occurrence and development of GDM.


PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=27682807

ABSTRACT

BACKGROUND: Mitochondrial dysfunction is involved in neurodegenerative diseases, such as Huntington's disease (HD). 3-Nitropropionic acid (3-NP) is a mitochondrial toxin that specifically inhibits complex II of the electron transport chain (ETC) and is used to generate an experimental model of HD. OBJECTIVE: To study the effect of fish liver oil (FO) over the mitochondrial dysfunction induced via partial ETC inhibition by 3-NP. METHODS: This study was performed in rats and consisted of two phases: (i) administration of increasing doses of 3-NP and (ii) administration of FO for 14 days before to 3-NP. The rats' exploratory activity; complex I, II, III, and IV activities; and rearing behavior were observed. Additionally, the number of TUNEL-positive cells and various mitochondrial parameters, including oxygen consumption, transmembrane potential, adenosine triphosphate synthesis, and ETC activity, were measured. RESULTS: We observed that FO exerted a protective effect against the 3-NP-induced toxicity, although complex II inhibition still occurred. Instead, this effect was related to strengthened mitochondrial complex III and IV activities. DISCUSSION: Our results show that FO exerts a beneficial prophylactic effect against mitochondrial damage. Elucidating the mechanisms linking the effects of FO with its prevention of neurodegeneration could be the key to developing recommendations for FO consumption in neurological pathologies.


ABSTRACT

OBJECTIVE: To determine the effect of (1) an oral fat load and (2) pro-protein convertase subtilisin/kexin type (PCSK) 9 loss-of-function (LOF) variant status on the ability of peripheral
blood mononuclear cells (PBMC) to inhibit human adipogenesis. METHODS: PBMC from subjects with one or more PCSK9 LOF variants versus non-variant controls were compared in the fasting state and after an oral fat load. RESULTS: Fasting triglyceride (TG) levels were lower in the LOF variant versus non-variant group but rose to the same level after the oral fat load. Conditioned medium from PBMC was obtained in fasting (PBMC-CM-F) and 4-h postprandial (PBMC-CM-PP) states. PBMC-CM-PP from non-variant controls inhibited adipogenesis of human preadipocytes more than did PBMC-CM-F. In contrast, PBMC-CM-F or -PP from PCSK9 LOF variant subjects had no effect on adipogenesis. After the oral fat load, PBMC from PCSK9 LOF variant subjects showed significant increases in mRNA levels of interleukin-1beta, tumor necrosis factor-alpha, sterol regulatory element binding protein-1c, CD36, and monocyte chemoattractant protein-1 (MCP-1), only MCP-1 mRNA levels increased in PBMC from non-variant controls. CONCLUSIONS: The absence of anti-adipogenic action of PBMC from PCSK9 LOF variant subjects points to a novel role for PCSK9 in PBMC-adipose cell interactions.


ABSTRACT

As the aging of the world's population is becoming increasingly serious, dementia-related diseases have become a hot topic in public health research. In recent years, human epidemiological studies have focused on lipid metabolism disorders and dementia. The efficacy of phytosterol intake as a cholesterol-lowering agent has been demonstrated. Phytosterols directly serve as ligands of the nuclear receptors, peroxisome proliferator-activated receptors (PPARs), activating Sirtuin 1 (SIRT-1), which are involved in the regulation of lipid metabolism and the pathogenesis of dementia. Moreover, phytosterols mediate cell and membrane cholesterol efflux or beta amyloid (Abeta) metabolism, which have preventative and therapeutic effects on dementia. Additionally, incorporation of plant sterols in lipid rafts can effectively reduce dietary fat and alter the dietary composition of fiber, fat and cholesterol to regulate appetite and calories. Overall, the objectives of this review are to explore whether phytosterols are a potentially effective target for the prevention of dementia and to discuss a possible molecular mechanism by which phytosterols play a role in the pathogenesis of dementia via the PPARs-SIRT-1 pathway.


ABSTRACT

The prevalence of asthma has increased in recent decades, which may be related to higher dietary intake of (n-6) polyunsaturated fatty acids (PUFA) and lower intake of (n-3) PUFA, e.g., those contained in fish oil. The objective of this study was to determine if dietary PUFA enrichment decreases mucus production or the inflammatory response associated with ovalbumin (OVA)-induced allergic lung inflammation. Mice (n = 10/group) were fed control, 20% fish oil, or 20% corn oil enriched diets for a total of 12 weeks. At 8 and 10 weeks, mice were given an intraperitoneal injection of saline (10 control-fed mice) or OVA (30 remaining mice). Once at 10 weeks and on 3 consecutive days during week 12, mice were challenged by nebulizing with saline or OVA. Mice were euthanized 24 hours after the last challenge and blood was collected for plasma FA analysis. Bronchoalveolar lavage (BAL) fluid was collected to determine cell composition and Th2-type cytokine (IL-4, IL-13) concentrations. Periodic acid-Schiff (PAS) + mucus-producing cells and CD45+ inflammatory cell infiltrates in lung tissue were quantified using morphometric analysis. Relative abundance of mRNA for mucin (Muc4, Muc5ac, and Muc5b) and Th2-type cytokine (IL-4, IL-5, and IL-13) genes were compared with ss-actin by qPCR. Supplementation with either corn oil or fish oil effectively altered plasma FA profiles towards more (n-6) FA or (n-3) FA, respectively (P < 0.0001). Sensitization and challenge with OVA increased the proportion of neutrophils, lymphocytes, and eosinophils, and decreased the proportion of macrophages and concentrations of IL-13 in BAL fluid; increased the percentage of PAS+ mucus-producing cells and CD45+ inflammatory cell infiltrates in lung tissue; and increased gene expression of mucins (Muc4, Muc5ac, and Muc5b) and Th2-type cytokines (IL-5 and IL-13) in lung tissue of control-fed mice. Dietary PUFA reversed the increase in PAS+ mucus-producing cells (P = 0.003). In addition, dietary enrichment with fish oil attenuated the percentage of CD45+ inflammatory cell infiltrates in lung tissue, and increased Muc4 and Muc 5b gene expression compared with OVA-sensitized and challenged control mice. In conclusion, dietary enrichment with either (n-3) or (n-6) PUFA decreased mucus production in lung tissues of OVA-sensitized and challenged mice. More specifically, enrichment with dietary (n-3) PUFA decreased CD45+ inflammatory cell infiltrates, thus inducing potentially beneficial changes in lung tissue of OVA-sensitized and challenged mice.


ABSTRACT

OBJECTIVE: IL-15 is an inflammatory cytokine secreted by many cell types. IL-15 is also produced during physical exercise by skeletal muscle and has been reported to reduce weight gain in mice. Contrarily, our findings on IL-15 knockout (KO) mice indicate that IL-15 promotes...
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obesity. The aim of this study is to investigate the mechanisms underlying the pro-obesity role of IL-15 in adipose tissues. METHODS: Control and IL-15 KO mice were maintained on high fat diet (HFD) or normal control diet. After 16 weeks, body weight, adipose tissue and skeletal mass, serum lipid levels and gene/protein expression in the adipose tissues were evaluated. The effect of IL-15 on thermogenesis and oxygen consumption was also studied in primary cultures of adipocytes differentiated from mouse preadipocyte and human stem cells. RESULTS: Our results show that IL-15 deficiency prevents diet-induced weight gain and accumulation of lipids in visceral and subcutaneous white and brown adipose tissues. Gene expression analysis also revealed elevated expression of genes associated with adaptive thermogenesis in the brown and subcutaneous adipose tissues of IL-15 KO mice. Accordingly, oxygen consumption was increased in the brown adipocytes from IL-15 KO mice. In addition, IL-15 KO mice showed decreased expression of pro-inflammatory mediators in their adipose tissues. CONCLUSIONS: Absence of IL-15 results in decreased accumulation of fat in the white adipose tissues and increased lipid utilization via adaptive thermogenesis. IL-15 also promotes inflammation in adipose tissues that could sustain chronic inflammation leading to obesity-associated metabolic syndrome.


ABSTRACT

OBJECTIVES: The metabolic syndrome (MetS) is a cluster of metabolic abnormalities and cardiovascular risk factors that are highly heritable and polygenic. We investigated the association of allelic variants of three candidate genes, rs1799883-FABP2, rs1501299-ADIPOQ and rs5065-ANP with MetS and its components, individually and in combination, using a genetic risk score. METHODS: A cross-sectional study was conducted in 462 Afro-Caribbeans subjects without cardiovascular complications or lipid-lowering medications. Cardiovascular risk factors and MetS components (NCEP-ATP III criteria) were recorded. The 3 SNPs were genotyped. The genetic risk score was calculated by summing the number of risk alleles at each locus. Logistic regressions were used. RESULTS: Fifty-eight participants (12.6%) were diabetics and 116 (25.1%) had a MetS. In a dominant model, rs1799883 was associated with hypertriglyceridemia (OR 2.22; P = 0.014) and hypertriglyceridemic waist (HTGW), (P = 0.014) but not significantly with overweight (P = 0.049), abdominal obesity (P = 0.033) and MetS (P = 0.068). In a dominant model, the OR of MetS and HTGW for rs1501299 were 1.80 (P = 0.028) and 2.19 (P = 0.040) respectively. In a recessive model, the OR of hypertriglyceridemia for rs5065 was 1.94 (P = 0.075). The genetic risk score was significantly associated with MetS. Subjects carrying 4-5 risk alleles (18.8%) had a nearly 2.5-fold-increased risk of MetS compared to those carrying 0-1 risk
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allele (24.3%): OR 2.31; P = 0.025. CONCLUSIONS: This study supports the association of FABP2, ANP and ADIPOQ gene variants with MetS or its components in Afro-Caribbeans and suggests a cumulative genetic influence of theses variants on this syndrome and a potential effect on lipid metabolism.


ABSTRACT

Statins improve pulmonary vascular remodeling and right ventricular hypertrophy in animal models of pulmonary arterial hypertension (PAH). However, clinical trials assessing the efficacy of statins in patients with PAH have reported mixed results. In this systematic review and meta-analysis, we assess the efficacy of statins in patients with PAH. We included randomized controlled clinical trials (RCTs) that evaluated the efficacy of statins in patients with PAH. Primary outcomes were mortality and change in 6-minute walk distance (6MWD). Data are presented as odds ratio (OR) and weighted mean difference (WMD), with 95% confidence intervals (CIs), for binary and continuous variables, respectively. We included 4 RCTs of high quality. The mean age of participants was 42 +/- 13 years, and 70% were women. The statins used were simvastatin at 40-80 mg in two trials, atorvastatin 10 mg in one trial, and rosuvastatin 10 mg in the other. In the pooled-data analysis, there was no statistically significant improvement in mortality (OR: 0.75 [95% CI: 0.32-1.74]), 6MWD (WMD: -9.27 [95% CI: -27.73 to 9.20]), or cardiac index (WMD: 0.11 [95% CI: -0.04 to 0.27]) with statin therapy when compared to placebo. There was no difference in adverse events leading to withdrawal of therapy between statin and placebo groups. These data suggest that statins are not beneficial in the treatment of PAH. There is a need for large, well-conducted clinical trials assessing the effects of statins in patients with PAH. Future trials should include homogeneous patient populations and should be long-term, event-driven trials with combined morbidity and mortality end points.


ABSTRACT

Pulmonary arterial hypertension (PAH) is a multifactorial disease characterized by interplay of many cellular, molecular, and genetic events that lead to excessive proliferation of pulmonary cells, including smooth muscle and endothelial cells; inflammation; and extracellular matrix
remodeling. Abnormal vascular changes and structural remodeling associated with PAH culminate in vasoconstriction and obstruction of pulmonary arteries, contributing to increased pulmonary vascular resistance, pulmonary hypertension, and right ventricular failure. The complex molecular mechanisms involved in the pathobiology of PAH are the limiting factors in the development of potential therapeutic interventions for PAH. Over the years, our group and others have demonstrated the critical implication of lipids in the pathogenesis of PAH. This review specifically focuses on the current understanding of the role of oxidized lipids, lipid metabolism, peroxidation, and oxidative stress in the progression of PAH. This review also discusses the relevance of apolipoprotein A-I mimetic peptides and microRNA-193, which are known to regulate the levels of oxidized lipids, as potential therapeutics in PAH.


ABSTRACT

BACKGROUND AND PURPOSE: Carotid plaque rupture is a major cause of stroke. Key issue for risk stratification is early identification of rupture-prone plaques. A noninvasive technique, compound ultrasound strain imaging, was developed providing high-resolution radial deformation/strain images of atherosclerotic plaques. This study aims at in vivo validation of compound ultrasound strain imaging in patients by relating the measured strains to typical features of vulnerable plaques derived from histology after carotid endarterectomy.

MATERIALS AND METHODS: Strains were measured in 34 severely stenotic (>70%) carotid arteries at the culprit lesion site within 48 hours before carotid endarterectomy. In all cases, the lumen-wall boundary was identifiable on B-mode ultrasound, and the imaged cross-section did not move out of the imaging plane from systole to diastole. After endarterectomy, the plaques were processed using a validated histology analysis technique. RESULTS: Locally elevated strain values were observed in regions containing predominantly components related to plaque vulnerability, whereas lower values were observed in fibrous, collagen-rich plaques. The median strain of the inner plaque layer (1 mm thickness) was significantly higher (P<0.01) for (fibro)atheromatous (n=20, strain=0.27%) than that for fibrous plaques (n=14, strain=−0.75%). Also, a significantly larger area percentage of the inner layer revealed strains above 0.5% for (fibro)atheromatous (45.30%) compared with fibrous plaques (31.59%). (Fibro)atheromatous plaques were detected with a sensitivity, specificity, positive predictive value, and negative predictive value of 75%, 86%, 88%, and 71%, respectively. Strain did not significantly correlate with fibrous cap thickness, smooth muscle cell, or macrophage concentration. CONCLUSIONS: Compound ultrasound strain imaging allows differentiating (fibro)atheromatous from fibrous carotid artery plaques.


ABSTRACT

AIM: The actual occurrence of spontaneous plaque rupture in mice has been a matter of debate. We report on an in vivo observation of the actual event of possible plaque disruption in a living ApoE(-/-) mouse. METHODS AND RESULTS: During live contrast-enhanced ultrasonography of a 50-week-old ApoE(-/-) male mouse, symptoms suggesting plaque disruption in the brachiocephalic artery were observed. Histological analysis confirmed the presence of advanced atherosclerotic lesions with dissections and intraplaque hemorrhage in the affected brachiocephalic trunk, pointing towards plaque rupture as the cause of the observed event. However, we did not detect a luminal thrombus or cap rupture, which is a key criterion for plaque rupture in human atherosclerosis. CONCLUSION: This study reports the real-time occurrence of a possible plaque rupture in a living ApoE(-/-) mouse.