
ABSTRACT

BACKGROUND: Over 200 clinical trials have examined the effect of eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) supplements on risk factors associated with cardiovascular disease. However, an updated analysis of the evidence is lacking. The aim of the present meta-analysis was to quantify the effect of supplements containing EPA and DHA on risk factors for cardiovascular disease. METHODS: An analysis was carried on 171 clinical trials with acceptable quality (Jadad score \( \geq 3 \)) that were identified from a comprehensive electronic search strategy of two databases (Pubmed and Cochrane Library). A random effect model was used to obtain an overall estimate on outcomes of interest. Heterogeneity between trial results was tested for using a standard chi-squared test. RESULTS: Compared with control, EPA and DHA supplements produced significant reductions of triglycerides of 0.368 mmol L\(^{-1}\) [95% confidence interval (CI) = -0.427 to -0.309], systolic blood pressure of 2.195 mmHg (95% CI = -3.172 to -1.217), diastolic blood pressure of 1.08 mmHg (95% CI = -1.716 to -0.444), heart rate of 1.37 bpm (95% CI = -2.41 to -0.325) and C-reactive protein of 0.343 mg L\(^{-1}\) (95% CI = -0.454 to -0.232). This analysis indicates an increase in both low-density lipoprotein cholesterol (mean difference = 0.150 mmol L\(^{-1}\); 95% CI = 0.058-0.243) and high-density lipoprotein cholesterol (mean difference = 0.039 mmol L\(^{-1}\); 95% CI = 0.024-0.054). The triglyceride-lowering effect was dose-dependent. CONCLUSIONS: The lipid-lowering, hypotensive, anti-arrhythmic and anti-inflammatory actions of EPA and DHA supplements were confirmed in this analysis of randomised placebo-control blinded clinical trials.


ABSTRACT

Vascular dementia (VaD) is the second commonest cause of dementia. Stroke is the leading cause of disability in adults in developed countries, the second major cause of dementia and the third commonest cause of death. Traditional vascular risk factors-diabetes, hypercholesterolaemia, hypertension and smoking-are implicated as risk factors for VaD. The associations between cholesterol and small vessel disease (SVD), stroke, cognitive impairment and subsequent dementia are complex and as yet not fully understood. Similarly, the effects of lipids and lipid-lowering therapy on preventing or treating dementia remain unclear; the few trials that have assessed lipid-lowering therapy for preventing (two trials) or treating (four trials) dementia found no evidence to support the use of lipid-lowering therapy for these indications. It is appropriate to treat those patients with vascular risk factors that meet criteria for lipid-lowering therapy for the primary and secondary prevention of cardiovascular and cerebrovascular events, and in line with current guidelines. Managing the individual patient in a holistic manner according to his or her own vascular risk profile is recommended. Although the
paucity of randomized controlled evidence makes for challenging clinical decision making, it provides multiple opportunities for on-going and future research, as discussed here.


ABSTRACT
Non-alcoholic fatty liver disease (NAFLD) is the most common liver disease (30% of the general population) and up to 40% of cases advance to the more severe form of the disease: non-alcoholic steatohepatitis (NASH), which is causally related to cirrhosis and cardiovascular disease (CVD). There is no generally accepted effective treatment for NAFLD/NASH. The joint guidelines of the European Association for the Study of the Liver (EASL), the European Association for the Study of Diabetes (EASD) and the European Association for the Study of Obesity (EASO) suggest the "off label" use of pioglitazone in patients without type 2 diabetes mellitus (T2DM) and pioglitazone in subjects with T2DM or vitamin E or their combination for the treatment of NASH; however pioglitazone has considerable limitations: weight gain, bone fractures in women, and heart failure. The aim of this narrative review is to assess the existing evidence supporting statin use for the treatment of NASH and the reduction of the high CVD risk of these patients. Animal data suggest that there is some benefit from statin use in liver histology in models of NASH. In humans, 3 post hoc analyses of randomised controlled trials (n=1,600, n=1,123, n=8,864) suggest that the use of atorvastatin (even in 80 mg/day) has a beneficial effect on NAFLD/NASH, in terms of liver enzyme reduction and ultrasonographic amelioration. Moreover, and most importantly, statin treatment halved CVD morbidity and mortality in statin-treated NAFLD/NASH patients compared with statin-treated participants with normal liver structure and function and reduced by 2/3rds CVD events in comparison with NAFLD/NASH patients that were not on a statin (90% of this population is not on statins because of the unjustified fear for liver damage). Three biopsy studies (n=20, n=107 and n=356) showed that statin treatment had a protective effect on steatosis, steatohepatitis and fibrosis. Data suggest that statin treatment in humans substantially improve or cure NAFLD/NASH, but above all substantially reduce CVD morbidity and mortality. Administration of potent statins appears safe and effective in saving lives in NAFLD/NASH patients.


ABSTRACT
BACKGROUND: The proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitor evolocumab is a low-density lipoprotein (LDL)-lowering drug with a new mechanism, which is currently available in Japan. Here, for the first time, we report the successful use of the PCSK9 inhibitor in a patient with refractory nephrotic syndrome. CASE PRESENTATION: A 61-year-old woman was diagnosed with minimal change-type nephrotic syndrome in October 2012. She received prednisolone (PSL) and cyclosporin A (CyA), but she experienced several cycles of relapse and remission and was hospitalized in May 2016 due to relapse. However, in spite of steroid pulse
therapy and adrenocorticotropic hormone (ACTH) administration, her urinary protein level did not improve. We started her on evolocumab with the expectation of equivalent LDL-lowering effects as seen with LDL apheresis. After that, the LDL cholesterol level and UP/UC were concomitantly decreased, and the serum albumin was increased. This was maintained even when we reduced the PSL dose. This suggests that evolocumab clinically improves the nephrotic condition. CONCLUSION: No other report has described the use of evolocumab for nephrotic syndrome (NS) or its effect on similar nephrotic conditions. We believe that the findings presented here are unique and may be beneficial when treating similar cases.


**ABSTRACT**

PURPOSE OF REVIEW: Familial hypercholesterolemia, represents one of the most extreme clinical entities associated with premature coronary artery disease (CAD). However, clinical manifestation of CAD varies across cohorts and individual patients suggesting the existence of additional non-LDL factors potentially contributing to their cardiovascular burden. RECENT FINDINGS: Changes in HDL-associated proteins appear as one of the potential additional factors contributing to the cardiovascular risk in familial hypercholesterolemia. Specifically, the content of Apo M-SP1 in HDL3 has been directly associated with cholesterol efflux capacity. In addition, a coordinated decrease in the content of Apo L1 and LCAT in HDL3 has been related to the presence of corneal arcus and to bad prognosis in familial hypercholesterolemia patients after an acute ischemic event. In fact, HDL3 particles of familial hypercholesterolemia patients have diminished antioxidant and anti-inflammatory function. SUMMARY: The identification of the specific changes in HDL-associated proteins that contribute to the increased cardiovascular risk of familial hypercholesterolemia patients could be useful for the development of novel therapeutic targets. These novel strategies, in combination with current lipid-lowering therapies, may help to reduce the residual risk found in these patients.


**ABSTRACT**

BACKGROUND: A low number (that is, \(<0.0038\) per 100 peripheral mononuclear cells) of circulating endothelial progenitor cells (EPC) is common in diabetic patients. Statins increase EPC levels. It is unclear whether intensity of statin therapy has a different impact on EPC levels. METHODS: Diabetic patients undergoing drug-eluting stent (DES) implantation were randomized to 1) High intensity statin therapy (atorvastatin 80mg/day; n=66) or 2) Moderate intensity statin therapy (atorvastatin 20mg/day; n=64). EPC levels were assessed at baseline, 24h and 3months. Endpoints assessed at 3months were 1) changes in the proportion of patients with low EPC levels, and 2) uncovered struts rate and neointima growth evaluated by optical coherence tomography. RESULTS: Low EPC levels rate significantly decreased in the High
intensity statin therapy group (from 31.7% to 12.7%; p=0.017) but not in the Moderate intensity statin therapy group (from 25.5% to 21.8%; p=0.81). Uncovered struts rate was similar in the 2 groups (2.4+/−2.6% vs 2.3+/−2.2%; p=0.82), whereas mean neointima area and volume were lower in the High intensity statin therapy group (0.68+/−0.69 vs 1.22+/−1.29mm2; p=0.001; and, respectively, 13.10+/−5.77 vs 20.19+/−24.08mm3; p=0.042). CONCLUSIONS: In diabetic patients, a high intensity statin therapy 1) significantly increases EPC levels and decreases instant neointima area and volume, and 2) does not have an impact on the degree of stent re-endothelialization at 3months after DES implantation.


ABSTRACT

OBJECTIVES: An observational, prospective, cohort study was performed to compare efficacy and safety of a switch from ritonavir-boosted protease inhibitor (PI/r) to nevirapine or raltegravir with that of rosvastatin addition to current antiretroviral therapy in HIV-infected patients with hyperlipidaemia. METHODS: All HIV-infected patients receiving a stable PI/r-based antiretroviral regimen, with persistently suppressed viremia, naive to non-nucleoside analogues and to integrase strand transfer inhibitors, with mixed hyperlipidaemia, and who underwent a switch from PI/r to nevirapine (Group A) or raltegravir (Group B) or who started rosvastatin at 10 mg daily (group C) with unchanged antiretroviral regimen were enrolled into the study. RESULTS: Overall, 136 patients were enrolled: 43 patients were included in the group A, 46 in the group B, and 47 in the group C. The mean age was 46.6 years, and 108 (79.4%) were males. After 48 weeks of follow-up, a significantly greater reduction in the mean low-density lipoprotein (LDL) cholesterol level was reported in group C (-28.2%) than in group A (-10.2%; p < .001) and B (-12.4%; p = .021), while a significantly greater reduction in the mean concentration of triglycerides was observed in group A (-31.2%) and B (-35.5%) than in group C (-11.9%; p = .034 and p = .004, respectively). The incidence of adverse events was <10% and comparable across the three groups. CONCLUSION: In HIV-positive subjects receiving a PI/r, the initiation of rosvastatin treatment after 48 weeks yielded a greater decline in LDL cholesterol, while the switch from PI/r to nevirapine or raltegravir led to a greater decline in triglycerides.


ABSTRACT

Atherosclerosis, the major cause of cardiovascular disease, is a chronic inflammatory disease characterized by the accumulation of lipids and inflammatory cells in the artery wall. Aberrant expression of microRNAs has been implicated in the pathophysiological processes underlying the progression of atherosclerosis. Here, we define the contribution of miR-21 in hematopoietic cells during atherogenesis. Interestingly, we found that miR-21 is the most abundant miRNA in
macrophages and its absence results in accelerated atherosclerosis, plaque necrosis, and vascular inflammation. miR-21 expression influences foam cell formation, sensitivity to ER-stress-induced apoptosis, and phagocytic clearance capacity. Mechanistically, we discovered that the absence of miR-21 in macrophages increases the expression of the miR-21 target gene, MKK3, promoting the induction of p38-CHOP and JNK signaling. Both pathways enhance macrophage apoptosis and promote the post-translational degradation of ABCG1, a transporter that regulates cholesterol efflux in macrophages. Altogether, these findings reveal a major role for hematopoietic miR-21 in atherogenesis.


**ABSTRACT**
The close association of obesity with an increased risk of metabolic diseases, such as insulin resistance, type 2 diabetes and nonalcoholic fatty liver disease (NAFLD), is now well established. In this review we aim first to describe the inflammatory process activated in response to over-nutrition, especially in the liver and the adipose tissue. We then discuss the systemic effects of low-grade inflammation on the onset of insulin resistance. Particular attention is given to a series of very recent reports that identify processes, but also molecules (lipids and metabolites) that interfere with the normal insulin signaling. Finally, special notes concerning the roles of PPARs in the various processes will be made. This article is protected by copyright. All rights reserved.


**ABSTRACT**
Diabetes is an independent risk factor for myocardial ischemia, and many epidemiological data and laboratory studies have revealed that diabetes significantly exacerbated myocardial ischemia/reperfusion injury and ameliorated protective effects. The present study aimed to determine whether pharmacological postconditioning with atorvastatin calcium lessened diabetic myocardial ischemia/reperfusion injury, and investigated the role of glycogen synthase kinase (GSK3beta) in this. A total of 72 streptozotocin-induced diabetic rats were randomly divided into six groups, and 24 age-matched male non-diabetic Sprague-Dawley rats were randomly divided into two groups. Rats all received 40 min myocardial ischemia followed by 180 min reperfusion, except sham-operated groups. Compared with the non-diabetic ischemia/reperfusion model group, the diabetic ischemia/reperfusion group had a comparable myocardial infarct size, but a higher level of serum cardiac troponin I (cTnI) and morphological alterations to their myocardial cells. Compared with the diabetic ischemia/reperfusion group, the group that received pharmacological postconditioning with atorvastatin calcium had smaller myocardial infarct sizes, lower levels of cTnI, reduced morphological alterations to myocardial cells, higher levels of p-GSK3beta, heat shock factor (HSF)-1 and heat shock protein (HSP)70. The cardioprotective effect conferred by atorvastatin calcium did not attenuate...
myocardial ischemia/reperfusion injury following application of TDZD-8, which phosphorylates and inactivates GSK3beta. Pharmacological postconditioning with atorvastatin calcium may attenuate diabetic heart ischemia/reperfusion injury in the current context. The phosphorylation of GSK3beta serves a critical role during the cardioprotection in diabetic rats, and p-GSK3beta may accelerate HSP70 production partially by activating HSF-1 during myocardial ischemic/reperfusion injury.


ABSTRACT

INTRODUCTION: Chronic complications of diabetes have become the leading cause of death in elderly patients with diabetes. Carotid atherosclerosis, one of the major complications was evaluated and the effect of atorvastatin on carotid atherosclerosis in very elderly patients with type 2 diabetes (T2D) were observed. MATERIAL AND METHODS: Patients were divided into 3 groups: 1) disease course < 5 years; 2) disease course = 5-10 years; 3) disease course > 10 years, and carotid atherosclerosis were evaluated. The very elderly patients were treated with statins, and the effect was observed. RESULTS: Carotid Intima-media thickness (IMT) values, plaque instability, and levels of homocysteine (Hcy), cystatin, C-reactive protein (CRP) in diabetic patients were significantly higher than those in the healthy control, while levels of C peptide and estimated glomerular filtration rate (eGFR) in the patients were significantly lower. In T2D > 10 years, IMT values and plaque instability were obviously higher than those in T2D < 5 years, while levels of fasting C peptide and eGFR were lower than those in T2D < 5 years. In the very elderly patients, after statins treatment, IMT values, levels of Hcy, and CRP were significantly reduced, as well as the number of unstable plaque. CONCLUSION: In the elderly patients with T2D, carotid atherosclerosis related factors increased obviously, and renal function declined obviously, which were closely related to the disease course. Atorvastatin significantly reduced Hcy and CRP, delayed and reversed the progress of the carotid atherosclerosis in very elderly patients with T2D. This article is protected by copyright. All rights reserved.


ABSTRACT

Arterial hypertension is a major risk factor for cardiovascular and renal events. Lowering blood pressure is thus an important strategy for reducing morbidity and mortality. Since low-dose aspirin is a cornerstone in the prevention of adverse cardiovascular outcomes, combined treatment with aspirin and antihypertensive drugs is very common. However, the impact of aspirin therapy on blood pressure control remains a subject of intense debate. Recent data suggest that the cardioprotective action of aspirin extends beyond its well-known antithrombotic effect. Aspirin has been shown to trigger the synthesis of specialized pro-
resolving lipid mediators from arachidonic acid and omega-3 fatty acids. These novel anti-inflammatory and pro-resolving mediators actively stimulate the resolution of inflammation and tissue regeneration. Additionally, they may contribute to other protective effects on redox status and vascular reactivity that have also been attributed to aspirin. Of note, aspirin has been shown to improve vasodilation through cyclooxygenase-independent mechanisms. On the other hand, higher aspirin doses have been reported to exert a negative impact on blood pressure due to inhibition of cyclooxygenase-2 activity, which reduces renal blood flow, glomerular filtration rate and sodium and water excretion. This review aims to provide an overview of the effects of aspirin on blood pressure and the underlying mechanisms, focusing on the interaction between aspirin and antihypertensive drugs. Studies in both experimental and human hypertension are presented.


**ABSTRACT**

Nuclear receptors (NR) are involved in the regulation of several metabolic processes and it is well known that these constituents may be modulated by different chemicals classes, including pharmaceuticals that may activate or antagonize NR. In mammals, some pharmaceuticals modulate the transcription of pregnane X receptor, Pxr, peroxisome proliferator activated receptor, Ppars, and aryl hydrocarbon receptor, Ahr, affecting mRNA expression of genes belonging to various regulatory pathways, including lipid metabolism and detoxification mechanisms. The aim of this study was to determine the effects of simvastatin (SIM), an anticholesterolemic drug, on selected NR and AhR mRNA transcription levels during zebrafish early development. Embryos were collected at different development stages (0, 2, 6, 14, 24, 48, and 72 hr post fertilization (hpf)) and mRNA of all target NR was detected at all time points. Embryos (1 and 24 hpf) were exposed to different concentrations of SIM (5 or 50 mg/L) in two differing assays with varying exposure times (2 or 80 hr). The transcription levels of ahr2, raraa, rarab, rarga, pparalphea, pparbeta1, ppargamma, pxr, rxraa, rxrab, rxrbb, rxrga, rxrgb, as well as levels of cholesterol (Chol) were measured after exposure. SIM exerted no marked effect on Chol levels, and depending upon exposure duration mRNA levels of NR and AhR either increased or decreased. After 2 hr SIM treatment in 24 hpf embryos, transcription of ppars, pxr, and ahr was up-regulated, while after 80 hr mRNA levels of pxr and ahr were decreased with no marked changes in ppar. Data demonstrate that SIM produced alterations in gene expression of NR which are involved in varying physiological functions and that may disturb regulation of different physiological processes which might impair fish survival and ecosystems regeneration.


**ABSTRACT**

Hyperlipidemia is characterized by high levels of plasma triglycerides and LDL-cholesterol, accompanied by reduced HDL-cholesterol levels, and is often associated with an increased risk
of cardiovascular diseases. However, few studies have shown the effects of hyperlipidemia on genomic stability. The aim of this study was to evaluate DNA damage provided by tyloxapol induced hyperlipidemia. Tyloxapol, a non-ionic surfactant, which increases the activity of the enzyme HMG-CoA reductase and decreases clearance of lipoproteins, was used to induce hyperlipidemia in Wistar rats. Genomic instability was assessed using the comet assay which evaluates DNA strand breaks in several tissues, and the micronucleus assay in bone marrow to detect chromosomal mutagenicity for clastogenic and/or aneugenic effects. Biochemical analyses confirmed hyperlipidemia in tyloxapol-treated rats, accompanied by hyperglycemia. Higher creatinine and urea levels were observed, suggesting kidney injury. The comet assay indicated increased DNA damage in blood, liver, and kidney, but not in brain tissue. However, no increase in micronucleus frequency was observed, indicating lack of mutagenic effects. Simvastatin, used as lipid lowering drug, decreased cholesterol and triglycerides in rats treated with tyloxapol. Those findings indicate that tyloxapol-induced hyperlipidemia is able to increase genomic instability, which is associated with higher cancer risk. Therefore, this surfactant might be used in models to evaluate new hypolipidemic drugs with associated chemopreventive properties.


ABSTRACT
Non-alcoholic fatty liver disease (NAFLD) and non-alcoholic steatohepatitis (NASH) as progressive form of the disease are associated with cardiovascular risk factors including obesity, dyslipidaemia, hyperglycaemia and hypertension. When NAFLD is associated with cardiovascular disease, mortality of NAFLD patients is increased due to cardiovascular disease. Prevalence of NAFLD and NASH is high, but it seems that epidemic of the disease is under-recognized and under-appreciated. Linking pathophysiological mechanisms are complex and still not well understood. The main related pathophysiological mechanisms are lipid factors, insulin resistance, inflammation, proinflammatory cytokines, oxidative stress, pro-coagulant status, hyperglycaemia and adipokines. First-line management focuses on lifestyle modifications in both diseases. Several therapeutic interventions, insulin sensitizer agents, lipid lowering drugs, antioxidants, such as vitamin E, have been proposed. Statins appear to be safe, but their use in the treatment of NAFLD and NASH is under-appreciated. Many different agents are being investigated as future drugs for the treatment of this clinical entity. The aim of the review is to examine the extent of the epidemic and the mediating mechanisms, to critically evaluate current guideline recommendations, and to consider current and future medications for this disease.


ABSTRACT
Aliskiren penetrates adipose and skeletal muscle in hypertensive patients with abdominal obesity and reduces renin-angiotensin-aldosterone system activity. After discontinuation, blood pressure-lowering effects are observed possibly through drug-tissue binding. We performed microdialysis evaluation of adipose tissue and skeletal muscle before and during an insulin-modified frequently sampled intravenous glucose tolerance test (IM-FSIGT). Aliskiren 300 mg (n = 8) or amlodipine 5 mg (n = 8) once daily were administered during a 12-week randomized treatment period. Aliskiren elicited variable changes in median interstitial angiotensin II (Ang II) in adipose (2.60-1.30 fmol/mL) and skeletal muscle (2.23-0.68 fmol/mL); amlodipine tended to increase adipose and skeletal muscle Ang II (P = .066 for skeletal muscle treatment difference). Glucose/insulin increased median plasma Ang II 1 hour after glucose injection (1.04-2.50 fmol/mL; P = .001), which was markedly attenuated by aliskiren but not amlodipine. Aliskiren increased glucose disposition index (P = .012) and tended to increase acute insulin response to glucose (P = .067). Fasting adipose glycerol (-17%; P = .064) and fasting muscle glucose dialysate (-17%; P = .025) were decreased by aliskiren but not amlodipine. In summary, aliskiren decreased Ang II production in response to glucose/insulin stimulus and elicited metabolic effects in adipose and skeletal muscle suggestive of increased whole-body glucose utilization.


ABSTRACT
BACKGROUND: Statins represent a class of medications widely prescribed to efficiently treat dyslipidemia. These drugs inhibit 3-betahydroxy 3beta-methylglutaryl Coenzyme A reductase (HMGR), the rate-limiting enzyme of mevalonate (MVA) pathway. Besides cholesterol, MVA pathway leads to the production of several other compounds, which are essential in the regulation of a plethora of biological activities, including in the central nervous system. For these reasons, statins are able to induce pleiotropic actions, and acquired increased interest as potential and novel modulators in brain processes, especially during pathological conditions.
OBJECTIVE: The purpose of this review is to summarize and examine the current knowledge about pharmacokinetic and pharmacodynamic properties of statins in the brain. In addition, statin effect on brain diseases are discussed providing the most up-to-date information.
METHODS: Relevant scientific information was identified from PubMed database using the following keywords: statins and brain, central nervous system, neurological diseases, neurodegeneration, brain tumors, mood, stroke. RESULTS: 315 scientific articles were selected and analyzed for the writing of this review article. Several papers highlighted that statin treatment is effective in preventing or ameliorating the symptomatology of a number of brain pathologies. However, other studies failed to demonstrate a neuroprotective effect.
CONCLUSION: Even though considerable research studies suggest pivotal functional outcomes induced by statin therapy, additional investigation is required to better determine the pharmacological effectiveness of statins in the brain, and support their clinical use in the management of different neuropathologies.

ABSTRACT
BACKGROUND: Fish oil supplementation has been shown to be associated with a lower risk of metabolic syndrome and benefit a wide range of chronic diseases, such as cardiovascular disease, type 2 diabetes and several types of cancers. However, the evidence of fish oil supplementation on glucose metabolism and insulin sensitivity is still controversial. This meta-analysis summarized the exist evidence of the relationship between fish oil supplementation and insulin sensitivity and aimed to evaluate whether fish oil supplementation could improve insulin sensitivity. METHODS: We searched the Cochrane Library, PubMed, Embase database for the relevant studies update to Dec 2016. Two researchers screened the literature independently by the selection and exclusion criteria. Studies were pooled using random effect models to estimate a pooled SMD and corresponding 95% CI. This meta-analysis was performed by Stata 13.1 software. RESULTS: A total of 17 studies with 672 participants were included in this meta-analysis study after screening from 498 published articles found after the initial search. In a pooled analysis, fish oil supplementation had no effects on insulin sensitivity compared with the placebo (SMD 0.17, 95%CI -0.15 to 0.48, p = 0.292). In subgroup analysis, fish oil supplementation could benefit insulin sensitivity among people who were experiencing at least one symptom of metabolic disorders (SMD 0.53, 95% CI 0.17 to 0.88, p < 0.001). Similarly, there were no significant differences between subgroups of methods of insulin sensitivity, doses of omega-3 polyunsaturated fatty acids (n-3 PUFA) of fish oil supplementation or duration of the intervention. The sensitivity analysis indicated that the results were robust. CONCLUSIONS: Short-term fish oil supplementation is associated with increasing the insulin sensitivity among those people with metabolic disorders.


ABSTRACT
Acute coronary events, the dreaded manifestation of coronary atherosclerosis, remain one of the main contributors to mortality and disability in the developed world. The majority of those events are associated with atherosclerotic plaques-related thrombus formation following an acute disruption, that being rupture or erosion, of an event-prone lesion. These historically termed vulnerable plaques have been the target of numerous benchtop and clinical research endeavors, yet to date without solid results that would allow for early identification and potential treatment. Technological leaps in cardiovascular imaging have provided novel insights into the formation and role of the event-prone plaques. From intracoronary optical coherence tomography that has enhanced our understanding of the pathophysiological mechanisms of plaque disruption, over coronary computed tomography angiography that enables non-invasive serial plaque imaging, and positron emission tomography poised to be rapidly implemented into clinical practice to the budding field of plaque imaging with cardiac magnetic resonance, we summarize the invasive and non-invasive imaging modalities currently available in our armamentarium. Finally, the current status and potential future imaging directions are critically appraised.

ABSTRACT

BACKGROUND: Although the beneficial effects of statin treatment in dyslipidemia and atherosclerosis have been well studied, there is limited information regarding the renal effects of statins in diabetic nephropathy. We aimed to investigate whether, and which, statins affected renal function in Asian patients with diabetes. METHODS: We enrolled 484 patients with diabetes who received statin treatment for more than 12 months. We included patients treated with moderate-intensity dose statin treatment (atorvastatin 10 to 20 mg/day or rosuvastatin 5 to 10 mg/day). The primary outcome was a change in estimated glomerular filtration rate (eGFR) during the 12-month statin treatment, and rapid renal decline was defined as a >3% reduction in eGFR in a 1-year period. RESULTS: In both statin treatment groups, patients showed improved serum lipid levels and significantly reduced eGFRs (from 80.3 to 78.8 mL/min/1.73 m(2) for atorvastatin [P=0.012], from 79.1 to 76.1 mL/min/1.73 m(2) for rosuvastatin [P=0.001]). A more rapid eGFR decline was observed in the rosuvastatin group than in the atorvastatin group (48.7% vs. 38.6%, P=0.029). Multiple logistic regression analyses demonstrated more rapid renal function loss in the rosuvastatin group than in the atorvastatin group after adjustment for other confounding factors (odds ratio, 1.60; 95% confidence interval, 1.06 to 2.42). CONCLUSION: These results suggest that a moderate-intensity dose of atorvastatin has fewer detrimental effects on renal function than that of rosuvastatin.


ABSTRACT

BACKGROUND AND PURPOSE: High-resolution 3T MR imaging can visualize intracranial atherosclerotic plaque. However, histologic validation is still lacking. This study aimed to evaluate the ability of 3T MR imaging to identify and quantitatively assess intracranial atherosclerotic plaque components ex vivo with histologic validation. MATERIALS AND METHODS: Fifty-three intracranial arterial specimens with atherosclerotic plaques from 20 cadavers were imaged by 3T MR imaging with T1, T2, and proton-density-weighted FSE and STIR sequences. The signal characteristics and areas of fibrous cap, lipid core, calcification, fibrous tissue, and healthy vessel wall were recorded on MR images and compared with histology. Fibrous cap thickness and maximum wall thickness were also quantified. The percentage of areas of the main plaque components, the ratio of fibrous cap thickness to maximum wall thickness, and plaque burden were calculated and compared. RESULTS: The signal intensity of the lipid core was significantly lower than that of the fibrous cap on T2-weighted, proton-density, and STIR sequences (P < .01) and was comparable on T1-weighted sequences (P = 1.00). Optimal contrast between the lipid core and fibrous cap was found on T2-weighted images. Plaque component mean percentages were comparable between MR imaging and histology: fibrous component (81.86% +/- 10.59% versus 81.87% +/- 11.59%, P =
.999), lipid core (19.51% +/- 10.76% versus 19.86% +/- 11.56%, P = .863), and fibrous cap (31.10% +/- 11.28% versus 30.83% +/- 8.51%, P = .463). However, MR imaging overestimated mean calcification (9.68% +/- 5.21% versus 8.83% +/- 5.67%, P = .030) and plaque burden (65.18% +/- 9.01% versus 52.71% +/- 14.58%, P < .001). CONCLUSIONS: Ex vivo 3T MR imaging can accurately identify and quantitatively assess intracranial atherosclerotic plaque components, providing a direct reference for in vivo intracranial plaque imaging.


ABSTRACT

Hypertriglyceridemia, defined as serum triglyceride (TG) levels >150 mg/dL, now affects over one-quarter of the US adult population and is associated with an increased risk of atherosclerotic cardiovascular disease. Available guidelines for managing hypertriglyceridemia vary with respect to TG thresholds and severity of disease. Lifestyle modifications and management of secondary causes (eg, diabetes) remain the first step in managing hypertriglyceridemia, with pharmacotherapy reserved to reduce the risk of pancreatitis and/or further reduce TG levels. Several classes of lipid-lowering agents are available with variable TG-lowering efficacy. Although there is no consensus regarding the choice of initial TG-lowering pharmacotherapy, there is general agreement that the decision depends on the degree of hypertriglyceridemia and atherosclerotic cardiovascular disease risk. This review will discuss available and emerging lipid-lowering therapies for the management of moderately elevated TG, defined as TG 150 to 499 mg/dL.


ABSTRACT


ABSTRACT

BACKGROUND: The mechanism of statin for atheroma stabilization remains unclear. We aimed to assess the relationship between on-treatment changes in serum inflammatory biomarker levels and plaque composition in differed nonculprit coronary lesions. METHODS AND RESULTS: The changes in serum biochemical values, and intravascular ultrasound data were evaluated in 218 patients with virtual histology (VH)-intravascular ultrasound-defined fibroatheroma-containing segments after 12-month rosuvastatin treatment. When stratifying patients into quartiles according to the change in high-sensitivity C-reactive protein (hsCRP), there was a significant positive linear relationship for the changes in %necrotic core (coefficient, 1.31; standard error, 0.54) and %dense calcium volumes (coefficient, 0.80; standard error, 0.27), but
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A negative linear relationship for the changes in %fibrous (coefficient, -0.94; standard error, 0.45) and %fibrofatty volumes (coefficient, -1.17; standard error, 0.56; all P<0.05). The decrease in hsCRP (-1.2 +/- 3.9 versus 0.5 +/- 3.4 mg/L; P=0.02) was greater in those without VH-defined thin-cap fibroatheroma (TCFA, defined as >30 degrees of necrotic core abutting the lumen in 3 consecutive slices) than those with VH-TCFA at follow-up. Diabetes mellitus, a larger normalized total atheroma volume, and the presence of VH-TCFA at baseline predicted the presence of VH-TCFA at follow-up (odds ratio, 4.01, 1.18, and 9.21, respectively; all P<0.05), whereas the change in hsCRP showed a trend (odds ratio, 1.19; P=0.07). The change in low-density lipoprotein-cholesterol had no relationship with the changes in hsCRP or plaque compositions.

CONCLUSIONS: With 12-month rosuvastatin therapy, a greater hsCRP reduction (not low-density lipoprotein-cholesterol) was associated with a greater decrease in %necrotic core volume and the absence of VH-TCFA, indicating a link between the anti-inflammatory action of statin and plaque stabilization by reducing NC and reinforcing fibrous cap.


ABSTRACT

BACKGROUND: The prophylactic efficacy of statin pretreatment for the prevention of contrast-induced nephropathy (CIN) in patients undergoing coronary angiography (CAG) or percutaneous coronary intervention (PCI) remains controversial. The aim of the study was to perform a meta-analysis of randomized controlled trials (RCTs) to assess the effectiveness of short-term moderate or high-dose rosuvastatin pretreatment in preventing CIN. METHODS: We included RCTs comparing short-term moderate or high-dose rosuvastatin treatment versus low-dose rosuvastatin treatment or placebo for preventing CIN. The primary endpoint was the incidence of CIN within 2 to 5 days after contrast administration, and related-parameters including serum creatinine (SCr), cystatin C (CysC), hypersensitive C-reactive protein (hs-CRP), urine microalbumin (mALB) were also extracted. RESULTS: Fifteen RCTs with a total of 2673 patients were identified and analyzed. Patients who received moderate or high-dose rosuvastatin pretreatment had a 55% lower risk of CIN compared with low-dose rosuvastatin pretreatment or placebo group based on a fixed effect model (RR = 0.45, 95% CI 0.35-0.58, P < .0001). The benefit of moderate or high-dose rosuvastatin was consistent in both comparisons with low-dose rosuvastatin (RR = 0.40, 95% CI 0.27-0.59, P < .0001) or placebo (RR = 0.45, 95% CI 0.35-0.58, P < .0001). And moderate (20 mg) or high dose (>/=40 mg) rosuvastatin significantly reduced the incidence of CIN compared with the control (RR = 0.39, 95% CI 0.29-0.54, P < .0001, RR = 0.56, 95% CI 0.37-0.85, P = .006, respectively). Subgroup analysis showed that moderate or high-dose rosuvastatin pretreatment could decrease the incidence of CIN in patients with chronic kidney disease (CKD) (RR = 0.53, 95% CI 0.30-0.93, P = .03) or diabetes mellitus (DM) (RR = 0.51, 95% CI 0.31-0.86, P = .01) or acute coronary syndrome (ACS) patients undergoing PCI (RR = 0.52, 95% CI 0.35-0.76, P = .0009) or in studies which received mean contrast volume >/=110 mL (RR = 0.43, 95% CI 0.32-0.58, P < .0001). The SCr, CysC, hs-CRP, and mALB after the operation in the moderate or high-dose rosuvastatin group were lower than...
those of low-dose rosuvastatin group. CONCLUSION: This meta-analysis demonstrated that moderate or high-dose rosuvastatin treatment could reduce the incidence of CIN in patients undergoing CAG or PCI. Moreover, moderate or high-dose rosuvastatin would be beneficial in high-risk patients with CKD or DM or undergoing PCI.


**ABSTRACT**

AIM: This study aims to investigate the prevalence and risk factors of statin-induced myopathy. SUBJECTS AND METHODS: A total of 200 patients aged >/= 40 years and taking atorvastatin 10 mg/day or more for at least 2 weeks were recruited in the study. A detailed history of participants and anthropometry of study participants was recorded, and features of myopathy were explained. Biochemical investigations along with thyroid stimulating hormone (TSH) and Vitamin D were done in all patients. RESULTS: Mean age of study population was 54.81 +/- 9.10 years. Sixty-five percent (65.5%) of atorvastatin users had coronary heart disease, 62.5% were hypertensive, 38% had diabetes. Thirty-five percent (35.5%) patients were taking 10 mg/day atorvastatin, 45% were taking 20 mg/day, and 19.5% were taking 40 mg/day. The overall frequency of myopathy among statin users was 7.5% which was significantly higher with increasing dose of atorvastatin (1.4% in 10 mg/day group, 10% in 20 mg/day group, and 12.8% in 40 mg/day, P < 0.05). The frequency of atorvastatin-related myopathy was higher in females 8.65% compared to 6.25% in males. Serum TSH levels in patients with myopathy were 4.05 +/- 7.76 muIU/ml while in those without myopathy were 3.13 +/- 2.88 muIU/ml (P = 0.649). Serum 25-hydroxy Vitamin D levels were measured in 66 patients randomly. Mean levels in patients with myopathy were 15.98 +/- 12.94 ng/ml and without myopathy were 10.20 +/- 5.64 ng/ml (P = 0.285). CONCLUSION: The present study demonstrates that a significantly higher number of patients taking atorvastatin develop myopathy in real life clinical condition. The frequency of myopathy increases with increase in atorvastatin dose.


**ABSTRACT**

Toluene, used as a pure substance or in solvent mixtures, is the cause of occupational exposures of large numbers of workers in the world. The organic anion transporting polypeptides (OATP: human; Oatp: rodents) are drug carriers which have been frequently associated to drug-drug interactions. The objective of this study was to evaluate the influence of inhalation exposure to toluene in Oatp in vivo activity using pravastatin as a probe drug in rats. Male Wistar rats were exposed to 85 mg/m3 toluene by inhalation or air in a nose only exposure system for 6 hours/day, 5 days/week during 4 weeks, in order to simulate the occupational exposure to toluene at level slightly above the occupational exposure limit proposed by ACGIH. After 4 weeks of exposure, animals received a single dose of 20 mg/kg pravastatin orally. Areas under concentration x time curves extrapolated to infinite (AUC0-
ABSTRACT


OBJECTIVE: Arterial stiffness (AS) and non-alcoholic fatty liver diseases (NAFLD) are 2 related, prevalent, risk predictors of cardiovascular disease (CVD). We assessed the effect of low dose (5 mg/day) vs high dose (20-40 mg/day) rosvastatin on aortic elasticity and central haemodynamics as well as on NAFLD in patients with arterial hypertension (AH).

METHODS: Forty patients with optimally controlled AH were randomised to 2 rosvastatin doses and followed for 6 months. 24h AS was assessed by Mobil-O-Graph, which calculates (adjusted for age and gender) pulse wave velocity (PWV), adjusted for heart rate (HR) augmentation index (AIx75%) and central haemodynamics. The diagnosis of NAFLD was based on ≥5% liver steatosis on ultrasound and moderately elevated serum levels of liver enzymes.

RESULTS: Both doses of rosvastatin reduced central pulse pressure (cPP), PWV and AIx75% (adjusted for HR) to normal values (p = NS adjusted for age, gender and HR). Liver enzymes were reduced in those with NAFLD to normal, but steatosis was reduced more by the 20-40 mg/day rosvastatin dose (p=0.01) compared with the 5 mg/day dose.

CONCLUSIONS: Both doses of rosvastatin had a beneficial effect on AS; the high dose was more efficient in reducing PWVs and central haemodynamics, and also the high dose was more effective in ameliorating NAFLD. Given that AH control was optimal and lipid values attained targets, 4 other CVD predictors were also addressed. Larger and longer term studies are needed to demonstrate the clinical benefit of such treatment preference.


ABSTRACT

Fluvastatin, which is one of the hydroxymethylglutaryl-CoA (HMG-CoA) reductase inhibitors (statins), is primarily metabolized by CYP2C9 and to a lesser extent by CYP3A4 and CYP2C8. Predictions of drug-drug interactions (DDI) are important for the safety of combination therapies with statins, in particular drugs that are metabolized by CYP3A4. Little information is...
available regarding drug interactions with fluvastatin. Since CYP2C9 is a polymorphic enzyme, we investigated the effect of DDI via CYP2C9, CYP3A4, and CYP2C8 on fluvastatin pharmacokinetics by using a validated prediction method in relation to CYP2C9 variants. The predicted increases in the area under the concentration-time curve (AUC) ratios of fluvastatin in carriers with CYP2C9*1/*2, CYP2C9*1/*3, CYP2C9*2/*2, CYP2C9*2/*3, and CYP2C9*3/*3 versus that found in carriers with CYP2C9*1/*1 were 1.16, 1.35, 1.37, 1.65, and 2.06, respectively. Our in silico model predicted that administration of fluvastatin in conjunction with the potent inhibitors that completely inhibited CYP3A4 and CYP2C8 in carriers with the CYP2C9*3/*3 variant would cause a 3.23- and 2.60-fold increase in the AUC ratios, respectively, when compared to that for the carriers with the CYP2C9*1/*1 taking fluvastatin alone. We also predicted the effect of telmisartan when coadministered with fluvastatin. Our prediction results showed that the interaction between telmisartan and fluvastatin via CYP enzymes were negligible in clinical situations.


ABSTRACT
BACKGROUND: Radiotherapy in patients with pelvis malignancy causes testes irradiation and resulted in testicular damages. Atorvastatin (ATV) in the low-dose is considered as antioxidant and anti-inflammatory properties. OBJECTIVE: This experimental study was investigated protective effects of ATV on irradiation-induced testicular injury. MATERIAL AND METHODS: Sixty male balb/c mice were randomly divided into 6 groups: 1: control, 2: irradiated (IR), 3, 4 and 5: IR plus ATV (10, 20 and 50mg/kg), 6: only ATV (50mg/kg). The ATV treated groups were received ATV for 7 days via oral gavage before IR. Irradiated groups exposed to 2Gy whole body X-ray on day 8. Biochemical, histological and immunohistological parameters were evaluated for radioprotective effect of ATV. RESULTS: In the ATV pretreatment groups, MDA levels were significantly decreased compared with the IR group. The effect of all three doses of ATV caused reduced MDA level, but ATV to dose of 50mg/kg had more effect than other doses of ATV. Significant decrease in the concentration of testosterone was observed in ATV pre-treated groups in compared with the group that received only irradiation. In addition, the histological examination showed Johnson's Score in the IR group was lower compared to ATV pretreated groups. ATV significantly reduced apoptosis index induced by irradiation. CONCLUSION: The results from this study suggest that ATV at low dose has a protective effect against irradiation-induced testicular damage. This result provides a new indication of ATV for protection of testis during radiation therapy in treatment of cancer patients.


ABSTRACT
INTRODUCTION: The present study is the largest registry study ever conducted in Japan exploring the prevalence of familial hypercholesterolaemia (FH) among patients with acute
coronary syndrome (ACS). Our study aims to (1) evaluate the status of lipid management and the subsequent risk of major cardiovascular events following hospitalisation of Japanese patients with ACS in real-world clinical practice; (2) determine the proportion of Japanese patients with ACS who achieve the lipid management goal and have a reduction of event risks with strict lipid management (low-density lipoprotein-cholesterol <1.81 mmol/L); (3) determine the prevalence of FH and (4) investigate the clinical significance of proprotein convertase subtilisin kexin 9 (PCSK9) level. METHODS AND ANALYSIS: We will conduct a multicentre, prospective, observational study of approximately 2000 Japanese patients with ACS with/without FH hospitalised between April 2015 and August 2016. The primary end point is the incidence of major adverse cardiovascular events (MACEs) after initial hospitalisation. The secondary end points are (1) MACE developed from visit 1 to visit 2 (day 30); (2) MACE developed from visit 2 (day 30) to visit 5 (day 730); (3) treatment rate by lipid-lowering therapies (any statin or intensive, PCSK9 inhibitor, fibrates and ezetimibe); (4) incidence of events by the addition of the following outcomes to the primary end point: coronary revascularisation due to myocardial ischaemia, revascularisation other than coronary artery, inpatient treatment for occurrence or exacerbation of heart failure, transient ischaemic attack, acute arterial occlusion, central retinal artery occlusion and other adverse events prolonging or requiring hospitalisation and (5) proportion of subjects achieving target lipid levels. ETHICS AND DISSEMINATION: The study protocol was submitted to the ethical review committee of each participating centre for approval. Participation in the study is voluntary and anonymous. The study findings will be disseminated in international peer-reviewed journals and presented at relevant conferences. CLINICAL TRIAL REGISTRATION: UMIN000018946.


ABSTRACT
A series of structurally interesting coumarin-chalcone fibrates were synthesized and evaluated for their PPARalpha/gamma agonist activities and antioxidant activities. Among these compounds, compounds 5a, 5d, and 7a were identified as potent PPARalpha and gamma dual agonists, and their PPARalpha agonist activities were found to be more potent than that of Fenofibrate. Furthermore, the results of antioxidant investigations revealed that compounds 5d and 6a-6d had greater potency than Trolox with IC50 values ranging from 9.40 µM to 18.63 µM. The structure-activity relationship revealed that the electron-withdrawing nitro group substituted at the C6' position of the benzopyran moiety increased the PPARalpha and gamma agonist efficacy. Moreover, the presence of a double bond on the benzopyran moiety was essential for PPARalpha and gamma agonist efficacy. The agonist activity of PPARalpha exhibited by compound 5d was examined by molecular docking studies. Taken together, the results we obtained showed that compound 5d had the potential to be a lead compound for further research.
OBJECTIVE: To investigate whether lipid-lowering drugs are associated with new-onset diabetes after adjusting for baseline clinical risk factors for diabetes. DESIGN: A retrospective cohort study. SETTING: Japanese employees of large corporations and their dependents using health insurance claims data linked to clinical and laboratory data for annual health screenings. PARTICIPANTS: All persons aged 20 to 74 years with dyslipidaemia between 1 January 2005 and 31 March 2011. We defined the index date as the first date when the person met the criteria for dyslipidaemia. Persons were excluded if they had lipid-lowering drugs, or had a diagnosis, a treatment or a laboratory test result (haemoglobin A1c >/=6.5% or fasting blood glucose >/=126 mg/dL) indicating diabetes during the 6-month period before the index date. MAIN OUTCOME MEASURES: New-onset diabetes. RESULTS: We identified 68 620 persons with dyslipidaemia. During the mean follow-up period of 1.96 years, 3674 persons started treatment with a lipid-lowering drug: 979 with a low potency statin, 2208 with a high potency statin and 487 with a fibrate. Of 3674 new users of a lipid-lowering drug, 3621 had a period of non-use of any lipid-lowering drugs before starting a lipid-lowering drug. Among statin users, the incidence rate of new-onset diabetes was 124.6 per 1000 person-years compared with 22.6 per 1000 person-years in non-users. After adjusting for confounding factors including clinical data in health screening using Cox proportional hazards models, the HR was 1.91 (95% CI 1.38 to 2.64) for low potency statins and 2.61 (2.11 to 3.23) for high potency statins. CONCLUSION: The use of statins was associated with a 1.9-fold to 2.6-fold increase in the risk of new-onset diabetes in a Japanese population of working age, despite adjusting for clinical risk factors for diabetes.

CONTEXT: PCSK9 mediates the degradation of the low-density lipoprotein receptor (LDLR) thereby increasing plasma low density lipoprotein cholesterol (LDL-C). Variations in the PCSK9 gene that are associated with loss-of-function (LOF) of PCSK9 result in a greater expression of hepatic LDLR, lower concentrations of LDL-C, and protection from cardiovascular disease (CVD). Apolipoprotein-B (apo) remnants also contribute to CVD risk and are similarly cleared by the LDLR. We hypothesized that PCSK9-LOF carriers would have significantly lower fasting and postprandial remnant lipoproteins on top of lower LDL-C. OBJECTIVE: To compare fasting and postprandial concentrations of triglycerides (TG), total-apoB and apoB48 as indicators of remnant lipoprotein metabolism in PCSK9-LOF carriers with controls with no PCSK9 variants. DESIGN: Case-control, metabolic study. SETTING: Clinical Research Center of the Ottawa Hospital. PARTICIPANTS: Subjects with 1 or more copies of the L10ins/A53V and/or I474V and/or R46L PCSK9 variant, and no PCSK9 variants (non-carrier controls). INTERVENTION(S): Oral fat tolerance test. MAIN OUTCOMES MEASURED: Fasting and postprandial plasma TG,
apoB48, total-apoB, total cholesterol, and PCSK9 were measured at 0, 2, 4, and 6 hours after an oral fat load. RESULTS: Subjects with PCSK9-LOF variants (n=22) had significantly reduced fasting LDL-C (-14%) as well as lower fasting TG (-21%) compared to non-carrier controls (n=23). LOF variants also had significantly reduced postprandial total-apoB (-17%), apoB48 (-23%), and TG (-18%). Postprandial PCSK9 declined in both LOF and non-variant groups (-24% versus -16%, respectively). CONCLUSIONS: Subjects carrying PCSK9-LOF variants had attenuated levels of fasting and postprandial TG, apoB48 and total-apoB. This may confer protection from CVD and further validate the use of PCSK9 inhibitors to lower CVD risk.


ABSTRACT
Non-alcoholic fatty liver disease (NAFLD) is becoming the most common chronic liver disease. NAFLD may evolve to non-alcoholic steatohepatitis (NASH), which is causally related to cirrhosis and cardiovascular disease (CVD) mortality. There is no generally accepted effective treatment for NAFLD/NASH. Chronic kidney disease (CKD) is relatively common and might co-exist with NAFLD/NASH, aggravate one another, and increase CVD risk. Common therapies could improve outcome. Potent statins at high doses, such as atorvastatin and rosuvastatin, ameliorate NAFLD/NASH and reduce the mortality rates by half as compared with those on the same statins but without liver disease. and CVD-related events are reduced by atorvastatin for patients with all stages of CKD. The new anti-diabetic medication classes, the sodium-glucose co-transporter-2 inhibitors (SGLT2i) and the glucagon like peptide receptor agonists (GLP1 RA) for patients with NAFLD/NASH, CKD and T2DM are useful because they ameliorate NAFLD/NASH, delay the evolution of CKD, and substantially reduce CVD and all-cause mortality. Thus, the common use of high potency statins, renin-angiotensin-aldosterone system inhibitors, and the newer anti-diabetic agents increase compliance and can substantially reduce CVD risk and the rate of liver and kidney adverse events, improving quality of life and survival.


ABSTRACT
Nonalcoholic fatty liver disease (NAFLD), the most common chronic liver disease in Western countries with potential progression to nonalcoholic steatohepatitis (NASH) and cirrhosis, is associated with cardiovascular disease (CVD) mortality. Several studies have reported a relationship between uric acid and NAFLD/NASH and it seems that serum uric acid (SUA) is a significant independent factor for the development of NAFLD. Potential mediating mechanisms include insulin resistance, endothelial dysfunction, and activation of inflammasome, especially NLRP3. Moreover, emerging evidence indicates a strong association between elevated SUA, metabolic syndrome (MetS), NAFLD, and CVD. The emphasis of the present review is whether common therapy of elevated SUA levels and NAFLD can improve compliance. There are several
drugs with "off target" properties that show some separate benefit on SUA reduction (e.g. losartan) or NAFLD/NASH (pioglitazone); however, there is no randomized controlled trial (RCT) of a single drug with beneficial outcome for both diseases. Allopurinol reduces SUA levels and ameliorates NAFLD/NASH; however, no RCTs have been performed up to now to explore potential survival benefits. Atorvastatin, which has proven safe in NAFLD/NASH, reduces SUA levels, ameliorates NAFLD/NASH, prevents liver fibrosis, and above all substantially reduces CVD morbidity and mortality in comparison with those on statins but without NAFLD/NASH. This drug could be a solution to improve compliance in both diseases, which are prevalent and becoming even more common with the obesity, MetS, and type 2 diabetes mellitus epidemic.


ABSTRACT


ABSTRACT

It is becoming increasingly apparent that mutual interactions between adipocytes and immune cells are key to the integrated control of adipose tissue inflammation and lipid metabolism in obesity, but little is known about the non-inflammatory functions of adipose tissue macrophages (ATMs) and how they might be impacted by neighboring adipocytes. In the current study we used metabololipidomic analysis to examine the adaptations to lipid overload of M1 or M2 polarized macrophages co-incubated with adipocytes and explored potential benefits of omega-3 polyunsaturated fatty acids (PUFA). Macrophages adjust their metabolism to process excess lipids and M2 macrophages in turn modulate lipolysis and fatty acids (FA) re-esterification of adipocytes. While M1 macrophages tend to store surplus FA as triacylglycerols and cholesteryl esters in lipid droplets, M2 macrophages channel FA toward re-esterification and beta-oxidation. Dietary omega-3 PUFA enhance beta-oxidation in both M1 and M2. Our data document that ATMs contribute to lipid trafficking in adipose tissue and that omega-3 PUFA could modulate FA metabolism of ATMs.


ABSTRACT

Amikacin (AMIK) is an aminoglycoside antibiotic that possesses considerable nephrotoxic adverse effects. This study examined the protective effects of vitamin E (VIT. E) or rosvastatin (ROSU) against AMIK-induced nephrotoxicity. For this purpose, eight groups of rats were used. Two control groups received saline and vehicle, AMIK group (1.2 g/kg, i.p.), VIT. E group (1000 mg/kg; p.o.), ROSU group (10 mg/kg; p.o.), AMIK + VIT. E group, AMIK + ROSU group, and
combination group. The results showed that AMIK significantly increased serum levels of urea and creatinine. Meanwhile, serum levels of total protein and albumin were decreased. The kidney content of malondialdehyde was increased, whereas glutathione content and catalase activity were decreased. Tumor necrosis factor-alpha and nuclear transcriptional factor levels were increased. Conversely, administration of VIT. E and/or ROSU with AMIK ameliorated such damage and reduced DNA fragmentation, apoptosis, and necrosis. In conclusion, co-administration of VIT. E, ROSU, or their combination alleviated AMIK-induced nephrotoxicity.

ABSTRACT
BACKGROUND: Dyslipidaemia is a risk factor for macrovascular complications in patients with type 2 diabetes mellitus (T2DM). Our aim was to assess the use of lipid lowering drugs (LLDs) in patients with T2DM and co-existing dyslipidaemia. METHOD: A multicentre, non-interventional survey conducted in 6 Middle Eastern countries (Bahrain, Oman, Qatar, United Arab Emirates, Kingdom of Saudi Arabia and Kuwait). Patients with T2DM (n = 3338) who received LLD treatment for >/=3 months with no dose change for >/=6 weeks were enrolled. RESULTS: The mean age (SD) of T2DM patients was 56.6 +/-10.6 years; the majority (99%) were on statin monotherapy. Only 48% of these patients achieved their low density lipoprotein cholesterol (LDL-C) goal and 67.7% of the patients had a high cardiovascular disease (CVD) risk according to the National Cholesterol Education Program (NCEP) Adult Treatment Panel (ATP) III guidelines. Of those who achieved LDL-C goals (n=1589), approximately one-third were at very high CVD risk and the patients who had received statin monotherapy showed the highest proportion in LDL-C goal attainment, followed by those treated with fibrate monotherapy. In a multivariate logistic regression model, taking drugs daily (odds ratio, OR: 1.64, 95% CI 1.25, 2.15) and older age (OR: 1.09, 95% CI 1.01, 1.18) were significantly associated with better odds of attaining LDL-C target. In contrast, patients with higher levels of ApoA1 (OR: 0.73, 95% CI [0.67,0.79 ]), Metabolic Syndrome (OR: 0.64, 95% CI [0.53, 0.76]), higher CV risk (OR: 0.33, 95% CI 0.27, 0.41), those who forgot to take their medication (OR: 0.74, 95% CI 0.62,0.88) and those who stopped taking medication when cholesterol became normal (OR: 0.67, 95% CI 0.55,0.82) were significantly associated with lower odds of attaining LDL-C target. CONCLUSION: The results of this study highlight the suboptimal management of dyslipidaemia in T2DM patients at high and very high risk of CVD.

ABSTRACT
BACKGROUND: Serum small dense LDL-cholesterol (sdLDL-C) value is suggested to be an important risk factor for atherosclerosis. Since sdLDL-C changes may be related to PCSK9 and SREBP-2 functions, the aim of this study was to investigate correlations between sdLDL-C,
circulating PCSK9, SREBP-2 expression and some lipid parameters in serum and butty coat fraction of healthy subjects. METHODS: One hundred and twenty-four subjects were randomly included in the study. The lipid profile was measured using routine laboratory methods. The serum sdLDL-C level was calculated by a heparin-related precipitation technique. The cellular LDL-C/protein and cholesterol/protein values were measured after lysing of cells with methanol/chloroform binary solvent. The circulating PCSK9 level was measured using ELISA technique. The SREBP-2 expression level was estimated using theRT-qPCR technique. RESULTS: Data showed significant correlations between LDL-C, TG and sdLDL-C levels (r=0.34, p=0.001; r=0.2, p=0.04). The circulating PCSK9 level was correlated to LDL-C (r=0.29, p=0.04), but not to sdLDL-C (r=-0.08, p=0.57). Also, cellular LDL-C value was not related to serum LDL-C level (r=-0.12, p=0.39). Furthermore, there was an inverse correlation between cellular LDL-C/protein value and estimated de novo cholesterol/protein value (r= -0.5, p=0.001). Similar results were observed for cellular LDL-C/protein value and SREBP-2 expression level (r= -0.52, p=0.004).

CONCLUSIONS: We concluded that the serum sdLDL-C value is not related to circulating PCSK9. Furthermore, SREBP-2 regulatory system was able to elevate the cellular cholesterol level after reducing LDL influx. We suggest to investigate the cellular sdLDL fate and lipid synthesis pathways in PCSK9-targeting studies.


ABSTRACT

BACKGROUND: High-density lipoproteins (HDL) are well characterized for their role in reverse cholesterol transport but may confer other cardiovascular benefits-specifically, HDL may suppress the endothelial activation cascade in the initiating stages of atherogenesis. OBJECTIVE: It was the primary aim of this study to examine the relations of HDL cholesterol (HDL-C), total HDL particle (HDL-P) concentrations, and HDL-P subclasses with circulating levels of endothelial activation markers in a subcohort of Multi-Ethnic Study of Atherosclerosis participants.

METHODS: HDL-C was measured by enzymatic assay, and total HDL-P and subclass concentrations were assessed by nuclear magnetic resonance spectroscopy. Concentrations of circulating endothelial activation markers were determined through immunoassay. Multivariable linear regression was used to determine the cross-sectional associations between HDL variables and endothelial markers with statistical adjustment for age, race/ethnicity, sex, education, systolic blood pressure, hypertension medication use, body mass index, smoking status, lipid-lowering medication use, serum creatinine, diabetes, low-density lipoprotein cholesterol, and coronary artery calcium. RESULTS: HDL-C and HDL-P were found to be inversely associated with soluble vascular cell adhesion molecule-1, soluble vascular intracellular adhesion molecule-1, sL-selectin, and sP-selectin; HDL-P was additionally inversely associated with sE-selectin. Participants with low levels of HDL-C (<40 mg/dL) or HDL-P (<25th percentile) showed 3%-12% higher mean levels of soluble vascular cell adhesion molecule and compared with those above these levels (all P < .01). CONCLUSION: Coupled with previous evidence, our findings suggest a modest to moderate relation of HDL and circulating levels of endothelial
activation markers in humans. Whether this relationship may have clinical implications in suppressing atherogenesis or coronary heart disease development requires additional research.


ABSTRACT
BACKGROUND: In a recently described probe drug cocktail for clinically relevant drug transporters containing digoxin, furosemide, metformin and rosuvastatin, mutual interactions were essentially absent except for increases in the systemic exposure of rosuvastatin. To optimize the cocktail, we further examined the dose dependence of the effects of metformin and furosemide on rosuvastatin pharmacokinetics. METHODS: This was a randomized, open label, single center, six-treatment, six-period, six-sequence crossover trial. Eighteen healthy male subjects received 10 mg rosuvastatin as reference treatment and, as test treatments, 10 mg rosuvastatin combined with 10, 50 or 500 mg metformin (T1, T2 and T3) or with 1 or 5 mg furosemide (T4 and T5). Primary pharmacokinetic endpoints were rosuvastatin C max (maximum plasma concentration) and AUC0-tz (area under the plasma concentration-time curve from time zero to the last quantifiable concentration). RESULTs: The relative bioavailability of rosuvastatin was essentially unchanged when administered with metformin in T1 and T2, but in T3 it increased to 152% for AUC0-tz (90% CI 135-171%) and 154% for C max (90% CI 132-180%). Coadministration with furosemide did not change rosuvastatin relative bioavailability in T4, but in T5 it increased slightly to 116% for AUC0-tz (90% CI 102-132%) and 118% for C max (90% CI 98-142%). CONCLUSION: The increased systemic exposure of rosuvastatin when administered as part of the proposed transporter cocktail is most likely attributable to metformin and only to a minor degree to furosemide. Reduction of the doses of metformin and furosemide is expected to eliminate the previously described interaction. EudraCT no. 2015-003052-46, ClinicalTrials.gov identifier NCT02574845.


ABSTRACT


ABSTRACT
An imbalance between energy intake and expenditure leads to obesity. Adiposity associated with obesity progressively causes inflammation, type 2 diabetes, hypertension, hyperlipidemia and cardiovascular disease. Excessive dietary intake of fat results in its accumulation and storage in the white adipose tissue (WAT), whereas energy expenditure by fat utilization and oxidation predominately occurs in the brown adipose tissue (BAT). Recently, the presence of a
third type of fat, referred to as beige or brite (brown in white), has been recognized in certain kinds of WAT depots. It has been suggested that WAT can undergo the process of browning in response to stimuli that induce and enhance the expression of thermogenes characteristic of those typically associated with brown fat. The resultant beige or brite cells enhance energy expenditure by reducing lipids stored within adipose tissue. This has created significant excitement towards the development of a promising strategy to induce browning/beiging in WAT to combat the growing epidemic of obesity. This review systematically describes differential locations and functions of WAT and BAT, mechanisms of beiging of WAT and a concise analysis of drug molecules and natural products that activate the browning phenomenon in vitro and in vivo. This review also discusses potential approaches for targeting WAT with compounds for site-specific beiging induction. Overall, there are numerous mechanisms that govern browning of WAT. There are a variety of newly identified targets whereby potential molecules can promote beiging of WAT and thereby combat obesity.


ABSTRACT


ABSTRACT

BACKGROUND: Familial hypercholesterolemia is one of the most common inherited metabolic diseases and is an autosomal dominant disorder meaning heterozygotes, or carriers, are affected. Those who are homozygous have severe disease. The average worldwide prevalence of heterozygous familial hypercholesterolemia is at least 1 in 500, although recent genetic epidemiological data from Denmark and next generation sequencing data suggest the frequency may be closer to 1 in 250. Diagnosis of familial hypercholesterolemia in children is based on elevated total cholesterol and low-density lipoprotein cholesterol levels or DNA-based analysis, or both. Coronary atherosclerosis has been detected in men with heterozygous familial hypercholesterolemia as young as 17 years old and in women with heterozygous familial hypercholesterolemia at 25 years old. Since the clinical complications of atherosclerosis occur prematurely, especially in men, lifelong treatment, started in childhood, is needed to reduce the risk of cardiovascular disease. In children with the disease, diet was the cornerstone of treatment but the addition of lipid-lowering medications has resulted in a significant improvement in treatment. Anion exchange resins, such as cholestyramine and colestipol, were found to be effective, but they are poorly tolerated. Since the 1990s studies carried out on children aged 6 to 17 years with heterozygous familial hypercholesterolemia have demonstrated significant reductions in their serum total and low-density lipoprotein cholesterol levels. While statins seem to be safe and well-tolerated in children, their long-term safety in this age group is not firmly established. This is an update of a previously published version of this Cochrane Review. OBJECTIVES: To assess the effectiveness and safety of statins in children with heterozygous familial hypercholesterolemia. SEARCH METHODS: Relevant studies were
identified from the Group's Inborn Errors and Metabolism Trials Register and Medline. Date of most recent search: 20 February 2017. SELECTION CRITERIA: Randomized and controlled clinical studies including participants up to 18 years old, comparing a statin to placebo or to diet alone. DATA COLLECTION AND ANALYSIS: Two authors independently assessed studies for inclusion and extracted data. MAIN RESULTS: We found 26 potentially eligible studies, of which we included nine randomized placebo-controlled studies (1177 participants). In general, the intervention and follow-up time was short (median 24 weeks; range from six weeks to two years). Statins reduced the mean low-density lipoprotein cholesterol concentration at all time points (moderate quality evidence). Serum aspartate and alanine aminotransferase, as well as creatinine kinase concentrations, did not differ between treated and placebo groups at any time point (low quality evidence). The risks of myopathy (low quality evidence) and clinical adverse events (moderate quality evidence) were very low and also similar in both groups. In one study simvastatin was shown to improve flow-mediated dilatation of the brachial artery (low quality evidence), and in another study treatment with pravastatin for two years induced a significant regression in carotid intima media thickness (low quality evidence). AUTHORS' CONCLUSIONS: Statin treatment is an effective lipid-lowering therapy in children with familial hypercholesterolemia. No significant safety issues were identified. Statin treatment seems to be safe in the short term, but long-term safety remains unknown. Children treated with statins should be carefully monitored and followed up by their pediatricians and their care transferred to an adult lipidologist once they reach 18 years of age. Large long-term randomized controlled trials are needed to establish the long-term safety issues of statins.


ABSTRACT
BACKGROUND: Current international guidelines on dyslipidemia are not concordant on various aspects of management. Also, there are no uniformly accepted Indian guidelines. We, therefore, performed a physician survey to understand lipid management practices in India. METHODS: An anonymous survey questionnaire was administered to gauge physicians' self-reported behavior regarding lipid management aspects. Results were expressed in terms of percentages based on the number of responses obtained. RESULTS: A total of 404 physicians participated in the survey. Eighty-eight percent respondents ordered a lipid profile before starting statin therapy, and 80% preferred to set lipid targets, though the tools used for calculating cardiovascular risk varied. Atorvastatin was preferred over rosuvastatin in primary prevention (72.9 vs. 32.4%), secondary prevention (54.6 vs. 46.7%), diabetic patients (56.3 vs. 40.3%) and post-ACS (78.3 vs. 34%). High-intensity statins were preferred by 73.7% of respondents in post-ACS cases. Fifty percent doctors chose not to use a statin in diabetic patients, irrespective of their LDL-C levels. The most preferred drug option for managing atherogenic dyslipidemia and moderate hypertriglyceridemia was statin-fibrate combination (55.1%) and fibrates (35.4%), respectively. Sixty-three percent doctors preferred to prescribe statins in patients with moderately high LDL-C and normal triglycerides, without CHD or CHD risk equivalents. Around 28% of doctors preferred not to use pharmacotherapy for managing isolated low HDL. Of the participants, 73% used fibrates in &le;20% of their dyslipidemic
patients, with fenofibrate being the most preferred (90.5%). Ezetimibe was mainly used in patients with uncontrolled LDL-C despite statin therapy (52.4% respondents). Most preferred approaches to manage statin intolerance included reducing statin dose (39%) and stopping and restarting statins at a lower dose (34.5%). Fifty-two percent of doctors chose not to alter pre-existing therapy in patients who had LDL-C levels at goal but elevated non-HDL-C levels.

CONCLUSION: This is the first survey in India that provides useful insights into Indian physicians' self-reported perspectives on managing dyslipidemia in routine clinical practice. Despite concordance with the currently available guidelines in certain aspects, there is incongruence in managing specific dyslipidemia problems. Further continuing medical education and the development of evidence-based, India-specific lipid guidelines can help reduce some of these differences.


ABSTRACT

BACKGROUND: The platelet to lymphocyte ratio (PLR), an indirect inflammatory biomarker, has been recently demonstrated to be associated with severity of coronary artery disease. In the present study, we sought to investigate whether PLR is associated with vulnerable plaque characteristics of non-culprit lesions in patients with acute coronary syndrome (ACS).

METHODS: The patients in our study were divided into two groups (high PLR group and low PLR group). A total of 119 non-culprit plaques from 71 patients with ACS were assessed by optical coherence tomography (OCT).

RESULTS: The non-culprit plaques in high PLR group exhibited thinner fibrous cap thickness (FCT) (88.60 +/- 44.70 vs. 119.28 +/- 50.22 mum, P = 0.001), greater maximum lipid arc (271.73 +/- 71.66 vs. 240.60 +/- 76.69 degrees, P = 0.027) and increased incidence of thin-cap fibroatheroma (TCFA) (34.0% vs. 15.9%, P = 0.022) compared with those in low PLR group. Meanwhile, PLR was negatively associated with FCT (r = -0.329, P < 0.001). Furthermore, multivariate regression analysis showed that PLR [OR: 1.023 (95% CI: 1.005-1.041), P = 0.012] and LDL-C [OR: 1.892 (95% CI: 1.106-3.239), P = 0.020] were significant predictors of TCFA.

CONCLUSIONS: High level of PLR may be associated with vulnerable plaque features of non-culprit lesions in patients with ACS. PLR, a cheap and easily available index, may serve as a useful inflammatory marker in reflecting plaque vulnerability.


ABSTRACT

The present report describes the case of a 57-year-old woman presenting with subarachnoid hemorrhage (SAH) and acute ischemic stroke (AIS) due to anterior cerebral artery (ACA) dissection, which exhibited severe stenosis at the origin with distal dilatation of the A2 segment and occlusion of the A3 segment. In this case, computed tomography (CT) revealed SAH in right superior frontal sulcus and the interhemispheric fissure. Magnetic resonance imaging
demonstrated acute infarct in the territory of the right ACA. Brain digital subtraction angiography showed severe stenosis at the origin of the A2 segment with distal dilatation and occlusion at the origin of the A3 segment of the right ACA, suggesting a diagnosis of dissection. Only treatment with atorvastatin, her clinical condition subsequently improved. The stenosis and dilatation of A2 segment were ameliorated as demonstrated by a follow-up CT angiography 5 months after onset. SAH concomitant with ischemia caused by ACA dissection is rare. Conservative treatment may be a safe and effective choice for patients with SAH concomitant with AIS due to ACA dissection.


ABSTRACT
Dyslipidemia is the risk of cardiovascular disease, and their relationship is clear. Lowering serum cholesterol can reduce the risk of coronary heart disease. At present, the main treatment is taking medicine, however, drug treatment has its limitations. Exercise not only has a positive effect on individuals with dyslipidemia, but can also help improve lipids profile. This review is intending to provide information on the effects of exercise training on both traditional lipids, for example, low-density lipoprotein cholesterol, high-density lipoprotein cholesterol, triglycerides and new lipids and lipoproteins such as non-high-density lipoprotein cholesterol, and postprandial lipoprotein. The mechanisms of aerobic exercise on lipids and lipoproteins are also briefly described.


ABSTRACT


ABSTRACT
PURPOSE: This study aimed to examine the impact of combined supplementation of fish oil (FO) with antioxidants like wheat germ oil (WGO) on mineral-bone and inflammatory markers in maintenance HD patients. METHODS: This randomized, double-blind, placebo-controlled trial involved 46 HD patients who were randomly assigned into two groups to receive daily 3000 mg of FO [1053 mg omega-3 fatty acids (omega-3 FAs)] plus 300 mg of WGO [0.765 mg vitamin E] or placebo for 4 months. Blood concentrations of hemoglobin (Hgb), white blood cells, mineral-bone parameters including serum calcium (Ca), phosphorus, calcium-phosphorus product, parathyroid hormone, alkaline phosphatase, and osteoprotegerin and serum concentrations of inflammatory markers including high-sensitivity C-reactive protein, ferritin, and uric acid were
measured before and after the intervention. RESULTS: Eighty-seven percentage of patients in each group completed the study. The mean serum Ca levels increased significantly in the supplemented group at the end of study (p = 0.0016), and this increment was also significant as compared to placebo group (p = 0.0418). No significant alterations were observed in the other measured parameters within each group during the study (as p values were >0.05).

CONCLUSION: FO plus WGO supplementation showed beneficial effect on serum Ca levels of HD patients without any statistically significant effect on other mineral-bone and inflammatory markers. Further investigations are required to confirm it.


ABSTRACT

OBJECTIVE: The purpose of this study was to investigate the effect of simvastatin on periprosthetic bone mineral density (BMD) in hypercholesterolaemic patients after total hip arthroplasty.

METHODS: From January 2012 to December 2015, a total of 42 consecutive hypercholesterolaemic patients with total hip arthroplasty were recruited for this study. The simvastatin group was 21 patients (15 males, 6 females) with average age of 69.4 +/- 6.6 years treated with simvastatin for one year post-operatively, and the control group was the other 21 patients (12 males, 9 females) who did not take simvastatin. These parameters of the periprosthetic bone mineral density after total hip arthroplasty were collected by dual energy X-ray absorptiometry (DEXA) one week and three, six, 12 months post-operatively.

RESULTS: In the control group patients showed significant loss of periprosthetic BMD in ROIs 1, 2, 6, and 7 throughout the study period. The loss of BMD in ROIs 3 and 5 was only significantly observed at three months follow-up and recovered thereafter. There were no significant detected changes of BMD in ROI 4. In the Simvastatin group, the percentage of BMD loss was significantly less (P < 0.05) in ROI 1, 2, 6 and 7 throughout the study period than the control group. The percentage of BMD loss were significant observed in ROI 3 and 5 at three months follow-up, which were also significantly less (P < 0.05) than in the control group. A slight gain of BMD was measured in ROI 4 at 12 months follow-up (1.419%, P < 0.05). CONCLUSION: Simvastatin administered for one year post-operatively can effectively prevent periprosthetic bone loss after total hip arthroplasty.