Sirtuin 6 (SIRT6) is a member of the sirtuin family NAD+-dependent deacetylases with multiple roles in controlling organism homeostasis, lifespan, and diseases. Due to its complex and opposite functional roles, this sirtuin is considered a two-edged sword in health and disease. Indeed, SIRT6 improves longevity, similarly to the founding yeast member, silent information regulator-2 (Sir2), and modulates genome stability, telomere integrity, transcription, and DNA repair. Its deficiency is associated with chronic inflammation, diabetes, cardiac hypertrophy, obesity, liver dysfunction, muscle/adipocyte disorders, and cancer. Besides, pieces of evidence showed that SIRT6 is a promoter of specific oncogenic pathways, thus disclosing its dual role regarding cancer development. Collectively, these findings suggest that multiple mechanisms, to date not entirely known, underlie the intriguing roles of SIRT6. Here we provide an overview of the current molecular mechanisms through which SIRT6 controls cancer and heart diseases, and describe its recent implications in the atherosclerotic plaque development.

Aims: Familial hypercholesterolemia (FH) is a common genetic disorder causing accelerated atherosclerosis and premature cardiovascular disease. The aim of this study was to examine the prevalence and prognostic significance of possible FH in patients with myocardial infarction (MI). METHODS AND RESULTS: By individual-level linkage of data from the Eastern Danish Heart Registry and national administrative registries, a study population of patients referred for coronary angiography due to MI was selected. The study population was divided into "unlikely FH" and "possible FH" based on the Dutch Lipid Clinic Network criteria, which included a plasma low-density lipoprotein cholesterol (LDL-C) and age for onset of cardiac disease. A score of >/=3 points was used as the cutpoint between the 2 groups. Among the study population of 13,174 MI patients, 1,281 (9.7%) had possible FH. These patients were younger (59.1 vs 65.7 years, P </= .0001), had similar levels of comorbidities, and were treated more aggressively with cholesterol-lowering drugs compared with patients with unlikely FH. During a median of 3.3 years of follow-up, the unadjusted and adjusted event rates of recurrent MI were higher in patients with possible FH compared with unlikely FH (16% vs 11%, adjusted hazard ratio 1.28, 95% CI 1.09-1.51, P = .003.). Differences in adjusted all-cause mortality were not statistically significant (17% vs 23%, adjusted hazard ratio 0.89 [0.74-1.04], P = .1). CONCLUSION: We found that MI patients with possible FH have higher risk of recurrent MI but similar risk of mortality compared with unlikely FH patients. Further studies on secondary prevention are warranted.
Leptin has potent effects on lipid metabolism in a number of peripheral tissues. In liver, an acute leptin infusion (~120-min) stimulates hepatic fatty acid oxidation (~30%) and reduces triglycerides (TG, ~40%), effects that are dependent on PI3-kinase (PI3K) activity. In the current study we addressed the hypothesis that leptin actions on liver-resident immune cells are required for these metabolic effects. Myeloid cell-specific deletion (My) of the leptin receptor (ObR) in mice or depletion of liver Kupffer cells (KC) in rats in vivo prevented the acute effects of leptin on liver lipid metabolism, while the metabolic effects of leptin were maintained in mice lacking ObR in hepatocytes (HepObR). Notably, liver TG were elevated in both lean and obese MYObR, but the degree of obesity and insulin resistance induced by a high fat diet was similar to control mice. In isolated primary hepatocytes (HEP), leptin had no effects on HEP lipid metabolism and only weakly stimulated PI3K. However, the co-culture of KC with HEP restored leptin action on HEP fatty acid metabolism and stimulation of HEP PI3K. Notably, leptin stimulated the release from KC of a number of cytokines. However, the exposure of HEP to these cytokines individually (GM-CSF, IL-1alpha, IL-1beta, IL-6, IL-10, IL-18) or in combination had no effects on HEP lipid metabolism. Together, these data demonstrate a role for liver mononuclear cells in the regulation of liver lipid metabolism by leptin.


ABSTRACT
Atorvastatin (ATV) has an important pro-survival role in cardiomyocytes after acute myocardial infarction (AMI). The objectives of this study were to: 1) determine whether ATV could affect autophagy of cardiomyocytes via the AMP-activated protein kinase (AMPK)/mammalian target of rapamycin (mTOR) pathway, and 2) investigate the balance between autophagy and apoptosis pathways. Male Wistar rats (n = 100) were randomly divided into sham, control, ATV, Compound C, and ATV+ Compound C groups. In this AMI model, drug treatments were administered for 1 week before induction of MI by surgical ligation, and measurements were taken 1 and 4 weeks after AMI induction. Transthoracic echocardiography showed that the ejection fraction in the ATV group increased by 11.7% +/- 6.83% over the control group 4 weeks after AMI. The fibrosis, infarcted area, and inflammatory level were determined by pathological and histological studies; these were found to be decreased substantially with ATV treatment (P<0.05). The expression of apoptotic, autophagic, and AMPK pathway proteins was detected by immunohistochemical staining and western blotting, while expression of their corresponding genes was measured with real-time polymerase chain reaction (PCR). ATV treatment increased AMPK/mTOR activity and the expression of autophagic protein LC3 in infarcted myocardium (P<0.05). The treatment also inhibited induction of pro-apoptotic protein Bax. AMPK inhibitor Compound C reversed these beneficial effects. In conclusion, ATV improves survival of cardiomyocytes and decreases alterations in morphology and function of infarcted hearts by inducing autophagy and inhibiting apoptosis through the activation of AMPK/mTOR pathway.
BACKGROUND AND AIMS: Observational studies show a peak incidence of cardiovascular events after major surgery. For example, the risk of myocardial infarction increases 25-fold early after hip replacement. The acuteness of this increased risk suggests abrupt enhancement in plaque vulnerability, which may be related to intra-plaque inflammation, thinner fibrous cap and/or necrotic core expansion. We hypothesized that acute systemic inflammation following major orthopedic surgery induces such changes. METHODS: ApoE-/- mice were fed a western diet for 10 weeks. Thereafter, half the mice underwent mid-shaft femur osteotomy followed by realignment with an intramedullary K-wire, to mimic major orthopedic surgery. Mice were sacrificed 5 or 15 days post-surgery (n = 22) or post-saline injection (n = 13). Serum amyloid A (SAA) was measured as a marker of systemic inflammation. Paraffin embedded slides of the aortic root were stained to measure total plaque area and to quantify fibrosis, calcification, necrotic core, and inflammatory cells. RESULTS: Surgery mice showed a pronounced elevation of serum amyloid A (SAA) and developed increased plaque and necrotic core area already at 5 days, which reached significance at 15 days (p = 0.019; p = 0.004 for plaque and necrotic core, respectively). Macrophage and lymphocyte density significantly decreased in the surgery group compared to the control group at 15 days (p = 0.037; p = 0.024, respectively). The density of neutrophils and mast cells remained unchanged. CONCLUSIONS: Major orthopedic surgery in ApoE-/- mice triggers a systemic inflammatory response. Atherosclerotic plaque area is


ABSTRACT

OBJECTIVE: The calcium composition of atherosclerotic plaque is thought to be associated with increased risk for cardiovascular events, but whether plaque calcium itself is predictive of worsening clinical outcomes remains highly controversial. Inflammation is likely a key mediator of vascular calcification, but immune signaling mechanisms that promote this process are minimally understood. APPROACH AND RESULTS: Here, we identify Rac2 as a major inflammatory regulator of signaling that directs plaque osteogenesis. In experimental atherogenesis, Rac2 prevented progressive calcification through its suppression of Rac1-dependent macrophage interleukin-1beta (IL-1beta) expression, which in turn is a key driver of vascular smooth muscle cell calcium deposition by its ability to promote osteogenic transcriptional programs. Calcified coronary arteries from patients revealed decreased Rac2 expression but increased IL-1beta expression, and high coronary calcium burden in patients with coronary artery disease was associated with significantly increased serum IL-1beta levels. Moreover, we found that elevated IL-1beta was an independent predictor of cardiovascular death in those subjects with high coronary calcium burden. CONCLUSIONS: Overall, these studies identify a novel Rac2-mediated regulation of macrophage IL-1beta expression, which has the potential to serve as a powerful biomarker and therapeutic target for atherosclerosis.


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enlarged after surgery mainly due to an increase of the necrotic core. The role of intra-plaque inflammation in this response to surgical injury remains to be fully elucidated.

**PM:** http://www.ncbi.nlm.nih.gov/pubmed/?term=27821353

**ABSTRACT**

BACKGROUND AND AIMS: Peripheral arterial disease (PAD) is a common manifestation of atherosclerosis with an increasing incidence worldwide. The disease is still associated with high morbidity and mortality risks. Previous research in carotid arteries indicates that atherosclerotic plaque characteristics have stabilized over time in patients considered for surgery. It is currently unknown whether this time-dependent stabilization occurs in ilio-femoral arteries as well. Our objective was to analyze whether local ilio-femoral atherosclerotic plaque characteristics have changed over time. METHODS: 497 patients within the Athero-Express biobank who underwent primary endarterectomy of the iliac or femoral artery between 2002 and 2013 were analyzed. We investigated six histological plaque characteristics: calcification, collagen, fat content, intraplaque haemorrhage, macrophages and smooth muscle cells. RESULTS: Over the course of 10 years, we observed a lower percentage of all plaque characteristics that are considered indicators of a vulnerable plaque, such as: plaques with a large lipid core from 37.9% to 14.9% and plaques with intraplaque haemorrhage from 69.0% to 34.8% when the two-year cohorts 2003-2004 and 2011-2012 were compared, respectively. Multivariable analyses showed that time-dependent changes occurred independently of changing procedural and patient characteristics. CONCLUSIONS: In this cohort of peripheral arterial disease patients undergoing primary endarterectomy, we observed a time dependent shift of plaque characteristics towards a less lipid rich lesion with less intraplaque haemorrhage. These findings indicate research in cardiovascular disease would benefit from contemporary patient characteristics and plaque specimens to optimize translational potential.

**PM:** http://www.ncbi.nlm.nih.gov/pubmed/?term=27816810

**ABSTRACT**

BACKGROUND AND AIMS: Atherosclerosis is a chronic inflammatory disease of medium and large vessels and is typically characterized by the predominant accumulation of low-density lipoprotein (LDL)-cholesterol inside macrophages that reside in the vessel walls. Previous studies clearly demonstrated an association specifically between the oxidized type of LDL (oxLDL) and atherosclerotic lesion formation. Further observations revealed that these atherosclerotic lesions displayed enlarged, lipid-loaded lysosomes. By increasing natural antibodies against oxLDL, pneumococcal vaccination has been shown to reduce atherosclerosis in LDL receptor knockout (Ldlr/-) mice. Relevantly, loss of the lysosomal membrane protein Niemann-Pick Type C1 (NPC1) led to lysosomal accumulation of various lipids and promoted atherosclerosis. Yet, the importance of lysosomal oxLDL accumulation inside macrophages, compared to non-modified LDL, in atherosclerosis has never been established. METHODS: By
transplanting NPC1 bone marrow into lethally irradiated Ldlr-/ mice, a hematopoietic mouse model for lysosomal cholesterol accumulation was created. Through injections with heat-inactivated pneumococci, we aimed to demonstrate the specific contribution of lysosomal oxLDL accumulation inside macrophages in atherosclerosis development. RESULTS: While there were no differences in plaque morphology, a reduction in plaque size and plaque inflammation was found in immunized NPC1mut-transplanted mice, compared to non-immunized NPC1mut-transplanted mice. CONCLUSIONS: Lysosomal oxLDL accumulation within macrophages contributes to murine atherosclerosis. Future intervention strategies should focus specifically on preventing oxLDL, unlike non-modified LDL, from being internalized into lysosomes. Such an intervention can have an additive effect to current existing treatments against atherosclerosis.


ABSTRACT

BACKGROUND AND AIMS: Homozygous familial hypercholesterolemia (FH) is a rare but serious, inherited disorder of lipid metabolism characterized by very high total and LDL cholesterol levels from birth. It presents as cutaneous and tendon xanthomas since childhood, with or without cardiac involvement. FH is commonly caused by mutations in three genes, i.e. LDL receptor (LDLR), apolipoprotein B (ApoB) and PCSK9. We aimed to determine the spectrum of mutations in cases of homozygous FH in Asian Indians and evaluate if there was any similarity to the mutations observed in Caucasians. METHODS: Sixteen homozygous FH subjects from eleven families were analyzed for mutations by Sanger sequencing. Large rearrangements in LDLR gene were evaluated by multiplex ligation probe dependent amplification (MLPA) technique. RESULTS: Ten mutations were observed in LDLR gene, of which four mutations were novel. No mutation was detected in ApoB gene and common PCSK9 mutation (p.D374Y). Fourteen cases had homozygous mutations; one had compound heterozygous mutation, while no mutation was detected in one clinically homozygous case. We report an interesting "Triple hit" case with features of homozygous FH. CONCLUSIONS: The spectrum of mutations in the Asian Indian population is quite heterogeneous. Of the mutations identified, 40% were novel. No mutation was observed in exons 3, 9 and 14 of LDLR gene, which are considered to be hot spots in studies done on Asian Indians in South Africa. Early detection followed by aggressive therapy, and cascade screening of extended families has been initiated to reduce the morbidity and mortality in these patients.


ABSTRACT

BACKGROUND AND AIMS: Focal adhesions (FA) play an important role in the tissue remodeling and in the maintenance of tissue integrity and homeostasis. Talin and vinculin proteins are among the major constituents of FAs contributing to cellular well-being and intercellular communication. METHODS: Microarray analysis (MA) and qRT-PCR low-density array were implemented to analyze talin-1, talin-2, meta-vinculin and vinculin gene expression in
circulating blood and arterial plaque. RESULTS: All analyzed genes were significantly and consistently downregulated in plaques (carotid, abdominal aortic and femoral regions) compared to left internal thoracic artery (LITA) control. The use of LITA samples as controls for arterial plaque samples was validated using immunohistochemistry by comparing LITA samples with healthy arterial samples from a cadaver. Even though the differences in expression levels between stable and unstable plaques were not statistically significant, we observed further negative tendency in the expression in unstable atherosclerotic plaques. The confocal tissue imaging revealed gradient of talin-1 expression in plaque with reduction close to the vessel lumen. Similar gradient was observed for talin-2 expression in LITA controls but was not detected in plaques. This suggests that impaired tissue mechanostability affects the tissue remodeling and healing capabilities leading to development of unstable plaques.

CONCLUSIONS: The central role of talin and vinculin in cell adhesions suggests that the disintegration of the tissue in atherosclerosis could be partially driven by downregulation of these genes, leading to loosening of cell-ECM interactions and remodeling of the tissue.


ABSTRACT
We evaluated the effects of simvastatin and antiandrogen enzalutamide on growth and androgen signaling in androgen-sensitive LNCaP and VCaP prostate cancer cells. Simvastatin alone abolished androgen-induced growth in both cell lines but decreased androgen receptor (AR) and prostate-specific antigen protein expression only in LNCaP, indicating that statin-induced growth inhibition is beyond AR transcriptional activity in VCaP. Combination of simvastatin and enzalutamide exerted additive growth inhibition in both cell lines accompanied with strong induction of autophagy in LNCaP. The data provide new insight into statins' effects on androgen signaling and their proposed role in enhancing androgen deprivation therapy in prostate cancer.


ABSTRACT
High-density lipoprotein (HDL) possesses multiple biological activities; small, dense HDL3c particles displaying distinct lipidomic composition exert potent antiatherogenic activities which can be compromised in dyslipidemic, hyperglycemic insulin-resistant states. However, it remains indeterminate (i) whether such functional HDL deficiency is related to altered HDL composition, and (ii) whether it originates from atherogenic dyslipidemia, dysglycemia, or both. In the present work we analyzed compositional characteristics of HDL subpopulations and functional activity of small, dense HDL3c particles in treatment-naive patients with well-controlled (n=10) and poorly-controlled (n=8) type 2 diabetes (T2D) and in normolipidemic age- and sex-matched controls (n=11). Our data reveal that patients with both well- and poorly-
controlled T2D displayed dyslipidemia and low-grade inflammation associated with altered HDL composition. Such compositional alterations in small, dense HDL subfractions were specifically correlated with plasma HbA1c levels. Further analysis using a lipidomic approach revealed that small, dense HDL3c particles from T2D patients with poor glycemic control displayed additional modifications of their chemical composition. In parallel, antioxidative activity of HDL3c towards oxidation of low-density lipoprotein was diminished. These findings indicate that defective functionality of small, dense HDL particles in patients with T2D is not only affected by the presence of atherogenic dyslipidemia, but also by the level of glycemic control, reflecting compositional alterations of HDL.


**ABSTRACT**

**BACKGROUND:** Atherosclerosis appears to have multifactorial causes - microbial component like lipopolysaccharides (LPS) and other pathogen associated molecular patterns may be plausible factors. The gut microbiota is an ample source of such stimulants, and its dependent metabolites and altered gut metagenome has been an established link to atherosclerosis. In this exploratory pilot study, we aimed to elucidate whether microbial intervention with probiotics L. rhamnosus GG (LGG) or pharmaceuticals telmisartan (TLM) could improve atherosclerosis in a gut microbiota associated manner. METHODS: Atherosclerotic phenotype was established by 12 weeks feeding of high fat (HF) diet as opposed to normal chow diet (ND) in apolipoprotein E knockout (ApoE-) mice. LGG or TLM supplementation to HF diet was studied. RESULTS: Both LGG and TLM significantly reduced atherosclerotic plaque size and improved various biomarkers including endotoxin to different extents. Colonial microbiota analysis revealed that TLM restored HF diet induced increase in Firmicutes/Bacteroidetes ratio and decrease in alpha diversity; and led to a more distinct microbial clustering closer to ND in PCoA plot. Eubacteria, Anaeroplasma, Roseburia, Oscillospira and Dehalobacteria appeared to be protective against atherosclerosis and showed significant negative correlation with atherosclerotic plaque size and plasma adipocyte - fatty acid binding protein (A-FABP) and cholesterol. CONCLUSION: LGG and TLM improved atherosclerosis with TLM having a more distinct alteration in the colonic gut microbiota. Altered bacteria genera and reduced alpha diversity had significant correlations to atherosclerotic plaque size, plasma A-FABP and cholesterol. Future studies on such bacterial functional influence in lipid metabolism will be warranted.


**ABSTRACT**
Acute brain dysfunction is a frequent condition in sepsis patients and is associated with increased mortality and long-term neurocognitive consequences. Impaired memory and executive function are common findings in sepsis survivors. Although neuroinflammation and blood-brain barrier dysfunction have been associated with acute brain dysfunction and its consequences, no specific treatments are available that prevent cognitive impairment after sepsis. Experimental sepsis was induced in Swiss Webster mice by intraperitoneal injection of cecal material (5 mg/kg, 500 μl). Control groups (n= 5/group each experiment) received 500 μl of saline. Support therapy recover (saline 0.9%, 1 mL and imipenem 30 mg/kg) were applied (6, 24 and 48 h post injection, n=5-10/group, each experiment), together or not with additive orally treatment with statins (atorvastatin/simvastatin 20 mg/ kg b.w.). Survival rate was monitored at 6, 24 and 48 h. In a setting of experiments, animals were euthanized at 6 and 24 hours after induction for biochemical, immunohistochemistry and intravital analysis. Statins did not prevented mortality in septic mice, however survivors presented lower clinical score. At another setting of experiments, after 15 days, mice survivors from fecal supernatant peritoneal sepsis presented cognitive dysfunction for contextual hippocampal and aversive amygdala-dependent memories, which was prevented by atorvastatin/simvastatin treatment. Systemic and brain tissue levels of proinflammatory cytokines/chemokines and activation of microglial were lower in septic mice treated with statins. Brain lipid peroxidation and myeloperoxidase levels were also reduced by statins treatment. Intravital examination of the brain vessels of septic animals revealed decreased functional capillary density and increased rolling and adhesion of leukocytes, and blood flow impairment, which were reversed by treatment with statins. In addition, treatment with statins restored the cholinergic vasodilator response due to sepsis. Taken together, these data demonstrated that statins reverse microvascular dysfunction and reduce neuroinflammation during sepsis, preventing the development of long-term cognitive decline.


ABSTRACT

BACKGROUND: Ticagrelor inhibits the equilibrative-nucleoside-transporter-1 and thereby, adenosine cell re-uptake. Ticagrelor limits infarct size (IS) in non-diabetic rats and the effect is adenosine-dependent. Statins, via ecto-5'-nucleotidase activation, also increase adenosine levels and limit IS. HYPOTHESIS: Ticagrelor and rosuvastatin have additive effects on myocardial adenosine levels, and therefore, on IS and post-reperfusion activation of the NLRP3-inflammasome. METHODS: Diabetic ZDF rats received via oral gavage; water (control), ticagrelor (150 mg/kg/d), prasugrel (7.5 mg/kg/d), rosuvastatin (5 mg/kg/d), ticagrelor + rosuvastatin and prasugrel + rosuvastatin for 3d. On day 4, rats underwent 30 min coronary artery occlusion and 24 h of reperfusion. Two additional groups received, ticagrelor + rosuvastatin or water in combination with CGS15943 (CGS, an adenosine receptor antagonist, 10 mg/kg i.p. 1 h before ischemia). RESULTS: Both ticagrelor and rosuvastatin increased myocardial adenosine levels with an additive effect of the combination whereas prasugrel had no effect. Similarly, both ticagrelor and rosuvastatin significantly reduced IS with an additive
effect of the combination whereas prasugrel had no effect. The effect on IS was adenosine dependent as CGS15943 reversed the effect of ticagrelor + rosvustatin. The ischemia-reperfusion injury increased myocardial mRNA levels of NLRP3, ASC, IL-1beta and IL-6. Ticagrelor and rosvustatin, but not prasugrel, significantly decreased these pro-inflammatory mediators with a trend to an additive effect of the combination. The combination also increased the levels of anti-inflammatory 15-epilipoxin A4. CONCLUSIONS: Ticagrelor and rosvustatin when given in combination have an additive effect on local myocardial adenosine levels in the setting of ischemia reperfusion. This translates into an additive cardioprotective effect mediated by adenosine-induced effects including downregulation of pro- but upregulation of anti-inflammatory mediators.


ABSTRACT

Except for conversion to bile salts, there is no major cholesterol degradation pathway in mammals. Efficient excretion from the body is therefore a crucial element in cholesterol homeostasis. Yet, the existence and importance of cholesterol degradation pathways in humans is a matter of debate. We quantified cholesterol fluxes in 15 male volunteers using a cholesterol balance approach. Ten participants repeated the protocol after 4 weeks of treatment with ezetimibe, an inhibitor of intestinal and biliary cholesterol absorption. Under basal conditions, about 65% of daily fecal neutral sterol excretion was bile derived, with the remainder being contributed by direct transintestinal cholesterol excretion (TICE). Surprisingly, ezetimibe induced a 4-fold increase in cholesterol elimination via TICE. Mouse studies revealed that most of ezetimibe-induced TICE flux is mediated by the cholesterol transporter Abcg5/Abcg8. In conclusion, TICE is active in humans and may serve as a novel target to stimulate cholesterol elimination in patients at risk for cardiovascular disease.


ABSTRACT


ABSTRACT

BACKGROUND: Multiple circulating biomarkers have been associated with the incidence of cardiovascular events and proposed as potential tools for risk stratification in stable ischemic heart disease (IHD), yet current guidelines do not make any firm recommendations concerning the use of biomarkers for risk stratification in this setting. This state-of-the-art review provides an overview of biomarkers for risk stratification in stable IHD. CONTENT: Circulating biomarkers associated with the risk of cardiovascular events in patients with stable IHD reflect different
pathophysiological processes, including myocardial injury, myocardial stress and remodeling, metabolic status, vascular inflammation, and oxidative stress. Compared to the primary prevention setting, biomarkers reflecting end-organ damage and future risk of heart failure development and cardiovascular death may play more important roles in the stable IHD setting. Accordingly, biomarkers that reflect chronic, low-grade myocardial injury, and stress, i.e., high-sensitivity cardiac troponins and natriuretic peptides, provide graded and incremental prognostic information to conventional risk markers. In contrast, in stable IHD patients the prognostic value of traditional metabolic biomarkers, including serum lipids, is limited. Among several novel biomarkers, growth-differentiation factor-15 may provide the most robust prognostic information, whereas most inflammatory markers provide limited incremental prognostic information to risk factor models that include conventional risk factors, natriuretic peptides, and high-sensitivity troponins. SUMMARY: Circulating biomarkers hold promise as useful tools for risk stratification in stable IHD, but their future incorporation into clinically useful risk scores will depend on prospective, rigorously performed clinical trials that document enhanced risk prediction.

ABSTRACT
INTRODUCTION: The objective of this study was twofold: 1) to assess the residual cardiovascular (CV) risk among patients treated with statins according to guidelines and at the recommended dosages; and 2) to assess the difference, if any, in the frequency of CV events when patients were treated with other lipid-lowering agents alongside statins. METHODS: A retrospective observational study including one local health unit was conducted. Administrative databases were linked to laboratory test database in order to collect cholesterol values at baseline. Patients were included if they had filled at least one prescription for statins between January 1, 2009 and December 31, 2011; patients' records were considered for a 12-month time span. RESULTS: A total of 27,330 patients treated with statins were included (50% male, mean age 68.0 +/- 11.5 years). Among them, 770 were treated with statins according to guidelines and at the recommended dosages and had a low density lipoprotein-cholesterol value below the therapeutic target. Nevertheless, the risk of myocardial infarction or stroke remained: incidence rates were 1.3 +/- 1.0 per patient per year for moderate CV risk, 4.1 +/- 2.6 for high risk, and 12.5 +/- 11.0 for very high risk. This incremental risk was confirmed further using the Cox model, by correcting for age, sex, use of antiplatelet and/or antihypertensive therapy, and adherence to treatment. As a second analysis, we compared, after a propensity score matching, patients extracted from the overall sample who were treated with fibrates. Based on the Cox model, patients on fibrates had a risk for myocardial infarction or stroke lower than patients on statins. CONCLUSION: Among patients treated with statins according to guidelines and at the recommended dosages, a residual CV risk was observed. We concluded that intervention for managing residual CV risk during statin therapy should be implemented.
Atherosclerosis is the narrowing of arteries due to the accumulation of macrophages overloaded with lipids resulting in foam cell formation, and these events occur preferentially at the branching points of arteries which are particularly susceptible to hyperlipidemic stress-induced inflammation and oxidative stress. The different stages of atherogenesis rely on oxidative stress, endothelial dysfunction, and inflammation, and hypertension or dyslipidemia can independently trigger these stages. Dyslipidemia and hypertension are pathological conditions that damage the endothelium, triggering cell proliferation, vascular remodeling, apoptosis, and increased cellular permeability with increased adhesion molecules that bind monocytes and T lymphocytes to create a vicious cocktail of pathophysiological factors. Correspondingly, the factors are redirected by chemo-attractants and pro-inflammatory cytokines into the intima of the vascular, where monocytes differentiate into macrophages taking up oxidized LDL uncontrollably to form foam cells and atherosclerotic lesions. Moreover, endothelial damage also causes loss of vasomotor activity, disproportionate vascular contractility, and elevation of blood pressure in dyslipidemic patients, while in hypertensive patients, further elevation of blood pressure occurs, creating a self-perpetuating vicious cycle that aggravates the development and progression of atherosclerotic lesions. This review offers an in-depth analysis of atherosclerosis and the related interplay between dyslipidemia/hypertension and critically appraises the current diagnosis, etiology, and therapeutic options.

Purpose of Review: Despite the important progress in identifying high-risk atherosclerotic plaques, many key elements are elusive. Advanced imaging modalities provide valuable information about the anatomic and functional plaque characteristics and underscore the presence of multiple plaque morphologies. However, how the heterogeneity of atherosclerotic plaque can alter our current understanding of coronary artery disease is not fully understood.

Recent Findings: Along the length of an individual plaque, the morphology patterns display marked heterogeneity. Contrary to previous beliefs, plaque morphology is also highly dynamic over time, with the vast majority of high-risk plaques becoming quiescent and mild plaques becoming severely obstructive in a short period of time. Endothelial shear stress, a local hemodynamic factor known for its critical effects in plaque initiation and progression, also displays longitudinal heterogeneity contributing to the arterial wall response in all time points. Risk stratification of plaques based on the morphological characteristics at one region of the plaque, usually the minimal lumen diameter, and at one point in time may be misleading. The evaluation of both morphological and hemodynamic characteristics along the length of a plaque will improve the risk assessment of individual plaques.


ABSTRACT

INTRODUCTION: Epidemiological studies suggest that statins may promote the development or exacerbation of diabetes, but whether this occurs through inhibition of insulin secretion is unclear. This lack of understanding is partly due to the cellular models used to explore this phenomenon (cell lines or pooled islets), which are non-physiologic and have limited clinical transferability. METHODS: Here, we study the effect of simvastatin on insulin secretion using single-islet cultures, an optimal compromise between biological observability and physiologic fidelity. We develop and validate a microfluidic device to study single-islet function ex vivo, which allows for switching between media of different compositions with a resolution of seconds. In parallel, fluorescence imaging provides real-time analysis of the membrane voltage potential, cytosolic Ca²⁺ dynamics, and insulin release during perfusion under 3 or 11 mM glucose. RESULTS: We found that simvastatin reversibly inhibits insulin secretion, even in high-glucose. This phenomenon is very rapid (<60 s), occurs without affecting Ca²⁺ concentrations, and is likely unrelated to cholesterol biosynthesis and protein isoprenylation, which occur on a time span of hours. CONCLUSIONS: Our data provide the first real-time live demonstration that a statin inhibits insulin secretion in intact islets and that single islets respond differently from cell lines on a short time scale. FUNDING: University of Padova, EASD Foundation.


ABSTRACT

The rupture and erosion of atherosclerotic plaque can induce coronary thrombosis. Prolyl-4-hydroxylase (P4H) plays a central role in the synthesis of all known types of collagens, which are the most abundant constituent of the extracellular matrix in atherosclerotic plaque. The pathogenesis of atherosclerosis is thought to be in part caused by shear stress. In this study, we aimed to investigate a relationship between P4Halpha1 and shear stress-induced atherosclerotic plaque. Carotid arteries of ApoE-/- mice were exposed to low and oscillatory shear stress conditions by the placement of a shear stress cast for 2 weeks; we divided 60 male ApoE-/- mice into three groups for treatments with saline (mock) (n = 20), empty lentivirus (lenti-EGFP) (n = 20), and lentivirus-P4Halpha1 (lenti-P4Ha1) (n = 20). Our results reveal that after 2 weeks of lenti-P4Halpha1 treatment both low and oscillatory shear stress-induced plaques increased collagen and the thickness of fibrous cap and decreased macrophage accumulation but no change in lipid accumulation. We also observed that overexpression of P4Ha1 increased plaque size. Our study suggests that P4Ha1 overexpression might be a potential therapeutic target in stabilizing vulnerable plaques.

[24] Handelsman Y, Shapiro MD. TRIGLYCERIDES, Atherosclerosis, and Cardiovascular Outcome Studies: Focus on Omega-3 Fatty Acids. Endocrine practice : official journal of
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**ABSTRACT**

Despite improved atherosclerotic cardiovascular disease (ASCVD) outcomes with statin therapy, residual risk remains. Recent genetic insights provide further compelling evidence that triglycerides are in the causal pathway for the development of atherosclerosis, thereby renewing interest in targeting triglycerides to improve ASCVD outcomes. Fibrates, niacin, and omega-3 fatty acids (OM3FAs) are 3 classes of triglyceride-lowering drugs. Outcome studies with triglyceride-lowering agents have been inconsistent. With regard to OM3FAs, the Japan Eicosapentaenoic Acid (EPA) Lipid Intervention Study (JELIS) showed that EPA significantly reduced major coronary events in statin-treated hypercholesterolemic patients. Regarding other agents, extended-release niacin and fenofibrate are no longer recommended as statin add-on therapy (by some guidelines though not all) because of the lack of convincing evidence from outcome studies. Notably, subgroup analyses from outcome studies have generated the hypothesis that triglyceride lowering may provide benefit in statin-treated patients with persistent hypertriglycerideremia. Two ongoing outcome studies are testing this hypothesis in high-risk, statin-treated patients with triglyceride levels 200-500 mg/dL: the Reduction of Cardiovascular Events with EPA-Intervention Trial (REDUCEIT) is evaluating EPA (icosapent ethyl) and the Statin Residual Risk Reduction With Epanova in High CV Risk Patients With Hypertriglycerideremia study (STRENGTH) is evaluating omega-3-carboxylic acids (EPA plus docosahexaenoic acid). These studies will determine the role of triglyceride lowering in statin-treated patients with high-dose prescription OM3FAs in terms of improved ASCVD outcomes.


**ABSTRACT**

Statins have been effective in reducing adverse cardiovascular events. Their benefits have been proportional to the level of plasma LDL-cholesterol reduction and seem to extend to patients with 'normal' levels of cholesterol at outset. Statins are also inexpensive and have a favourable side effect profile. As a result, they are used widely (almost indiscriminately) in patients with atherosclerotic vascular disease, and in those at risk of disease. Next generation lipid-modifying drugs seem unlikely to offer the same simplicity of application. The recent trials of new classes of lipid modifying drugs underline the need for a risk stratification tool which is not based on patients' category of diagnosis (for example post myocardial infarction) but based on the characterisation of disease in that individual patient. Mechanistic staging, a process that matches the target of the drug action with an identifiable disease characteristic, may offer an opportunity to achieve more precise intervention. The upshots of this targeted approach will be greater efficacy, requiring smaller clinical trials to demonstrate effectiveness; a reduced number needed to treat to yield benefits (NNT) and more cost effective prescribing. This will be important, as purchasers require ever more rigorous demonstration of both efficacy and cost-effectiveness. In this context, we will discuss available pharmacological strategies of lipid
reduction in anti-atherosclerotic treatment and how plaque imaging techniques may provide an ideal method in stratifying patients for new lipid-modifying drugs.


**ABSTRACT**
Polypill is a medication designed for preventing heart attacks through a combination of drugs. Current formulations contain blood pressure-lowering drugs and others, such as statins or acetylsalicylic acid. These drugs exhibit different physical chemical features, and consequently different release kinetics. Therefore, the concentration in plasma of some of them after the release process can be out of the therapeutic range. This paper investigates a new methodology for the control dosage of a polypill recently reported containing hydrochlorothiazide, amlodipine, losartan and simvastatin in a 12.5/2.5/25/40 weight ratio. The procedure is based on mesoporous silica nanoparticles (MSN) with MCM-41 structure (MSN-41) used as carrier, aimed to control release of the four drugs included in the polypill. In vitro release data were obtained by HPLC and the curves adjusted with a kinetic model. To explain the release results, a molecular model was built to determine the drug-matrix interactions, and quantum mechanical calculations were performed to obtain the electrostatic properties of each drug. Amlodipine, losartan and simvastatin were released from the polypill-MSN-41 system in a controlled way. This would be a favourable behavior when used clinically because avoid too quick pressure decrease. However, the diuretic hydrochlorothiazide was quickly released from our system in the first minutes, as is needed in hypertensive urgencies. In addition, an increase in the stability of amlodipine and hydrochlorothiazide occurred in the polypill-MSN-41 system. Therefore, the new way of polypill dosage proposed can result in a safer and effective treatment.


**ABSTRACT**
PURPOSE: Lipid lowering therapy constitutes the basis of cardiovascular disease therapy. The purpose of this study was to investigate effects of ezetimibe, a selective inhibitor of intestinal cholesterol absorption, on platelets and endothelial cells in an in vitro endothelial cell model. METHODS: After a 24h incubation period with ezetimibe (concentrations 1, 50, 100 and 1000ng/ml), human umbilical vein endothelial cells (HUVEC) were stimulated for 1h with lipopolysaccharide (LPS) and were then incubated in direct contact with activated platelets. Following this, the expression of CD40L and CD62P on platelets, and the expression of ICAM-1, VCAM-1, uPAR, and MT1-MMP on endothelial cells were measured by flow cytometry. Supernatants were analysed by enzyme linked immunosorbent assay for soluble MCP-1, IL-6 and MMP-1. RESULTS: The increased expression of uPAR on endothelial cells by proinflammatory stimulation with LPS and by direct endothelial contact with activated platelets was significantly reduced through pre-incubation with 100ng/ml and 1000ng/ml ezetimibe.
(p<0.05). Platelets directly incubated with ezetimibe but without endothelial cell contact showed significantly reduced CD62P and CD40L surface expression (p<0.05). Ezetimibe had no significant effects on HUVEC expression of MT1-MMP, ICAM-1 and VCAM-1 and on CD40L expression on platelets in direct contact with endothelial cells. Levels of soluble IL-6 in HUVEC supernatants were significantly lower after pre-incubation with ezetimibe. CONCLUSION: In this in vitro analysis, ezetimibe directly attenuates platelet activation and has significant endothelial cell mediated effects on selected markers of atherosclerosis.


ABSTRACT
Fasting hypertriglyceridemia is positively associated with the morbidity of coronary heart disease (CHD), and postprandial (non-fasting) hypertriglyceridemia is also correlated with the risk status for CHD, which is related to the increase in chylomicron (CM) remnant lipoproteins produced from the intestine. CM remnant particles, as well as oxidized low density lipoprotein (LDL) or very low density lipoprotein (VLDL) remnants, are highly atherogenic and act by enhancing systemic inflammation, platelet activation, coagulation, thrombus formation, and macrophage foam cell formation. The cholesterol levels of remnant lipoproteins significantly correlate with small, dense LDL; impaired glucose tolerance (IGT) and CHD prevalence. We have developed an assay of apolipoprotein (apo)B-48 levels to evaluate the accumulation of CM remnants. Fasting apoB-48 levels correlate with the morbidity of postprandial hypertriglyceridemia, obesity, type III hyperlipoproteinemia, the metabolic syndrome, hypothyroidism, chronic kidney disease, and IGT. Fasting apoB-48 levels also correlate with carotid intima-media thickening and CHD prevalence, and a high apoB-48 level is a significant predictor of CHD risk, independent of the fasting TG level. Diet interventions, such as dietary fibers, polyphenols, medium-chain fatty acids, diacylglycerol, and long-chain n-3 polyunsaturated fatty acids (PUFA), ameliorate postprandial hypertriglyceridemia, moreover, drugs for dyslipidemia (n-3 PUFA, statins, fibrates or ezetimibe) and diabetes concerning incretins (dipeptidyl-peptidase IV inhibitor or glucagon like peptide-1 analogue) may improve postprandial hypertriglyceridemia. Since the accumulation of CM remnants correlates to impaired lipid and glucose metabolism and atherosclerotic cardiovascular events, further studies are required to investigate the characteristics, physiological activities, and functions of CM remnants for the development of new interventions to reduce atherogenicity.


ABSTRACT
Buchang NaoXinTong (NXT) is a Chinese medicine which has been used for many years for treatment of patients with coronary heart disease (CHD) in China. Statins substantially reduce hypercholesterolemia and CHD mortality and morbidity. However, there is still a lot of CHD patients do not respond well to statin therapy. Herein, we report the effects of NXT on
atorvastatin-inhibited atherosclerosis and atorvastatin-induced hepatic side effects. After 10 weeks high-fat diet (HFD) feeding, apoE deficient mice were randomly divided into 4 groups, and received the following treatment for another 8 weeks: group 1, HFD; group 2, HFD containing NXT; group 3, HFD containing atorvastatin; and group 4, HFD containing both NXT and atorvastatin. After treatment, serum lipid profiles, atherosclerotic lesions, and hepatic lipid content and inflammation were determined. NXT moderately increased HDL-cholesterol levels while had little effect on atorvastatin-induced reduction of LDL-cholesterol levels. Both NXT and atorvastatin reduced en face lesions and sinus lesions of aortic root. In addition, NXT enhanced atorvastatin-induced lesion plaque stability by increasing smooth muscle cell/collagen content, and reducing macrophage accumulation and calcification in lesion areas. The co-treatment of NXT and atorvastatin further reduced hepatic triglyceride levels by down-regulating DGAT1 while activating HSL, AGTL and CGI-58 expression. The AMPKalpha pathway was also further activated by the co-treatment. More importantly, the liver injuries caused by atorvastatin, such as hepatic inflammation and elevated serum aminotransferase activities, were substantially attenuated by NXT. Therefore, our study demonstrates that NXT enhances atorvastatin-induced plaque stability, and ameliorates atorvastatin-induced hepatic side effects.


**ABSTRACT**

In the present study, an ecotoxicological approach to the evaluation of Gemfibrozil (GEM) as an emerging organic pollutant was done. In order to assess its toxicity, tests were conducted using the cladocera Daphnia magna. Experiments were carried out at 22 degrees C and 28 degrees C. EC50, feeding behavior, and chronic toxicity tests (21 days) were evaluated in D. magna exposed to GEM as well as cholesterol levels at 21-day chronic exposure. D. magna GEM EC50 values (24 h) in our experimental conditions were 148.75 and 116.24 mg L-1 at 22 degrees C and 28 degrees C, respectively. Test concentrations of 0.1, 0.5, 1.0, 5.0 and 7.5 mg L-1 were selected for subacute and chronic experiments. Subacute short-term test (feeding study) was assessed after exposure to the toxicant. Filtration and ingestion rates of D. magna exposed animals did not show any significant difference (P > 0.05) with respect to control daphniids neither at 22 degrees C nor at 28 degrees C. Therefore, GEM test concentrations used in the present study did not reduce feeding behavior in D. magna. Temperature increased from 22 degrees C to 28 degrees C, which resulted in a decrease of the daphniids reproductive parameters such as brood size and number of young per female. Other parameters as longevity were not affected. The GEM concentrations used in the chronic test with D. magna did not affect daphniids longevity but some reproductive parameters as number of young per female or brood size were affected. Finally, a significant decreased in cholesterol levels was found in those animals exposed to the highest toxicant concentrations. More studies must be done to determine the possible implications of GEM in aquatic fauna and to derive its possible effects on the environment.
ABSTRACT

The tumor necrosis factor receptor superfamily (TNFRSF), which includes CD40, LIGHT, and OX40, plays important roles in the initiation and progression of cardiovascular diseases, involving atherosclerosis. CD137, a member of TNFRSF, is a well-known activation-induced T cell co-stimulatory molecule and has been reported to be expressed in human atherosclerotic plaque lesions, and plays pivotal roles in mediating disease processes. In this review, we focus on and summarize recent advances in mouse studies on the involvement of CD137 signaling in the pathogenesis and plaque stability of atherosclerosis, thereby highlighting a valuable therapeutic target in atherosclerosis.

ABSTRACT

BACKGROUND: High-fat diets may contribute to metabolic disease via postprandial changes in serum endotoxin and inflammation. It is unclear how dietary fat composition may alter these parameters. We hypothesized that a meal rich in n-3 (omega3) fatty acids would reduce endotoxemia and associated inflammation but a saturated or n-6 (omega6) fatty acid-rich meal would increase postprandial serum endotoxin concentrations and systemic inflammation in healthy adults. METHODS: Healthy adults (n = 20; mean age 25 +/- 3.2 S.D. years) were enrolled in this single-blind, randomized, cross-over study. Participants were randomized to treatment and reported to the laboratory, after an overnight fast, on four occasions separated by at least one week. Participants were blinded to treatment meal and consumed one of four isoenergetic meals that provided: 1) 20 % fat (control; olive oil) or 35 % fat provided from 2) n-3 (omega3) (DHA = 500 mg; fish oil); 3) n-6 (omega6) (7.4 g; grapeseed oil) or 4) saturated fat (16 g; coconut oil). Baseline and postprandial blood samples were collected. Primary outcome was defined as the effect of treatment meal on postprandial endotoxemia. Serum was analyzed for metabolites, inflammatory markers, and endotoxin. Data from all 20 participants were analyzed using repeated-measures ANCOVA. RESULTS: Participant serum endotoxin concentration was increased during the postprandial period after the consumption of the saturated fat meal but decreased after the n-3 meal (p < 0.05). The n-6 meal did not effect a different outcome in participant postprandial serum endotoxin concentration from that of the control meal (p > 0.05). There was no treatment meal effect on participant postprandial serum biomarkers of inflammation. Postprandial serum triacylglycerols were significantly elevated following the n-6
meal compared to the n-3 meal. Non-esterified fatty acids were significantly increased after consumption of the saturated fat meal compared to other treatment meals. CONCLUSIONS: Meal fatty acid composition modulates postprandial serum endotoxin concentration in healthy adults. However, postprandial endotoxin was not associated with systemic inflammation in vivo. TRIAL REGISTRATION: This study was retrospectively registered at clinicaltrials.gov as NCT02521779 on July 28, 2015.


ABSTRACT

BACKGROUND: Hyperlipidemia is one of the most common chronic diseases worldwide. Cholesteryl ester transfer protein (CETP) is a hydrophobic glycoprotein that facilitates the transfer of cholesteryl ester from the atheroprotective high-density lipoprotein (HDL) to the proatherogenic low-density lipoprotein (LDL) and very low-density lipoprotein (VLDL).

METHODS: In this work, synthesis and characterization of five fluorinated 3-benzylamino benzamides 8a-8c, 13a and 13b that target CETP activity was carried out. RESULTS: Benzamides 8b and 8a showed the highest CETP inhibitory activities with an IC50 of 0.75 microM and 4.1 microM respectively. It was found that presence of p-OCF3 group (as in 8a-8c) enhances CETP inhibitory activity more than p-OCF2CHF2 (as in 13a and 13b) which could be attributed to the bulkiness of the tetrafluoroethoxy group hindering their proper orientation in the binding domain. Additionally m-F derivatives were found to have higher activity against CETP than p-F ones leaving the o-F analogues with the weakest anti-CETP bioactivity. CONCLUSION: Ligand-based and structure-based drug design strategies confirm that hydrophobic interaction mediates ligand/protein complex formation and explain the activity of our verified molecules.


ABSTRACT

Myocardial ischaemia might be reduced in four to six months by lipid lowering drugs, research suggests.


ABSTRACT

PURPOSE: To assess the efficacy of 2 forms of oral long-chain omega-3 (omega-3) essential fatty acid (EFA) supplements, phospholipid (krill oil) and triacylglyceride (fish oil), for treating dry eye disease (DED). DESIGN: Randomized, double-masked, placebo-controlled clinical trial. PARTICIPANTS: This study was conducted at a single site and involved 60 participants with mild to moderate DED who were randomized (1:1:1) to 1 of 3 groups: placebo (olive oil), krill oil, or
fish oil supplements. METHODS: Participants received 1 of the 3 interventions: placebo (olive oil 1500 mg/day), krill oil (945 mg/day eicosapentaenoic acid [EPA], + 510 mg/day docosahexaenoic acid [DHA]), or fish oil (1000 mg/day EPA + 500 mg/day DHA) for 90 days, with monthly study visits. MAIN OUTCOME MEASURES: Primary outcome measures were mean change in (1) tear osmolarity and (2) DED symptoms (Ocular Surface Disease Index [OSDI] score) between days 1 and 90. Secondary outcomes included mean change in key clinical signs (tear stability, tear production, ocular surface staining, bulbar and limbal redness, tear volume, anterior blepharitis, meibomian gland capping) and tear inflammatory cytokine levels. RESULTS: In total, 54 participants completed the study. At day 90, tear osmolarity was reduced from baseline with both krill oil (mean +/- standard error of the mean: -18.6+/-4.5 mOsmol/l; n = 18; P < 0.001) and fish oil (-19.8+/-3.9 mOsmol/l; n = 19; P < 0.001) supplements, compared with placebo (-1.5+/-4.4 mOsmol/l; n = 17). OSDI score was significantly reduced at day 90 relative to baseline in the krill oil group only, compared with placebo (-18.6+/-2.4 vs. -10.5+/-3.3; P = 0.02). At day 90, there were also relative improvements in tear breakup time and ocular bulbar redness, compared with placebo, for both forms of omega-3 EFAs. Basal tear levels of the proinflammatory cytokine interleukin 17A were significantly reduced in the krill oil group, compared with placebo, at day 90 (-27.1+/-10.9 vs. 46.5+/-30.4 pg/ml; P = 0.02). CONCLUSIONS: A moderate daily dose of both forms of long-chain omega-3 EFAs, for 3 months, resulted in reduced tear osmolarity and increased tear stability in people with DED. Omega-3 EFAs in a predominantly phospholipid form (krill oil) may confer additional therapeutic benefit, with improvements in DED symptoms and lower basal tear levels of interleukin 17A, relative to placebo.


ABSTRACT
PURPOSE: LY3015014 is a humanized immunoglobulin G4 (IgG4) monoclonal antibody that binds to the catalytic domain of PCSK9 and reduce low-density lipoprotein cholesterol (LDL-C) in patients with hypercholesterolemia that is poorly controlled by maximally tolerated statin therapy. The objective of this pharmacokinetic/pharmacodynamics (PK/PD) analysis was to characterize the PK and PD properties of LY3015014 and assess the effect of covariates on the LY3015014 PK-PD profiles. METHODS: Single and multiple dose data from three phase1 studies in healthy subjects (n = 133), as well as a phase 2 study in hypercholesterolemia patients (n = 527) were combined into a single dataset for analysis. In this dataset, healthy subjects received single intravenous (IV) doses of 0.03 to 10 mg/kg, or multiple subcutaneous (SC) doses of 1.0 to 3.0 mg/kg, administered every 2 to 4 weeks, while patients received 20 to 300 mg every 4 weeks or 100 to 300 every 8 weeks. PK/PD analysis was performed using NONMEM (ICON, software version 7.0 level 3). PK and PD modeling were conducted sequentially, with PK parameters fixed during the development of the PK/PD model. PD parameters and estimated intersubject and intrasubject variability were obtained based on pharmacological drug exposure-response relationships. Age, baseline total PCSK9, body weight, diabetes diagnosis, hypercholesterolemia disease status, dose, ezetimibe administration, gender, ethnic origin,
metabolic syndrome, and statin administration were evaluated as potential covariates in the PK model. Baseline total PCSK9, baseline LDL-C, diabetes diagnosis, disease status, ezetimibe administration, gender, ethnic origin, metabolic syndrome, and Statin administration were evaluated as potential covariates in the PD model. RESULTS: LY3015014 PK profile was consistent across all the studies and between healthy subjects and hypercholesterolemia patients. The PK time course data were well described by a two compartment PK model with first order absorption, and covariates identified for PK parameters included weight on both clearance (CL) and central volume (V2), dose on CL, race on bioavailability (F), and age on V2. The PD (LDL-C) was described using an indirect response model with LY3015014 acting to stimulate the elimination of LDL-C. Covariates identified to have a statistically significant impact on PD were coadministration of statins, baseline LDL-C, metabolic syndrome status and gender.

CONCLUSIONS: The population PK/PD model adequately describes the PK and PD profiles of LY3015014. Identification of clinically significant covariates will support the design and dose selection for the pivotal registration studies, ensuring that patients are dosed appropriately.


ABSTRACT

BACKGROUND: Although intensive statin therapy is recommended for high risk patients, evidence of its benefit in patients with stable coronary artery disease (CAD) and very low low-density lipoprotein-cholesterol (LDL-C) has been very rare. In this study, we investigated whether higher statin intensity reduces cardiovascular risks in this population. METHODS: In this retrospective study, a total of 5234 patients with stable CAD were screened at three tertiary hospitals in Korea; 449 patients (mean age: 65 years, male: 69%) with LDL-C <80 mg/dL were finally analyzed. The statin intensities were classified according to the 2013 American College of Cardiology/American Heart Association guidelines. Patients who received statins equivalent to or weaker than atorvastatin 10 mg (group 1) were compared with those who took statins equivalent to or stronger than atorvastatin 20 mg (group 2). The impact of statin intensity on major adverse cardiac events (MACE) was evaluated during follow-up. RESULTS: Group 1 and group 2 consisted of 181 patients (40.3%) and 268 patients (59.7%), respectively. The mean LDL-C level decreased to 52 and 57 mg/dL in group 1 and group 2, respectively, during follow-up. In a median follow-up of 4.5 years, patients of group 2 had a lower incidence of MACE (30 [16.6%] vs. 12 [4.5%], p <0.001), which were mostly related to a lower incidence of coronary revascularization. Cox proportional hazard analyses identified the statin intensity of group 2 (adjusted hazard ratio: 0.25, confidence interval: 0.11-0.55, p <0.001) and the baseline high-density lipoprotein-cholesterol level as independent determinants of MACE. CONCLUSION: This study provides evidence that higher intensity statins are beneficial for cardiovascular outcomes in patients with stable CAD and very low LDL-C. Statins equivalent to or stronger than atorvastatin 20 mg are more effective than lower intensity statins.

ABSTRACT


ABSTRACT

Neuregulin 4 (Nrg4) has been identified as a new secreted adipokine that may protect against development of obesity and metabolic disorders. However, information is not available regarding the association between circulating Nrg4 and subclinical atherosclerosis in humans. We measured serum Nrg4 in 485 obese adult subjects (aged 40 years or older) who had the measurement of carotid intima-media thickness (CIMT) recruited from the community. Individuals with increased CIMT and carotid plaque had lower levels of circulating Nrg4 than controls (p < 0.05). The risks of increased CIMT and atherosclerotic plaque were significantly decreased by 28% and 31% [OR (95% CI): 0.72 (0.53-0.98) and 0.69 (0.50-0.96), respectively], adjusting for age, sex, current smoking, alcohol consumption, physical activity, BMI, systolic BP, fasting glucose, total cholesterol, HDL-c, HOMA-IR, and body fat. Importantly, individuals in the lowest quartile of serum Nrg4 were 3.70 times (p < 0.001) more likely to have increased CIMT and 2.06 times (p < 0.05) more likely to have atherosclerotic plaque than those in the highest quartile in multivariable logistic regression analyses. These findings suggest that circulating Nrg4 concentrations are inversely associated with subclinical atherosclerosis in obese adults, and indicating that circulating Nrg4 might play a role in identifying patients at high risk for CVD.


ABSTRACT

Myopathy is the most commonly reported adverse effect of statins. All statins are reported to induce myopathy, however with different rates. This could be referred to their different lipophilic/hydrophilic properties. This study aimed to compare the myopathic pattern of the lipophilic atorvastatin and the hydrophilic rosuvastatin in rats. Myopathy was evaluated using biochemical, functional and histopathological examinations. The possible deleterious effects of both statins on muscle mitochondria were also examined. Atorvastatin induced muscle wasting and prominent necrosis with a rise in serum CK and myoglobin levels. Rosuvastatin only induced a modest necrotic pattern but a rise in CK was noted. Motor activity, assessed by rotarod, showed that atorvastatin greatly decreased rats’ performance compared to rosvastatin treatment. Parallel results were obtained in mitochondrial dysfunction parameters. Atorvastatin induced an increase in LDH, lactate/pyruvate ratio while rosuvastatin only induced a slight increase in LDH. Atorvastatin induced a pronounced decline in ATP (approximately 80%) and pAkt (approximately 65%) while rosuvastatin showed a slight decrease in ATP (approximately 14%) and pAkt (approximately 12%). These results showed that rosvastatin induced less myopathic manifestations in rats. This could be explained by differential accumulation of the hydrophilic rosuvastatin and the lipophilic atorvastatin in rats' skeletal muscles.