BACKGROUND: Many epidemiological studies have proven that local infection may influence the levels of systemic lipid profile and inflammatory mediators. OBJECTIVES: The aim of this research was to evaluate the association between the state of the oral cavity, lipids and inflammatory mediator concentrations in Poles after acute myocardial infarction (MI).

MATERIAL AND METHODS: A total of 134 subjects with a mean age of 54.3 years (+/- 8.1) were included in the study. Sociodemographic and cardiologic variables were gathered. Subsequently, serum samples were collected for estimation of total cholesterol (TC), triglycerides (TG), low-density lipoprotein (LDL-C), high-density lipoprotein (HDL-C), high-sensitivity C-reactive protein (hsCRP), fibrinogen and white blood cell counts (WBC). The periodontal parameters measured included bleeding on probing index (BoP), pocket depth (PD), clinical attachment level (CAL), the number of bleeding periodontal pockets (bPP) and the number of lost teeth. RESULTS: Overall, patients shared high levels of periodontal inflammation and tissue breakdown. Multivariate analysis revealed a significant association between the serum concentration of LDL-C and bPP (standardized coefficient b = 0.3179; p = 0.0099) and PD (b = 0.3186; p = 0.0015); the level of fibrinogen and the number of lost teeth (b = 0.3669; p = 0.0013); WBC and bPP (b = 0.2726; p = 0.0035) independent of age, sex, income, education, atherosclerotic disease in the family, tobacco smoking, arterial hypertension, diabetes mellitus and BMI. No correlations were found regarding hsCRP serum concentration. CONCLUSIONS: To our knowledge, this study demonstrated for the first time that local inflammatory processes in the oral cavity are positively associated with the systemic levels of LDL-C, fibrinogen and WBC in adult Poles. This may underscore relationships between periodontitis and MI as well as potentially impinge on atherosclerotic processes and MI prognosis.


ABSTRACT
Current American College of Cardiology/American Heart Association guidelines for the management of patients with elevated blood cholesterol increasingly emphasize assessment of atherosclerotic cardiovascular disease (ASCVD) risk in deciding when to initiate pharmacotherapy. The decision to treat is based primarily on mathematical integration of traditional risk factors, including age, sex, race, lipid values, systolic blood pressure, hypertension therapy, diabetes mellitus, and smoking. Advanced risk testing is selectively endorsed for patients when the decision to treat is otherwise uncertain, or more broadly interpreted as those patients who are at so-called "intermediate risk" of ASCVD events using traditional risk factors alone. These new guidelines also place new emphasis on a clinician-patient risk discussion, a process of shared decision making in which patient and physician consider the potential benefits of treatment, risk of adverse events, and patient preferences.
before making a final decision to initiate treatment. Advanced risk testing is likely to play an increasingly important role in this process as weaknesses in exclusive reliance on traditional risk factors are recognized, new non-statin therapies become available, and guidelines are iteratively updated. Comparative efficacy studies of the various advanced risk testing options suggest that coronary artery calcium scoring is most strongly predictive of ASCVD events. Most importantly, coronary artery calcium scoring appears to identify an important subgroup of patients with advanced subclinical atherosclerosis—who are "between" primary and secondary prevention—that might benefit from the most aggressive lipid-lowering pharmacotherapy.


**ABSTRACT**

The goal of this analysis was to evaluate the ability of insulin resistance, identified by the presence of prediabetes mellitus (PreDM) combined with either an elevated triglyceride (TG >1.7 mmol/l) or body mass index (BMI >/=27.0 kg/m2), to identify increased risk of statin-associated type 2 diabetes mellitus (T2DM). Consequently, a retrospective analysis of data from subjects without diabetes in the Treating to New Targets and the Stroke Prevention by Aggressive Reduction in Cholesterol Levels randomized controlled trials was performed, subdividing participants into 4 experimental groups: (1) normal fasting glucose (NFG) and TG </=1.7 mmol/l (42%); (2) NFG and TG >1.7 mmol/l (22%); (3) PreDM and TG </=1.7 mmol/l (20%); and (4) PreDM and TG >1.7 mmol/l (15%). Comparable groupings were created substituting BMI values (kg/m2 </=27.0 and >/=27.0) for TG concentrations. Patients received atorvastatin or placebo for a median duration of 4.9 years. Incident T2DM, defined by developing at least 2 fasting plasma glucose (FPG) concentrations >/=126 mg/dl, an increase in FPG >/=37 mg/dl, or a clinical diagnosis of T2DM, was observed in 8.2% of the total population. T2DM event rates (statin or placebo) varied from a low of 2.8%/3.2% (NFG and TG </=1.7 mmol/l) to a high of 22.8%/7.6% (PreDM and TG >1.7 mmol/l) with intermediate values for only an elevated TG >1.7 mmol/l (5.2%/4.3%) or only PreDM (12.8%/7.6%). Comparable differences were observed when BMI values were substituted for TG concentrations. In conclusion, these data suggest that (1) the diabetogenic impact of statin treatment is relatively modest in general; (2) the diabetogenic impact is accentuated relatively dramatically as FPG and TG concentrations and BMI increase; and (3) PreDM, TG concentrations, and BMI identify people at highest risk of statin-associated T2DM.


**ABSTRACT**

Statin drugs are leading medication prescribed for treatment of dyslipidemic patients aimed at preventing both primary and secondary incidences of atherosclerosis-related cardiovascular events. Statin drugs competitively inhibit HMG-CoA reductase enzyme activity, thereby
inhibiting cell-mediated cholesterol synthesis and reducing the low-density lipoprotein (LDL) cholesterol concentration of plasma. Conversely, the mechanism by which statins increase high-density lipoprotein (HDL) cholesterol concentration of plasma is not well understood. The plaque array method was used to examine the effect of statins on in vitro cholesterol particle formation. We observed that statins induced high-density cholesterol particle formation in buffer solution with or without the addition of human serum. Besides, simvastatin and lovastatin in their inactive pro-drug forms modulate formation of LDL and HDL cholesterol particles, indicating a novel nonenzymatic mechanism of statins. In a pilot study, screening of serum samples in the assay showed variation among patient samples in response to different statins. Specifically, screening of 50 serum samples with high cholesterol and statin treatment, compared with standard LDL-based measurement of statin efficacy, showed a good correlation for simvastatin (88%) and atorvastatin (84%). Taken together, our data indicate that statins, in addition to inhibiting enzyme-mediated cholesterol synthesis, have the capability to nonenzymatically modulate formation of LDL and HDL cholesterol particles in vitro. Similar interactions occurring in serum may provide a means to alter cholesterol particle formation in vivo.


**ABSTRACT**

Despite significant progress in pharmacologic treatment aimed at lowering low-density lipoprotein cholesterol to reduce cardiovascular disease risk, a number of patient groups that often prove difficult to treat remain. Patients with familial hypercholesterolemia may go undiagnosed and untreated or, despite treatment, have persistently elevated lipid levels that confer a high cardiovascular disease risk. Although the true prevalence is unknown, statin intolerance is a common clinical presentation that is difficult to assess and frequently leads to suboptimal lipid treatment. Additionally, some patients may not achieve the expected response to guideline-based therapy. For all 3 groups, a standardized approach offers the best chance for effective diagnosis and optimal treatment.


**ABSTRACT**

Although many clinical trials and meta-analyses have demonstrated that lower serum low-density lipoprotein cholesterol (LDL-C) levels are associated with proportionately greater reductions in the risk of cardiovascular disease events, not all patients with hypercholesterolemia are able to attain risk-stratified LDL-C goals with statin monotherapy. Elucidation of the pathophysiology of genetic disorders of lipid metabolism (e.g., familial hypercholesterolemia) has led to the development of several novel lipid-lowering strategies, including blocking the degradation of hepatic LDL-C receptors that are important in LDL-C clearance, or the inhibition of apoprotein synthesis and lipidation. Mipomersen and lomitapide are highly efficacious new agents available for the treatment of patients with homozygous
familial hypercholesterolemia. The recent introduction of PCSK9 inhibitors (alirocumab and evolocumab) have made it possible for many patients to achieve very low LDL-C concentrations (e.g., <40 mg/dl) that are usually not attainable with statin monotherapy. Ongoing clinical trials are examining the impact of very low LDL-C levels on cardiovascular disease event rates and the long-term safety of this approach.


ABSTRACT


ABSTRACT

Non-alcoholic steatohepatitis (NASH), especially as part of the metabolic syndrome (MS), is an increasing burden in western countries. Statins are already used in metabolic syndrome and seem to be beneficial in liver diseases. The aim of this study was to investigate the molecular mechanisms underlying pleiotropic effects on small GTPases of statins in NASH. NASH within MS was induced in 12-week-old ApoE/- mice after 7 weeks of western diet (NASH mice). Small GTPases were inhibited by activated simvastatin (SMV), NSC23766 (NSC) or Clostridium sordellii lethal toxin (LT) using subcutaneous osmotic mini-pumps. Hepatic steatosis, inflammation and fibrosis were assessed by histology, Western blot and RT-PCR, measurements of cholesterol and hydroxyproline content. SMV treatment significantly decreased hepatic inflammation and fibrosis, but had no significant effect on steatosis and hepatic cholesterol content in NASH. SMV blunted fibrosis due to inhibition of both RhoA/Rho-kinase and Ras/ERK pathways. Interestingly, inhibition of RAC1 and Ras (by LT) failed to decrease fibrosis to the same extent. Inhibition of RAC1 (by NSC) showed no significant effect at all. Inhibition of RhoA and Ras downstream signaling by statins is responsible for the beneficial hepatic effects in NASH.


ABSTRACT

BACKGROUND: Angiopoietin-like protein 3 (ANGPTL3) is a major lipoprotein regulator and shows positive correlation with high-density lipoprotein-cholesterol (HDL-c) in population studies and ANGPTL3 mutated subjects. However, no study has looked its correlation with HDL components nor with HDL function in patients with type 2 diabetes mellitus (T2DM). METHODS: We studied 298 non-diabetic subjects and 300 T2DM patients who were randomly recruited in the tertiary referral centre. Plasma levels of ANGPTL3 were quantified by ELISA. Plasma samples were fractionated to obtain HDLs. HDL components including apolipoprotein A-I (apoA-I), triglyceride, serum amyloid A (SAA), phospholipid and Sphingosine-1-phosphate were
measured. HDLs were isolated from female controls and T2DM patients by ultracentrifugation to assess cholesterol efflux against HDLs. A Pearson unadjusted correlation analysis and a linear regression analysis adjusting for age, body mass index and lipid lowering drugs were performed in male or female non-diabetic participants or diabetic patients, respectively. RESULTS: We demonstrated that plasma level of ANGPTL3 was lower in female T2DM patients than female controls although no difference of ANGPTL3 levels was detected between male controls and T2DM patients. After adjusting for confounding factors, one SD increase of ANGPTL3 (164.6 ng/ml) associated with increase of 2.57 mg/dl cholesterol and 1.14 mug/mL apoA-I but decrease of 47.07 mug/L of SAA in HDL particles of non-diabetic females (p < 0.05 for cholesterol and SAA; p < 0.0001 for apoA-I). By contrast, 1-SD increase of ANGPTL3 (159.9 ng/ml) associated with increase of 1.69 mg/dl cholesterol and 1.25 mug/mL apoA-I but decrease of 11.70 mug/L of SAA in HDL particles of female diabetic patients (p < 0.05 for cholesterol; p < 0.0001 for apoA-I; p = 0.676 for SAA). Moreover, one SD increase of ANGPTL3 associated with increase of 2.11 % cholesterol efflux against HDLs in non-diabetic females (p = 0.071) but decrease of 1.46 % in female T2DM patients (p = 0.13) after adjusting for confounding factors. CONCLUSIONS: ANGPTL3 is specifically correlated with HDL-c, apoA-I, SAA and HDL function in female non-diabetic participants. The decrease of ANGPTL3 level in female T2DM patients might contribute to its weak association to HDL components and function. ANGPTL3 could be considered as a novel therapeutic target for HDL metabolism for treating diabetes.


ABSTRACT

PURPOSE: Even with statins and other lipid-lowering therapy (LLT), many patients with heterozygous familial hypercholesterolemia (heFH) continue to have elevated low-density lipoprotein cholesterol (LDL-C) levels. ODYSSEY HIGH FH (NCT01617655) assessed the efficacy and safety of alirocumab, a proprotein convertase subtilisin/kexin type 9 monoclonal antibody, versus placebo in patients with heFH and LDL-C >/= 160 mg/dl despite maximally tolerated statin +/- other LLT. METHODS: Patients were randomized to subcutaneous alirocumab 150 mg or placebo every 2 weeks (Q2W) for 78 weeks. The primary endpoint was percent change in LDL-C from baseline to week 24. RESULTS: Mean baseline LDL-C levels were 196.3 mg/dl in the alirocumab (n = 71) and 201.0 mg/dl in the placebo groups (n = 35). Significant mean (standard error [SE]) reductions in LDL-C from baseline to week 24 were observed with alirocumab (-45.7 [3.5] %) versus placebo (-6.6 [4.9] %), a difference of -39.1 (6.0) % (P < 0.0001). Absolute mean (SE) LDL-C levels were reduced from baseline by 90.8 (6.7) mg/dl with alirocumab at week 24, with reductions maintained to week 78. Treatment-emergent adverse events were generally comparable between groups. Injection-site reactions were more frequent in the alirocumab group (8.3 %) versus placebo (5.7 %); most were mild in severity and did not result in study medication discontinuation. CONCLUSIONS: In patients with heFH and very high LDL-C baseline levels despite maximally tolerated statin +/- other LLT, alirocumab 150 mg Q2W demonstrated
significant reductions in LDL-C levels with 41% of patients achieving predefined LDL-C goals. Alirocumab was generally well tolerated.


ABSTRACT

BACKGROUND: Splenectomy can potentially impact atherosclerosis through multiple mechanisms including altered lipid homeostasis, increased coagulation, and altered macrophage recruitment to the plaque. In patients, splenectomy has been associated with increased rates of coronary artery events, while in experimental mice, splenectomy causes increased atherosclerosis but reduces systemic monocyte supply. In this study, the direct impact of splenectomy on human coronary artery atherosclerotic plaque severity and macrophage content was investigated. METHODS: Coronary artery atherosclerotic plaque severity was determined at autopsy in 18 long-term (>=/=10 years) splenectomy patients and 90 matched control patients. Coronary artery macrophage content was evaluated in mild atherosclerotic plaques of 11 mid- to long-term (>=/=1 year) splenectomy patients and 11 matched control patients. RESULTS: Splenectomy was associated with reduced coronary artery atherosclerosis (P=.03). The association was most pronounced for the subgroup of patients who had undergone splenectomy 20 years or more prior to death (P=.02). There was no difference in the density of macrophages in the plaque, media, or adventitia upon comparing splenectomy and control patients. In the control group, there was no correlation between the macrophage densities in the three arterial layers. However, in the splenectomy patients, there was a strong correlation in the macrophage densities across the plaque, media, and adventitia (P<=.0002), with resulting slopes that were significantly greater than seen in the control patients (P=.0007-.011). CONCLUSIONS: These findings indicate that, in humans, splenectomy is associated with lower coronary artery atherosclerotic plaque severity and altered coronary artery macrophage distribution. These results suggest that the spleen can modulate the recruitment of macrophages into human coronary arteries and the progression of atherosclerosis.


ABSTRACT

Hepatitis C virus (HCV) infection affects roughly 170 million people worldwide. Sofosbuvir/Ledipasvir (Sof/Led) is a new once daily direct acting antiviral combination pill that was approved in October 2014 for use in patients with HCV genotype 1 infection. Coadministration of Sof/Led is studied only with rosvustatin which shows significantly increased level of drug and is associated with increased risk of myopathy, including rhabdomyolysis. There is no mention of such HMG-CoA reductase inhibitor interaction as a class, as pravastatin did not have any clinically significant interaction with Sof/Led. Other myotoxic drugs, including colchicine are not studied. We present a case of a serious drug interaction between Sof/Led and atorvastatin, in the background of CKD and colchicine use.
ABSTRACT
A common complication in paediatric patients with nephrotic syndrome (NS) is hyperlipidaemia. About 20% of children do not respond to treatment with corticosteroids, presenting with a cortico-resistant NS (CRNS), which can progress to kidney failure. It has been observed that paediatric patients with CRNS have an elevated low density lipoprotein cholesterol (LDL-c), very low density lipoprotein cholesterol (VLDL-c), and triglycerides levels, as well as elevated Lipoprotein-a [Lp (a)] levels. The case is presented of a 5 year old boy, diagnosed with CRNS, presenting with dyslipidaemia with increased LDL-c, Apo-B100, and Lp(a) levels. After the poor prognosis of the renal function, immunosuppressant treatment was started with tacrolimus and atorvastatin to control dyslipidaemia. Although tacrolimus causes an elevation of total cholesterol and LDL-c, the significant alterations of the children lipid profile suggest the existence of a high cardiovascular risk. In these cases, it would be interesting to have reference values in children in our health area.


ABSTRACT
OPINION STATEMENT: Both HeFH and HoFH require dietary and lifestyle modification. Pharmacotherapy of adult HeFH patients is largely driven by the American Heart Association (AHA) algorithm. A high-potency statin is started initially with a goal low-density lipoprotein cholesterol (LDL-C) reduction of >50%. The LDL-C target is adjusted to <100 or <70 mg/dL in subjects with coronary artery disease (CAD) with ezetimibe being second line. If necessary, a third adjunctive therapy, such as a PSCK9 inhibitor (not yet approved in children) or bile acid-binding resin, can be added. Finally, LDL-C apheresis can be considered in patients with LDL-C >300 mg/dL (or >200 mg/dL with significant CAD, although now approved for LDL-C as low as 160 mg/dL with CAD). Due to the early, severe LDL-C elevation in HoFH patients, concerning natural history, rarity of the condition, and nuances of treatment, all HoFH patients should be treated at a pediatric or adult center with HoFH experience. LDL-C apheresis should be considered as early as 5 years of age. However, apheresis availability and tolerability is limited and pharmacotherapy is required. Generally, the AHA algorithm with reference to the European Atherosclerosis Society Consensus Panel recommendations is reasonable with all patients initiated on high-dose, high-potency statin, ezetimibe, and bile acid-binding resins. In most, additional LDL-C lowering is required with PCSK9 inhibitors and/or lomitapide or mipomersen. Liver transplantation can also be considered at experienced centers as a last resort.
OBJECTIVE: To evaluate the epidemiological and morphological characteristics of coronary plaque in diabetic patients with symptomatic coronary heart disease (CHD) by dual-source computed tomography (DSCT). MATERIALS AND METHODS: From June 2013 to December 2014, 267 consecutive patients with type 2 diabetes mellitus were examined by DSCT. Plaque type, distribution, as well as extent and obstructive characteristics were determined for each segment. RESULTS: A total of 225 patients were included in the final study. Among the 225 cases, patients with calcium score &gt;10 accounted for 76.9%. With the increase in calcium score, the number of obstructive stenoses increased from 17 (22.7%) to 150 (66.4%) segments, and non-obstructive stenosis decreased from 58 (77.3%) to 76 (33.6%) segments. A total of 862 (3.8 +/- 3.0 per patient) plaques were detected, of which 448 (52%) were calcified plaque, 272 (32%) mixed plaques and 142 (16%) soft plaques. Regarding the stenosis type, there were significantly more mild (54%), followed by moderate (26%) and severe stenosis (20%); 152 (67.6%) patients had &gt;=2 vascular lesions, while 73 (32.4%) patients with single diseased vessel. 190 (84.40%) patients with atherosclerotic plaque were located in left anterior descending (LAD) coronary artery, 146 (64.9%) patients in right coronary artery (RCA), 114 (50.7%) patients in left circumflex (LCX) coronary artery. The most common site of all detected plaques was the proximal segment of the LAD (18.7%). CONCLUSION: DSCT showed that coronary arteries of diabetic patients with symptomatic CHD were more prone to calcification. There was more non-obstructive than obstructive lumen narrowing; obstructive stenosis and calcification score was positively correlated; coronary plaques were widely distributed, and mainly located in multiple diseased vessels.

AIM: To examine the lipid and glycaemic effects of 52 weeks of evolocumab treatment. MATERIALS AND METHODS: DESCARTES was a 52-week placebo-controlled trial of evolocumab. DESCARTES randomised 905 patients from 88 study centres in nine countries with 901 receiving at least one dose of study drug. For this post-hoc analysis, DESCARTES patients were categorized by baseline glycaemic status - type 2 diabetes, impaired fasting glucose (IFG), metabolic syndrome (MetS), or none of these. Monthly subcutaneous evolocumab (420 mg) or placebo was administered. The main outcomes measured were percentage change in LDL-cholesterol (LDL-C) at week 52 and safety. RESULTS: 413 patients had dysglycaemia (120 type 2 diabetes, 293 IFG), 289 MetS (194 also had IFG), and 393 none of these conditions. At week 52, evolocumab reduced LDL-C by &gt; 50% in all subgroups, with favourable effects on other lipids. No significant differences in fasting plasma glucose, HbA1c, insulin, C-peptide or HOMA indices were seen in any subgroup between evolocumab and placebo at week 52. The overall incidence


of new-onset diabetes mellitus did not differ between placebo (6.6%) and evolocumab (5.6%); in those with baseline normoglycaemia, the incidences were 1.9% and 2.7%, respectively. Incidences of AEs were similar in evolocumab- and placebo-treated patients. CONCLUSIONS: Evolocumab showed encouraging safety and efficacy at 52 weeks in patients with or without dysglycaemia or MetS. Changes in glycaemic parameters did not differ between evolocumab- and placebo-treated patients within the glycaemic subgroups examined. NCT01516879, ClinicalTrials.gov.


ABSTRACT
This study aimed to investigate the effect of simvastatin (SV) loaded nanostructured lipid carriers (SV loaded NLCs) on atherogenic index (AI), erythrocytes membrane lipid and antioxidant/pro-oxidant status in hyperlipidemic rats. SV loaded NLCs were successfully prepared with desired nano-particles size, spherical shape, high encapsulation efficiency (EE %) and sustained SV release. The results of biological studies revealed that administration of SV loaded NLCs to rats increased SV bioavailability compared to SV suspension. Intraperitoneal injection of tyloxapol as hyperlipidemic agent induces a significant increase of plasma AI, uric acid, lipid peroxidation and protein oxidation. While, plasma total antioxidant capacity and paraoxonase-1 activity were significantly decreased. Moreover, tyloxapol induced hyperlipidemia increases erythrocyte's membrane cholesterol and deteriorates erythrocyte's antioxidant enzyme activity, GSH/GSSG ratio and NO level However, the propagation of erythrocyte's pro-oxidant activity and hemolysis was observed. On the contrast, the treatment of these rats with SV loaded NLCs improved the measured parameters compared to rats received SV suspension and hyperlipidemic rats. The predominant effect of SV loaded NLCs may be attributed to the enhancement of absorption, prolonged duration and improvement of bioavailability of SV. Accordingly, SV loaded NLCs showed advantageous effects on the blood lipid levels and atherogenic risk of erythrocytes in hyperlipidemic conditions compared to SV suspension.

[18] Lee DH, Han DH, Nam KT et al. Ezetimibe, an NPC1L1 inhibitor, is a potent Nrf2 activator that protects mice from diet-induced nonalcoholic steatohepatitis. Free radical biology & medicine 2016.

ABSTRACT
Oxidative stress is important for the pathogenesis of nonalcoholic fatty liver disease (NAFLD), a chronic disease that ranges from hepatic steatosis to nonalcoholic steatohepatitis (NASH). The nuclear factor erythroid 2-related factor 2-Kelch-like ECH associated protein 1 (Nrf2-Keap1) pathway is essential for cytoprotection against oxidative stress. In this study, we found that oxidative stress or inflammatory biomarkers and TUNEL positive cells were markedly increased in NASH patients compared to normal or simple steatosis. In addition, we identified that the hepatic mRNA levels of Nrf2 target genes such as Nqo-1 and GSTA-1 were significantly increased in NASH patients. Ezetimibe, a drug approved by the Food and Drug Administration
for the treatment of hypercholesterolemia, improves NAFLD and alleviates oxidative stress. However, the precise mechanism of its antioxidant function remains largely unknown. We now demonstrate that ezetimibe activates Nrf2-Keap1 pathway which was dependent of autophagy adaptor protein p62, without causing cytotoxicity. Ezetimibe activates AMP-activated protein kinase (AMPK), which in turn phosphorylates p62 (p-S351) via their direct interaction. Correspondingly, Ezetimibe protected liver cells from saturated fatty acid-induced apoptotic cell death through p62-dependent Nrf2 activation. Furthermore, its role as an Nrf2 activator was supported by methionine- and choline- deficient (MCD) diet-induced NASH mouse model, showing that ezetimibe decreased the susceptibility of the liver to oxidative injury. These data demonstrate that the molecular mechanisms underlying ezetimibe's antioxidant role in the pathogenesis of NASH.


ABSTRACT
BACKGROUND: Recent guidelines recommended both low-density lipoprotein cholesterol (LDL-C) and non-high-density lipoprotein cholesterol (non-HDL-C) are the primary target of lipid modulating therapy. However, which lipid measure is most closely related to the severity of coronary atherosclerosis has not yet been assessed. METHODS: We studied 1757 consecutive subjects undergoing coronary angiography who were not receiving any lipid-lowering therapy. Low-density lipoprotein cholesterol was measured directly, and non-HDL-C was calculated. The severity of coronary stenosis was determined using the Gensini Score (GS) system. RESULTS: In the overall population, LDL-C and non-HDL-C were all dramatically increased according to the quartiles of GS (p<0.001, both). In patients with coronary atherosclerosis (n=1097), non-HDL-C (r=0.138, p<0.001) was more closely related to GS than LDL-C (r=0.113, p<0.001) tested by Spearman correlation analysis. Multivariate logistic regression analysis suggested that non-HDL-C (OR=1.326, 95% CI 1.165-1.508, p<0.001) was slightly superior to LDL-C (OR=1.286, 95% CI 1.130-1.463, p<0.001) in predicting high GS after adjusting for potential confounders. Among patients with LDL-C less than the median, discordant non-HDL-C could not provide extra value in predicting high GS (OR=0.759, 95% CI 0.480-1.201). However, among patients with LDL-C greater than or equal to the median, the cardiovascular risk was overestimated for patients with discordant non-HDL-C (OR=0.458, 95% CI 0.285-0.736). CONCLUSIONS: Our data support the use of non-HDL-C ahead of LDL-C in predicting the severity of coronary atherosclerosis, especially among patients with LDL-C greater than or equal to the median.


ABSTRACT
BACKGROUND: The PCSK9 antibody alirocumab (75 mg every 2 weeks; Q2W) as monotherapy reduced low-density lipoprotein-cholesterol (LDL-C) levels by 47%. Because the option of a monthly dosing regimen is convenient, ODYSSEY CHOICE II evaluated alirocumab 150 mg Q4W
in patients with inadequately controlled hypercholesterolemia and not on statin (majority with statin-associated muscle symptoms), receiving treatment with fenofibrate, ezetimibe, or diet alone. METHODS AND RESULTS: Patients were randomly assigned to placebo, alirocumab 150 mg Q4W or 75 mg Q2W (calibrator arm), with dose adjustment to 150 mg Q2W at week (W) 12 if W8 predefined LDL-C target levels were not met. The primary efficacy endpoint was LDL-C percentage change from baseline to W24. Mean baseline LDL-C levels were 163.9 mg/dL (alirocumab 150 mg Q4W, n=59), 154.5 mg/dL (alirocumab 75 mg Q2W, n=116), and 158.5 mg/dL (placebo, n=58). In the alirocumab 150 mg Q4W and 75 mg Q2W groups (49.1% and 36.0% of patients received dose adjustment, respectively), least-squares mean LDL-C changes from baseline to W24 were -51.7% and -53.5%, respectively (placebo [+4.7%]; both groups P<0.0001 versus placebo). In total, 63.9% and 70.3% of alirocumab-treated patients achieved their LDL-C targets at W24. Treatment-emergent adverse events occurred in 77.6% (alirocumab 150 mg Q4W), 73.0% (alirocumab 75 mg Q2W), and 63.8% (placebo) of patients, with injection-site reactions among the most common treatment-emergent adverse events. CONCLUSIONS: Alirocumab 150 mg Q4W can be considered in patients not on statin with inadequately controlled hypercholesterolemia as a convenient option for lowering LDL-C. CLINICAL TRIAL REGISTRATION: URL: http://www.clinicaltrials.gov/. Unique identifier: NCT02023879.


ABSTRACT

Plasma C-reactive protein (CRP) concentration is associated positively with cardiovascular risk, including dyslipidemia. We suggested a regulating role of CRP on pro-protein convertase subtilisin/kexin type 9 (PCSK9), a key regulator of low-density lipoprotein (LDL) metabolism, and demonstrated the PCSK9 as a pathway linking CRP and LDL regulation. Firstly, experiments were carried out in the presence of human CRP on the protein and mRNA expression of PCSK9 and LDL receptor (LDLR) in human hepatoma cell line HepG2 cells. Treatment with CRP (10 μg/ml) enhanced significantly the mRNA and protein expression of PCSK9 and suppressed the expression of LDLR. Of note, a late return of LDLR mRNA levels occurred at 12 hrs, while the LDLR protein continued to decrease at 24 hrs, suggesting that the late decrease in LDLR protein levels was unlikely to be accounted for the decrease in LDL mRNA. Secondly, the role of PCSK9 in CRP-induced LDLR decrease and the underlying pathways were investigated. As a result, the inhibition of PCSK9 expression by small interfering RNA (siRNA) returned partly the level of LDLR protein and LDL uptake during CRP treatment; CRP-induced PCSK9 increase was inhibited by the p38MAPK inhibitor, SB203580, resulting in a significant rescue of LDLR protein expression and LDL uptake; the pathway was involved in hepatocyte nuclear factor 1alpha (HNF1alpha) but not sterol responsive element-binding proteins (SREBPs) preceded by the phosphorylation of p38MAPK. These findings indicated that CRP increased PCSK9 expression by activating p38MAPK-HNF1alpha pathway, with a certain downstream impairment in LDL metabolism in HepG2 cells.

**ABSTRACT**

Statins, 3-hydroxyl-3-methylglutaryl coenzyme A reductase inhibitors, are the first-line medications prescribed for the prevention and treatment of coronary artery diseases. The efficacy of statins has been attributed not only to their systemic cholesterol-lowering actions but also to their pleiotropic effects that are unrelated to cholesterol reduction. These pleiotropic effects have been increasingly recognized as essential in statins therapy. This study was designed to investigate the pleiotropic actions of simvastatin, one of the most commonly prescribed statins, on macrophage cholesterol homeostasis with a focus on lysosomal free cholesterol egress. With simultaneous nile red and filipin staining, analysis of confocal/multiphoton imaging demonstrated that simvastatin markedly attenuated unesterified (free) cholesterol buildup in macrophages loaded with oxidized low-density lipoprotein but had little effect in reducing the sizes of cholesteryl ester-containing lipid droplets; the reduction in free cholesterol was mainly attributed to decreases in lysosom-compartmentalized cholesterol. Functionally, the egression of free cholesterol from lysosomes attenuated pro-inflammatory cytokine secretion. It was determined that the reduction of lysosomal free cholesterol buildup by simvastatin was due to the up-regulation of Niemann-Pick C1 (NPC1), a lysosomal residing cholesterol transporter. Moreover, the enhanced enzymatic production of 7-hydroxycholesterol by cytochrome P450 7A1 and the subsequent activation of liver X receptor alpha underscored the up-regulation of NPC1. These findings reveal a novel pleiotropic effect of simvastatin in affecting lysosomal cholesterol efflux in macrophages and the associated significance in the treatment of atherosclerosis.


**ABSTRACT**

Regulatory T cells (Tregs) inhibit the activation of the immune response which could down-regulate the systemic and focal activation observed during ischemic stroke. In fact, in animal models, Tregs infiltrate the infarcted brain and reduce the pro-inflammatory cytokine production and infarct volume, mainly in late stages of ischemia. Recently, an expansion and greater suppressive capacity of circulating Tregs after treatment with statins was observed, in addition to their cardio- and neuroprotective actions demonstrated previously. Thus, to determine whether Treg modulation mediated by statins can also be beneficial during stroke, cerebral ischemia was artificially induced in Wistar rats by transient middle cerebral artery occlusion (tMCAO) during 60 minutes with subsequent reperfusion for 7 days. Six hours after surgery, some animals were treated with atorvastatin (ATV, 10 mg/kg) or carboxymethylcellulose as vehicle at the same concentration every other day during 7 days. Some animals were sham operated as control group of surgery. Interestingly, ATV treatment
prevented the development of infarct volume, reduced the neurological deficits, and the circulating and cervical lymph node CD25+FoxP3+ Treg population. Moreover, there was a reduction of glial cell activation, which correlated with decreased circulating Tregs. Remarkably, treatment with ATV induced an increase in the frequency of CD4+CD25+ T cells, in particular of those expressing CTLA-4, in brain samples. Together, these results suggest that ATV can modulate Tregs in peripheral tissue and favor their accumulation in the brain, where they can exert neuroprotective actions maybe by the reduction of glial cell activation.


ABSTRACT
Despite the high prevalence of progressing stroke in patients with acute stroke, preventative treatments are still the unmet needs for those patients. The aim of this study was to evaluate, prospectively, the efficacy and safety of ezetimibe in the prevention of acute progressing stroke and thereby the improvement of patient outcome. A total of 423 patients (267 men and 156 women with a mean age of 65.2 years) were randomly assigned to receive ezetimibe (10 mg daily oral administration, n = 209) or placebo (n = 214) for 14 consecutive days. Analytical procedures performed at baseline (i.e., day 1) and 14 days after the treatments were completed. These included a real-time three-dimensional ultrasound (RT-3DU) examination for carotid plaque volume, clinical laboratory analyses of serum levels of IL-6 and MMP-9, as well as lipid parameters and liver dysfunction marker ALT and TBIL. Ezetimibe significantly reduced the average NIHSS score after 14 days of treatment and attenuated the stroke progression rate, which was associated with reduction in carotid plaque volume and attenuation of serum levels of IL-6, MMP-9, and LDL, without inducing liver dysfunction. Ezetimibe treatment may be a beneficial and effective strategy for preventing progressing stroke.


ABSTRACT
BACKGROUND: Studies conducted in animal models have shown that statins (3-hydroxy-3-methylglutaryl-coenzyme A reductase inhibitors) reduce adhesion formation by upregulating fibrinolysis. The aim of this study was to determine the effect of orally administered statins on the promoters and inhibitors of the fibrinolytic pathway. METHODS: In a previously described double-blinded clinical trial, 144 patients undergoing elective colorectal resection, or reversal of Hartmann's procedure were randomized to receive 40 mg once daily oral simvastatin 3-7 d before surgery or placebo. For the purposes of the present study, peritoneal drain fluid was collected postoperatively from patients to measure active tissue plasminogen activator (tPA), tissue plasminogen activator total antigen, active plasminogen activator inhibitor-1 (PAI-1), plasminogen activator inhibitor total antigen (PAI-1TA), plasminogen activator inhibitor-1 and tissue plasminogen activator complex (PAI-1/tPA). These were analyzed using ELISA. The number of hospitalizations and complications related to small bowel obstruction (SBO) were recorded at 2 y after surgery. RESULTS: A total of 95 patients (72%) had sufficient peritoneal
drain fluid suitable for ELISA analysis. Of them, 46 patients (48%) were from the oral simvastatin group. Mean tPA and tPA total antigen concentrations in peritoneal fluid were similar between the two groups. Mean PAI-1 and PAI-1 TA concentrations in the statin and placebo group were also similar. Mean PAI-1/tPA complex concentration was similar between the two groups. The number of hospitalizations from SBOs were 5 and 4 in the statin and placebo groups respectively (P = 0.46). The overall mortality at 2-year post-surgery was similar between the two groups (P = 0.59). CONCLUSIONS: In this pilot study involving humans, oral simvastatin had no measured effect on the peritoneal fibrinolytic pathway in the first 24 h after colorectal surgery. Analysis of clinical outcomes also showed that oral simvastatin did not reduce hospitalizations for SBO in the 2 y after surgery. Further studies may be useful to evaluate whether fibrinolytic pathways beyond 24 h are altered after systemic administration of statins and to evaluate the use of higher doses of statins, perhaps used intraperitoneally rather than systemically.


ABSTRACT

[27] Hannan PA, Khan JA, Ullah I, Ullah S. Synergistic combinatorial antihyperlipidemic study of selected natural antioxidants; modulatory effects on lipid profile and endogenous antioxidants. Lipids in health and disease 2016; 15:151.

ABSTRACT

BACKGROUND: Hyperlipidemia, a major pathological condition associated with disrupted lipid levels and physiological redox homeostasis. The excessive release of reactive oxygen species (ROS) leads to enhanced lipid peroxidation, aggravated atherosclerosis and oxidative stress. Integration of natural antioxidant blends in alone or with conventional treatments can alleviate these issues synergistically contributing least side effects. Published literature reported the efficacy of natural antioxidants as individual and in combinations in various conditions but less data is available on their evaluation in low dose ratio blends particularly in hypercholesterolemic diet. METHODS: Antihyperlipidemic effects of selected natural antioxidants; the phenolic oligomeric proanthocyanidins (OPC) and pterostilbene (PT) with niacin (NA) were investigated in current study. Their effects on lipid profile, lipid peroxidation and their aptitude to establish redox state between oxidants and antioxidants in body were evaluated in high cholesterol diet fed animal model. Male albino rabbits (n = 6) weighing 1.2-1.6 kg, supplemented with high cholesterol diet (400 mg/kg) for 12 weeks were used in the experiment. Antioxidants were administered individual high (100 mg/kg) and in low dose combinations (total dose = 100 mg/kg). Student's t test and one way analysis of variance (ANOVA) followed by Dunnet's test were used as statistical tools for evaluation. RESULTS: The results showed synergistic effects of low dose antioxidant blends. Therapies retarded elevation in blood lipid levels, lipid peroxidation and blood antioxidant depletion and consequently contributed in reestablishing redox homeostasis. The LDL/HDL ratio and atherogenic index were suppressed significantly in blend therapies with maximum effects of 59.3 and 25 % (p >0.001)
observed in 50:30:20 ratios of OPC, NA and PT, compared to individual therapies 37 and 18 % max respectively. Moreover the results were also in close proximity with the statin therapy (52.66, 26.28 %). CONCLUSION: This study provides an evidence for natural antioxidants blends superiority over individual therapy in chronic diseases like hyperlipidemia. Such therapies in human equivalent doses can help in mitigating chronic illnesses in general populations.


ABSTRACT
BACKGROUND: The fatality rate for cardiovascular disease (CVD) has increased in recent years and higher levels of triglyceride have been shown to be an independent risk factor for atherosclerotic CVD. Dysfunction of endothelial cells (ECs) is also a key factor of CVD. APOC3 is an important molecule in lipid metabolism that is closely associated with hyperlipidemia and an increased risk of developing CVD. But the direct effects of APOC3 on ECs were still unknown. This study was aimed at determining the effects of APOC3 on inflammation, chemotaxis and exudation in ECs. METHODS: ELISA, qRT-PCR, immunofluorescence, flow cytometry and transwell assays were used to investigate the effects of APOC3 on human umbilical vein endothelial cells (HUVECs). SiRNA-induced TNF-alpha and JAM-1 silencing were used to observe how APOC3 influenced the inflammatory process in the ECs. RESULTS: Our results showed that APOC3 was closely associated with the inflammatory process in ECs, and that this process was characterized by the increased expression of TNF-alpha. Inflammatory processes further disrupted the tight junctions (TJs) between HUVECs by causing increased expression of JAM-1. JAM-1 was involved in maintaining the integrity of TJs, and it promoted the assembly of platelets and the exudation of leukocytes. Changes in its expression promoted chemotaxis and the exudation of ECs, which contributed to atherosclerosis. While the integrity of the TJs was disrupted, the adhesion of THP-1 cells to HUVECs was also increased by APOC3. CONCLUSIONS: In this study, we describe the mechanism by which APOC3 causes inflammation, chemotaxis and the exudation of ECs, and we suggest that controlling the inflammatory reactions that are caused by APOC3 may be a new method to treat CVD.


ABSTRACT
BACKGROUND: Eruptive xanthomas are benign skin lesions caused by localized deposition of lipids in the dermis. The lesions are generally caused by elevated levels of serum triglycerides that leak through the capillaries and are phagocytosed by macrophages in the dermis. Clinical manifestation varies from asymptomatic skin lesions to intense pruritus and tenderness. METHODS: We present a case of a middle-aged man admitted with diabetic ketoacidosis secondary to noncompliance with insulin. He was found to have skin lesions as multiple crusted papules on the extremities. Further evaluation revealed elevated serum triglycerides. A diagnosis of eruptive xanthomas was made on skin biopsy, and after starting treatment with lipid lowering agents his cutaneous lesions gradually subsided. CONCLUSION: Appearance of
eruptive xanthomas can signify the onset of serious complications. Prompt recognition of such skin manifestations is warranted to prevent development of fatal medical condition like coronary artery disease and pancreatitis.


ABSTRACT


ABSTRACT

Cholesterol reduction at the neuronal plasma membrane has been related to age-dependent cognitive decline. We have used senescent-accelerated mice strain 8 (SAMP8), an animal model for aging, to examine the association between cholesterol loss and cognitive impairment and to test strategies to revert this process. We show that the hippocampus of SAMP8 mice presents reduced cholesterol levels and enhanced amount of its degrading enzyme Cyp46A1 (Cyp46) already at 6 months of age. Cholesterol loss accounts for the impaired long-term potentiation in these mice. Plant sterol (PSE)-enriched diet prevents long-term potentiation impairment and cognitive deficits in SAMP8 mice without altering cholesterol levels. PSE diet also reduces the abnormally high amyloid peptide levels in SAMP8 mice brains and restores membrane compartmentalization of presenilin1, the catalytic component of the amyloidogenic gamma-secretase. These results highlight the influence of cholesterol loss in age-related cognitive decline and provide with a noninvasive strategy to counteract it. Our results suggest that PSE overtake cholesterol functions in the brain contributing to reduce deleterious consequences of cholesterol loss during aging.


ABSTRACT

The incidence of cardiovascular diseases (CVDs) in African populations residing in the African continent is on the rise fueled by both a steady increase in CVD risk factors and comorbidities such as human immunodeficiency virus/acquired immune deficiency syndrome (HIV/AIDS), tuberculosis, and parasitic diseases such as bilharzia. Statins are recommended together with lifestyle changes in the treatment of hypercholesterolemia and overall reduction of cardiovascular events. Rosuvastatin in particular is an attractive candidate in the management of CVDs in African populations often plagued with multimorbidities owing to both its potency and low drug-to-drug interaction potential. In this expert review, we describe the pharmacogenetics of rosuvastatin and how it may instrumentally affect the African populations. We describe polymorphisms in the candidate genes, ABCG2, SLCO1B1, CYP2C9, APOE, PCSK9,
LDLR, LPA, and HMGCR, and their role in the potency and safety of rosuvastatin therapy. We report on qualitative and quantitative differences in the distribution of genetic variants that affect efficacy and toxicity of rosuvastatin. These differences are observed across world populations (Caucasian, European, and Asian) as well as within African populations. Finally, we advocate for extensive pharmacogenetic studies in African populations that take into account the genetic diversity of intra-African ethnic groups and the genetic differences between African populations and other global populations, with a collaborative and collective aim to provide effective and safe use of rosuvastatin in management of CVD in Africa. Our key thesis presented in this innovation field analysis is that rosuvastatin precision medicine can serve as a veritable Glocal (Global and Local) model to offer pharmacogenetic-guided optimal therapeutics for the public in both developing and developed regions of the world.


ABSTRACT
Pitavastatin classically functions as a blood cholesterol-lowering drug. Previously, it was discovered with antglioma stem cell properties through drug screening. However, whether it can be used for liver cancer cell therapy has never been reported. In this study, the cell viability and colony formation assay were utilized to analyze the cytotoxicity of pitavastatin on liver cancer cells. The cell cycle alteration was checked after pitavastatin treatment. Apoptosis-related protein expression and the effect of caspase inhibitor were also checked. The in vivo inhibitory effect of pitavastatin on the growth of liver tumor was also tested. It was found that pitavastatin inhibited growth and colony formation of liver cancer Huh-7 cells and SMMC7721 cells. It induced arrest of liver cancer cells at the G1 phase. Increased proportion of sub-G1 cells was observed after pitavastatin treatment. Pitavastatin promoted caspase-9 cleavage and caspase-3 cleavage in liver cancer cells. Caspase inhibitor Z-VAD-FMK reversed the cleavage of cytotoxic effect of pitavastatin. Moreover, pitavastatin decreased the tumor growth and improved the survival of tumor-bearing mice. This study suggested the antiliver cancer effect of the old drug pitavastatin. It may be developed as a drug for liver cancer therapy.


ABSTRACT
BACKGROUND: Taiwan has the highest renal disease incidence and prevalence in the world. We evaluated the association of statin and renin-angiotensin system inhibitor (RASI) use with dialysis risk in hypertensive patients. METHODS: Of 248,797 patients who received a hypertension diagnosis in Taiwan during 2001-2012, our cohort contained 110,829 hypertensive patients: 44,764 who used RASIs alone; 7,606 who used statins alone; 27,836 who used both RASIs and statins; and 33,716 who used neither RASIs or statins. We adjusted for the following factors to reduce selection bias by using propensity scores (PSS): age; sex; comorbidities; urbanization level; monthly income; and use of nonstatin lipid-lowering drugs, metformin, aspirin, antihypertensives, diuretics, and beta and calcium channel blockers. The
statin and RASI use index dates were considered the hypertension confirmation dates. To examine the dose-response relationship, we categorized only statin or RASI use into four groups in each cohort: <28 (nonusers), 28-90, 91-365, and >365 cumulative defined daily doses (cDDDs). RESULTS: In the main model, PS-adjusted hazard ratios (aHRs; 95% confidence intervals [CIs]) for dialysis risk were 0.57 (0.50-0.65), 0.72 (0.53-0.98), and 0.47 (0.41-0.54) in the only RASI, only statin, and RASI + statin users, respectively. RASIs dose-dependently reduced dialysis risk in most subgroups and in the main model. RASI use significantly reduced dialysis risk in most subgroups, regardless of comorbidities or other drug use (P < 0.001). Statins at >365 cDDDs protected hypertensive patients against dialysis risk in the main model (aHR = 0.62, 95% CI: 0.54-0.71), regardless of whether a high cDDD of RASIs, metformin, or aspirin was used. CONCLUSION: Statins and RASIs independently have a significant dose-dependent protective effect against dialysis risk in hypertensive patients. The combination of statins and RASIs can additively protect hypertensive patients against dialysis risk.


**ABSTRACT**
We recently demonstrated that statins mediate protection against intracellular pathogens, Mycobacterium tuberculosis and Listeria monocytogenes in mice. Here, we investigated the immunomodulatory potential of simvastatin as a topical or systemic host-directed drug therapy in controlling inflammatory responses in an experimental mouse model of cutaneous leishmaniasis caused by Leishmania major (LV39). In an ear infection model, topical application of simvastatin directly on established lesions significantly reduced severity of the disease reflected by ear lesion size and ulceration. The host protective effect was further accompanied by decreased parasite burden in the ear and draining lymph nodes in both BALB/c and C57BL/6 mice. Pre-treatment of these mice on a low-fat cholesterol diet and systemic simvastatin also reduced footpad swelling, as well as parasite burdens and ulceration/necrosis in the more robust footpad infection model, demonstrating the prophylactic potential of simvastatin for cutaneous leishmaniasis. Mechanistically, following L. major infection, simvastatin-treated primary macrophages responded with significantly reduced cholesterol levels and increased production of hydrogen peroxide. Furthermore, simvastatin-treated macrophages displayed enhanced phagosome maturation, as revealed by increased LAMP-3 expression in fluorescent microscopy and Western blot analysis. These findings demonstrate that simvastatin treatment enhances host protection against L. major by increasing macrophage phagosome maturation and killing effector functions.


**ABSTRACT**
Liver injury is a common adverse effect of atorvastatin. This study aimed to investigate atorvastatin-induced hepatotoxicity in diabetic rats induced by high-fat diet combined with
streptozotocin. The results showed that 40 mg/kg atorvastatin was lethal to diabetic rats, whose mean survival time was 6.2 days. Severe liver injury also occurred in diabetic rats treated with 10 mg/kg and 20 mg/kg atorvastatin. The in vitro results indicated that atorvastatin cytotoxicity in hepatocytes of diabetic rats was more severe than normal and high-fat diet feeding rats. Expressions and activities of hepatic Cyp3a and SLCO1B1 were increased in diabetic rats, which were highly correlated with hepatotoxicity. Antioxidants (glutathione and N-Acetylcysteine), Cyp3a inhibitor ketoconazole and SLCO1B1 inhibitor gemfibrozil suppressed cytotoxicity and ROS formation in primary hepatocytes of diabetic rats. In HepG2 cells, up-regulations of CYP3A4 and SLCO1B1 potentiated hepatotoxicity and ROS generation, whereas knockdowns of CYP3A4 and SLCO1B1 as well as CYP3A4/SLCO1B1 inhibitions showed the opposite effects. Phenobarbital pretreatment was used to induce hepatic Cyp3a and SLCO1B1 in rats. Phenobarbital aggravated atorvastatin-induced hepatotoxicity, while decreased plasma exposure of atorvastatin. All these findings demonstrated that the upregulations of hepatic Cyp3a and SLCO1B1 in diabetic rats potentiated atorvastatin-induced hepatotoxicity via increasing ROS formation.


ABSTRACT

The risk of cardiovascular disease (CVD) in patients with rheumatoid arthritis (RA) is 1.5-2-fold higher than age- and sex-matched individuals from the general population. This excess risk is attributed to the systemic chronic inflammation which is a hallmark of RA. Challenges to optimizing CV risk management in RA include the need for improved methods to predict CV risk, and defining the target risk factor(s) to reduce CV risk. Lessons learned from RA studies can also inform CV risk prevention in the general population, where inflammation also has an important role in the pathogenesis of atherosclerosis.


ABSTRACT

Dyslipidemia in type 2 diabetics represents a complex change of lipoprotein metabolism that is highly proatherogenic. It originates on a genetic background in the context of insulin resistance and affects lipoprotein metabolism at multiple levels (e.g. hepatocyte, enterocyte, intravascular processing) mainly in the postprandial phase. The treatment of diabetic (atherogenic) dyslipidemia is an effective option to lower the risk of both macro- and microvascular complications of diabetes. Lifestyle changes effectively impact on dyslipidemia in diabetics, however, it is impossible to reach treatment goals and achieve necessary risk reduction without lipid lowering medications. Statins remain the corner stone of pharmacological therapy and they should be combined with ezetimibe (or a resin) in case of insufficient LDL-cholesterol lowering or with fenofibrate when triglyceride levels remain elevated. In near future these drugs will be available in new fixed-dose combination formulas. Moreover, very soon PCSK9 inhibitors will get to clinical practice offering patients with diabetes additional LDL-cholesterol
lowering by more than 50%. Selective modulators of PPARalpha receptors are under development and these shall offer better efficacy and tolerability compared with fibrates. Other future options for the management of diabetic dyslipidemia will be drugs utilizing the anti-sense technology interfering with translation of genes coding for metabolic pathways of lipoprotein species typically perturbed in type 2 diabetes (e.g. anti-sense oligonucleotides against mRNA of apolipoprotein CIII). KEY WORDS: anti-sense therapy - diabetic dyslipidemia - ezetimibe - fibrates - PCSK9 inhibitors - resins - statins.