Literature update week 26 (2017)


ABSTRACT
Context * Coronary heart disease (CHD) is a major public health problem in developing and developed countries. Elevated cholesterol levels, especially low-density lipoprotein (LDL) cholesterol, and the emergence of CHD, have been positively correlated in many clinical and epidemiological studies. The health benefits of probiotics have received a great deal of attention, including their blood cholesterol-lowering effects on humans. Objective * The research team intended to determine the current state of research examining the effects of various probiotic strains on lipid profiles, including measures in serum of total cholesterol, LDL cholesterol, triglycerides, and high-density lipoprotein (HDL) cholesterol. Design * The review examined studies, in both animal and human models and focused on the potential of various probiotic strains to be dietary adjuncts in lowering levels of serum cholesterol with the aim of reducing the risk of cardiovascular disease (CVD) and CHD. Articles were reviewed systematically from Web search bases including PubMed and Cochrane Clinical Trial Registry. Articles meeting the inclusion search criteria were selected for further review and analysis. Only randomized controlled trials evaluating the effects of probiotics on lipid profiles in animals or humans were considered for inclusion in the review. Setting * The selection of articles and further inclusion in the review was performed in Institute of Home Economics, University of Delhi (New Delhi, India). Results * Some of the studies, in both animal and human models, have revealed that several strains were able to improve at least 1 lipid fraction. Although the results from animal studies have been fairly consistent, the findings from studies on humans have varied. Some strains when evaluated in human studies have shown insignificant effects on lipid fractions. Conclusions * Although several mechanisms for cholesterol removal by probiotics have been proposed, they need further investigation to be validated.


ABSTRACT
In striated muscle, EPA and DHA have differential effects on the metabolism of glucose and differential effects on the metabolism of protein. We have shown that, despite similar incorporation, treatment of C2C12 myotubes (CM) with EPA but not DHA improves glucose uptake and protein accretion. We hypothesized that these differential effects of EPA and DHA may be due to divergent shifts in lipidomic profiles leading to altered proteomic profiles. We therefore carried out an assessment on the impact of treating CM with EPA and DHA on lipidomic and proteomic profiles. FAME analysis revealed that both EPA and DHA led to similar but substantial changes in fatty acid profiles. Global lipidomic analysis showed that EPA and DHA induced large alterations in the cellular lipid profiles and in particular, the phospholipid classes. Subsequent targeted analysis confirmed that the most differentially regulated species were phosphatidylcholines and phosphatidylethanolamines containing long chain fatty acids.
with 5 (EPA treatment) or 6 (DHA treatment) double bonds. As these are typically membrane associated lipid species we hypothesized that these treatments differentially altered the membrane-associated proteome. SILAC based proteomics of the membrane fraction revealed significant divergence in the effects of EPA and DHA on the membrane associated proteome. We conclude that the EPA specific increase in polyunsaturated long chain fatty acids in the phospholipid fraction is associated with an altered membrane associated proteome and these may be critical events in the metabolic remodelling induced by EPA treatment.


**ABSTRACT**

RATIONALE: Dysregulated neutrophil functions are described with age and sepsis. Statins are associated with improved infection survival in some observational studies but trials in critically ill patients have not shown benefit. Statins also alter neutrophil responses in vitro. OBJECTIVE: To assess neutrophil migratory accuracy with age during respiratory infections and determine if and how a statin intervention could alter these blunted responses. METHODS: Migratory accuracy of blood neutrophils from young (aged<35) and old (aged>60) patients in health, during a lower respiratory tract infection (LRTI), pneumonia (CAP) and pneumonia associated sepsis (S-CAP) was assessed with and without simvastatin. In vitro results were confirmed in a double-blinded randomised clinical trial in healthy elders. Cell adhesion markers were assessed.

RESULTS: In vitro neutrophil migratory accuracy in the elderly deteriorated as the severity of the infectious pulmonary insult increased, without recovery at six weeks. Simvastatin rescued neutrophil migration with age and during mild-moderate infection, at high dose in older adults, but not during more severe sepsis. Confirming in vitro results, high dose (80mg) simvastatin improved neutrophil migratory accuracy without impeding other neutrophil functions in a randomised, double-blinded clinical trial in healthy elders. Simvastatin modified surface adhesion molecule expression and activity, facilitating accurate migration in the elderly.


**ABSTRACT**

Health effects of dietary fats have been extensively studied for decades. However, controversies exist on the effects of various types of fatty acids, especially saturated fatty acid (SFA), on cardiovascular disease (CVD). Current evidence supports that different types of dietary fatty acids have divergent effects on CVD risk, and the effects also depend strongly on the comparison or replacement macronutrient. A significant reduction in CVD risk can be
achieved if SFAs are replaced by unsaturated fats, especially polyunsaturated fatty acids. Intake of industrially produced trans fat is consistently associated with higher CVD risk. Both n-6 and n-3 polyunsaturated fatty acids are associated with lower CVD risk, although the effects of fish oil supplementation remains inconsistent. The 2015-2020 Dietary Guidelines for Americans place greater emphasis on types of dietary fat than total amount of dietary fat and recommend replacing SFAs with unsaturated fats, especially polyunsaturated fatty acids for CVD prevention. Expected final online publication date for the Annual Review of Nutrition Volume 37 is August 21, 2017. Please see http://www.annualreviews.org/page/journal/pubdates for revised estimates.


ABSTRACT
SIGNIFICANCE: Oxidative stress represents the common hallmark of pathological conditions associated with cardiovascular disease (CVD), including atherosclerosis, heart failure, hypertension, aging, diabetes, and other vascular system-related diseases. The sirtuin (SIRT) family, comprising seven proteins (SIRT1-SIRT7) sharing a highly conserved nicotinamide adenine dinucleotide (NAD+)-binding catalytic domain, attracted a great attention for the past few years as stress adaptor and epigenetic enzymes involved in the cellular events controlling aging-related disorder, cancer, and CVD. Recent Advances: Among sirtuins, SIRT1 and SIRT6 are the best characterized for their protective roles against inflammation, vascular aging, heart disease, and atherosclerotic plaque development. This latest role has been only recently unveiled for SIRT6. Of interest, in recent years, complex signaling networks controlled by SIRT1 and SIRT6 common to stress resistance, vascular aging, and CVD have emerged. CRITICAL ISSUES: We provide a comprehensive overview of recent developments on the molecular signaling pathways controlled by SIRT1 and SIRT6, two post-translational modifiers proven to be valuable tools to dampen inflammation and oxidative stress at the cardiovascular level. FUTURE DIRECTIONS: A deeper understanding of the epigenetic mechanisms through which SIRT1 and SIRT6 act in the signalings responsible for onset and development CVD is a prime scientific endeavor of the upcoming years. Multiple "omic" technologies will have widespread implications in understanding such mechanisms, speeding up the achievement of selective and efficient pharmacological modulation of sirtuins for future applications in the prevention and treatment of CVD. Antioxid. Redox Signal. 00, 000-000.


ABSTRACT
BACKGROUND AND AIMS: Oxidative modification of lipoproteins is a crucial step in atherosclerosis development. Isotopic-reinforced polyunsaturated fatty acids (D-PUFAs) are more resistant to reactive oxygen species-initiated chain reaction of lipid peroxidation than regular hydrogenated (H-)PUFAs. We aimed at investigating the effect of D-PUFA treatment on
lipid peroxidation, hypercholesterolemia and atherosclerosis development. METHODS: Transgenic APOE*3-Leiden.CETP mice, a well-established model for human-like lipoprotein metabolism, were pre-treated with D-PUFAs or control H-PUFAs-containing diet (1.2%, w/w) for 4 weeks. Thereafter, mice were fed a Western-type diet (containing 0.15% cholesterol, w/w) for another 12 weeks, while continuing the D-/H-PUFA treatment. RESULTS: D-PUFA treatment markedly decreased hepatic and plasma F2-isoprostanes (approx. -80%) and prostaglandin F2alpha (approx. -40%) as compared to H-PUFA treatment. Moreover, D-PUFAs reduced body weight gain during the study (-54%) by decreasing body fat mass gain (-87%) without altering lean mass. D-PUFAs consistently reduced plasma total cholesterol levels (approx. -25%), as reflected in reduced plasma non-HDL-cholesterol (-28%). Additional analyses of hepatic cholesterol metabolism indicated that D-PUFAs reduced the hepatic cholesterol content (-21%). Sterol markers of intestinal cholesterol absorption and cholesterol breakdown were decreased. Markers of cholesterol synthesis were increased. Finally, D-PUFAs reduced atherosclerotic lesion area formation throughout the aortic root of the heart (-26%). CONCLUSIONS: D-PUFAs reduce body weight gain, improve cholesterol handling and reduce atherosclerosis development by reducing lipid peroxidation and plasma cholesterol levels. D-PUFAs, therefore, represent a promising new strategy to broadly reduce rates of lipid peroxidation, and combat hypercholesterolemia and cardiovascular diseases.


ABSTRACT

BACKGROUND AND AIMS: Several studies have confirmed the presence of bacterial DNA in atherosclerotic plaques, but its contribution to plaque stability and vulnerability is unclear. In this study, we investigated whether the bacterial plaque-profile differed between patients that were asymptomatic or symptomatic and whether there were local differences in the microbial composition within the plaque. METHODS: Plaques were removed by endarterectomy from asymptomatic and symptomatic patients and divided into three different regions known to show different histological vulnerability: A, upstream of the maximum stenosis; B, site for maximum stenosis; C, downstream of the maximum stenosis. Bacterial DNA composition in the plaques was determined by performing 454 pyrosequencing of the 16S rRNA genes, and total bacterial load was determined by qPCR. RESULTS: We confirmed the presence of bacterial DNA in the atherosclerotic plaque by qPCR analysis of the 16S rRNA gene but observed no difference (n.s.) in the amount between either asymptomatic and symptomatic patients or different plaque regions A, B and C. Unweighted UniFrac distance metric analysis revealed no distinct clustering of samples by patient group or plaque region. Operational taxonomic units (OTUs) from 5 different phyla were identified, with the majority of the OTUs belonging to Proteobacteria (48.3%) and Actinobacteria (40.2%). There was no difference between asymptomatic and symptomatic patients, or plaque regions, when analyzing the origin of DNA at phylum, family or OTU level (n.s.). CONCLUSIONS: There were no major differences in bacterial DNA amount or microbial composition between plaques from asymptomatic and symptomatic patients or between different plaque regions, suggesting that other factors are more important in determining plaque vulnerability.
BACKGROUND AND AIMS: Inflammation in atherosclerotic plaques is an important determinant of plaque vulnerability, and can be detected non-invasively using ultra-small superparamagnetic iron-oxide (USPIO) enhanced MRI. The aims of the current study were: 1) to determine whether ferumoxytol can be used for USPIO-MRI of atherosclerotic plaques, 2) to establish a protocol for quantitative USPIO-MRI of carotid artery plaques using ferumoxytol, and 3) to study the relation between USPIO uptake and plaque burden and 18F-fluorodeoxyglucose (FDG) uptake (measured by 18F-FDG PET/CT scan) in atherosclerotic plaques. METHODS: In 9 patients with carotid artery stenosis >30% and 4 healthy controls, quantitative R2* MRI scans of the carotid arteries were performed before and 72 h after USPIO administration (4 mg/kg ferumoxytol). USPIO uptake was assessed by quantifying the difference in R2* (DeltaR2*) between baseline and post-USPIO scans. In addition to MRI, 18F-FDG PET/CT was performed on both carotid arteries. MR and PET/CT images were coregistered, and 18F-FDG uptake was quantified in all slices containing atherosclerotic plaque. RESULTS: Infusion of ferumoxytol resulted in higher R2* values after 72 h in atherosclerotic plaques (DeltaR2* 24.6 +/- 19.8 s-1; p = 0.0003), but not in the healthy control vessel wall (DeltaR2* 2.6 +/- 5.6 s-1, p = 0.23). USPIO uptake in patients was higher in atherosclerotic plaques compared to the patient non-plaque vessel wall (DeltaR2* of 24.6 +/- 19.8 vs. 7.5 +/- 9.3 s-1, p = 0.004). No correlation was found between USPIO uptake and 18F-FDG uptake in atherosclerotic plaques (R2 = 0.03, p = 0.55). CONCLUSIONS: Ferumoxytol is selectively taken up by atherosclerotic plaques and can thus be used for carotid USPIO-MRI. As USPIO and 18F-FDG uptake in atherosclerotic plaque do not correlate in this cohort, these agents may visualize different pathophysiological aspects of plaque inflammation.


ABSTRACT

BACKGROUND: Tolerance to analgesic effects of opioids and dependence to them are main concerns in the treatment of chronic pain conditions, limiting clinical application of these drugs. This study aimed to evaluate the effect of simvastatin on the morphine-induced tolerance and dependence in mice. MATERIAL AND METHODS: For this purpose, mice were treated with either daily morphine (20 mg/kg, s.c.) alone, or in combination with simvastatin (2.5, 5 and 10mg/kg, i.p.), for 9 continuous days. Antinociceptive effect of morphine was assessed through measuring latency time withdrawal of paw exposed to thermal stimulus, in the hot plate test. Naloxone-precipitated morphine withdrawal (5mg/kg, i.p.), was used for dependence evaluation. Changes in brain gene expression levels of induced nitric oxide synthase (iNOS), astroglia marker, glial fibrillary acidic protein (GFAP), ionized calcium-binding protein (Iba1) a microglia activation marker, a pro-inflammatory mediator and tumor necrosis alpha (TNF-
alpha) were measured after withdrawal by real-time polymerase chain reaction (RT-PCR). RESULTS: Behavioral tests indicated that latency time increased after morphine treatment in the hot plate test. However, this effect decreased on day 7, demonstrating tolerance to antinociceptive effect of morphine. Reduced anti-nociceptive effect of morphine was returned in animals treated with simvastatin (5 and 10mg/kg) in combination with morphine. Simvastatin (5 and 10mg/kg) attenuated morphine dependence as indicated by a less severe antagonist-precipitated withdrawal syndrome. Administration of naloxone was associated with the increased expression of TNF-alpha, GFAP, Iba1 and iNOS in the brain samples of morphine dependent mice, while the nine days treatment with both 5 and 10mg/kg simvastatin reduced such changes. CONCLUSION: The obtained results showed that the protective effects of simvastatin against both tolerance to nociceptive effects of morphine as well as withdrawal-induced behavioral profile are meaningful. Inhibition of glia activity as well as antioxidant effects of pharmaceutical simvastatin further proves its neuroprotective property.


ABSTRACT


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ABSTRACT

BACKGROUND AND PURPOSE: Patients with active rheumatoid arthritis (RA) have increased cardiovascular mortality, paradoxically associated with reduced circulating lipid levels. The Janus kinase (Jak) inhibitor tofacitinib ameliorates systemic and joint inflammation in RA with a concomitant increase in serum lipids. We analyzed the effect of tofacitinib on the lipid profile of hyperlipidemic rabbits with chronic arthritis (CA) and on the regulation of reverse cholesterol transport (RCT) during chronic inflammation. EXPERIMENTAL APPROACH: CA was induced in previously immunized rabbits fed with a high-fat diet (HFD) by administering four intra-articular injections of ovalbumin. A group of rabbits received tofacitinib (10 mg kg-1 day-1 ) for two
weeks. Systemic and synovial inflammation and lipid content were evaluated. For in vitro studies, THP-1-derived macrophages were exposed to high lipid concentrations, and then stimulated with interferon gamma (IFN\(\gamma\)) in the presence or absence of tofacitinib in order to study RCT mediators. KEY RESULTS: Tofacitinib decreased systemic and synovial inflammation and increased circulating lipid levels. Although it did not modify synovial macrophage density, it was able to reduce the lipid content within synovial macrophages. In foam macrophages in culture, IFN\(\gamma\) further stimulated intracellular lipid accumulation, while Jak/STAT inhibition provoked by tofacitinib induced lipid release by increasing cellular liver X receptor alpha (LXR\(\alpha\)) and ATP-binding cassette transporter (ABCA1) synthesis. CONCLUSION AND IMPLICATIONS: Active inflammation could be associated with lipid accumulation within macrophages of CA rabbits. Jak inhibition induced lipid release though RCT activation, providing a plausible explanation for the effect of tofacitinib on the lipid profile of RA patients.


ABSTRACT

BACKGROUND: Recent observations have suggested a decline in vulnerable carotid artery and iliofemoral atherosclerotic plaque characteristics over the past decade. The aim of this study was to determine whether, in the presence of clinically manifest carotid or peripheral artery disease, secondary adverse cardiovascular events decreased over this period. METHODS: Patients included in the Athero-Express biobank between 2003 and 2012 were analysed. During 3-year follow-up, composite cardiovascular endpoints were documented yearly, including: myocardial infarction, coronary interventions, stroke, peripheral interventions and cardiovascular death. The major cardiovascular endpoint consisted of myocardial infarction, stroke and cardiovascular death. RESULTS: Some 1684 patients who underwent carotid endarterectomy (CEA) and another 530 who had iliofemoral endarterectomy (IFE) were analysed. In total, 405 (25.2 per cent) and 236 (45.9 per cent) patients had a composite cardiovascular endpoint within 3 years after CEA and IFE respectively. Corrected for possible confounders, the percentage of patients with a secondary cardiovascular event after CEA did not change over time (hazard ratio (HR) 0.91, 95 per cent c.i. 0.65 to 1.28; \(P = 0.590\), for 2011-2012 versus 2003-2004). In patients who had IFE, the incidence of secondary cardiovascular events significantly decreased only in the last 2 years (HR 0.62, 0.41 to 0.94; \(P = 0.024\)), owing to a decrease in peripheral (re)interventions in 2011-2012 (HR 0.59, 0.37 to 0.94; \(P = 0.028\)). No decrease in major cardiovascular events was observed in either group. CONCLUSION: In patients who had undergone either CEA or IFE there was no evidence of a decrease in all secondary cardiovascular events. There were no differences in major cardiovascular events.


ABSTRACT

AIM: Pitavastatin (Pit) has been proved to efficiently inhibit the onset and progression of atherosclerosis. However the mechanism by which Pit exert non-lipid related effects, such as anti-inflammatory actions, is not quite clear. Our study aimed at investigating the effect of Pit on the expression of eNOS and miR-155 in LPS-stimulated HUVECs to reveal the anti-inflammatory mechanism of pitavastatin. METHODS: HUVECs were isolated from newborn umbilical cords and used in the experiments at passages 2-5. Cells were treated with LPS (0.05, 0.1, 1 mug/L) or LPS (0.1 mug/L) + Pit (0.01, 0.1, 1mumol/L), untreated cells were used as control. For LPS + Pit induction, cells were firstly incubated with Pit for 1 h before co-incubation with LPS for 24 h. eNOS mRNA and miR-155 were detected by RT-PCR and western blotting was used to detect protein expression of eNOS. RESULTS: Treatment of HUVECs with LPS enhanced the expression of miR-155 and reduced the expression of eNOS in mRNA and protein level in a dose-dependent manner as revealed by RT-PCR and western blotting respectively. Pitavastatin ameliorated LPS-induced endothelial dysfunction through up-regulation of eNOS expression and down-regulation of miR-155 expression. CONCLUSION: Pitavastatin increases eNOS expression and inhibits of LPS-induced miR-155 expression. This article is protected by copyright. All rights reserved.


ABSTRACT

AIM: We previously demonstrated that anoxia-mediated Ca2+ handling dysfunction could be ameliorated through inhibition of mevalonate pathway via RhoA- and Ras-related mechanisms in H9c2 cells. In this study, we further explored whether inhibition of mevalonate pathway is associated with cardiac remodeling and dysfunction in ischemic cardiomyopathy, and discuss the possible role of Ras, Rac and RhoA in cardiac dysfunction. METHODS: We investigated the role of mevalonate pathway in cardiac remodeling and cardiomyocyte Ca2+ handling proteins expression in a rat model of cardiac dysfunction due to myocardial infarction (MI). After MI, adult male Sprague-Dawley rats were treated with drugs that antagonize key components in mevalonate pathway, including 3-hydroxy-3-methylglutaryl-CoA reductase, farnesyl pyrophosphate synthase and Rho-kinase for 10 weeks. The protein expression of ryanodine receptor 2 (RyR2), sarcoplasmic reticulum Ca2+ ATPase (SERCA) 2a, phospholamban (PLB), phospho-PLB at serine-16 (PSer16-PLB), FKB12.6 and RhoA as well as RyR2 and FKB12.6 mRNA levels were evaluated. RESULTS: Rosuvastatin and alendronate treatment prevented myocardial remodeling, improved cardiac function and reduced infarct size. Furthermore, rosuvastatin and alendronate promoted an increase in the protein expression of SERCA2a and PSer16-PLB ratio as well as partially restored the RyR2 and FKB12.6 gene and protein expression. Fasudil failed to exert these beneficial effects. CONCLUSIONS: The present findings indicate that mevalonate pathway inhibition by rosuvastatin and alendronate prevent cardiac remodeling and dysfunction possibly through RhoA-independent mechanisms. This article is protected by copyright. All rights reserved.

**PM:** http://www.ncbi.nlm.nih.gov/pubmed/?term=28652532

**ABSTRACT**

**BACKGROUND:** It has previously been reported that oral administration of purified eicosapentaenoic acid (EPA) generates EPA-rich high-density lipoprotein (HDL) particles with a variety of anti-inflammatory properties. In this study, the mechanism underlying the anti-atherogenic effects of EPA-rich HDL using reconstituted HDL (rHDL) was investigated.

**Methods and Results:** rHDL was generated by the sodium cholate dialysis method, using apolipoprotein A-I protein, cholesterol, and various concentrations of EPA-phosphatidylcholine (PC) or egg-PC. Increased EPA-PC contents in rHDL resulted in decreased particle size. Next, the effects of rHDL containing various amounts (0-100% of total PC) of EPA-PC on vascular cell adhesion molecule-1 (VCAM-1) expression in human umbilical vein endothelial cells (HUVECs) was examined. Cytokine-stimulated VCAM-1 expression was inhibited in a dose-dependent manner based on the amount of EPA-PC in rHDL. Surprisingly, the incubation of HUVECs with EPA-rich rHDL resulted in the production of resolvins E3 (RvE3), an anti-inflammatory metabolite derived from EPA. Incubation with EPA-PC alone did not adequately induce RvE3 production, suggesting that RvE3 production requires an endothelial cell-HDL interaction. The increased anti-inflammatory effects of EPA-rich HDL may be explained by EPA itself and RvE3 production. Furthermore, the increase in EPA-PC content enhanced cholesterol efflux. **CONCLUSIONS:** The EPA-enriched HDL particles exhibit cardioprotective properties via the production of anti-inflammatory lipid metabolites and the increase in cholesterol efflux.


**PM:** http://www.ncbi.nlm.nih.gov/pubmed/?term=28653144

**ABSTRACT**

**BACKGROUND:** Ethnic variability in the pharmacokinetics of organic anion transporting polypeptide (OATP) 1B1 substrates has been observed, but its basis is unclear. A previous study hypothesizes that, without applying an intrinsic ethnic variability in transporter activity, allele frequencies of transporters cannot explain observed ethnic variability in pharmacokinetics. However, this hypothesis contradicts the data collected from compounds that are OATP1B1 substrates but not breast cancer resistance protein (BCRP) substrates. **OBJECTIVE:** The objective of this study is to evaluate a hypothesis that is physiologically reasonable and more consistent with clinical observations. **METHODS:** We evaluated if allele frequencies of two transporters (OATP1B1 and BCRP) are key contributors to ethnic variability. In this hypothesis, the same genotype leads to the same activity independent of ethnicity, in contrast to the previous hypothesis of intrinsic ethnic variability in OATP1B1 activity. As a validation, we perform mechanistic pharmacokinetic modeling for SLCO1B1 (encoding OATP1B1) and ABCG2 (encoding BCRP) genotyped pharmacokinetic data from 18 clinical studies with healthy Caucasian and/or Asian subjects. **RESULTS:** Simulations based on the current hypothesis reasonably describe SLCO1B1 and ABCG2 genotyped pharmacokinetic time course data for five transporter
substrates (atorvastatin, pitavastatin, pravastatin, repaglinide, and rosvastatin) in Caucasian and Asian populations. CONCLUSION: This hypothesis covers the observations that can (e.g., ethnic differences in rosvastatin pharmacokinetics) or cannot (e.g., lack of differences for pitavastatin pharmacokinetics) be explained by the previous hypothesis. It helps to characterize sources of ethnic variability and provides a foundation for predicting ethnic variability in transporter substrate pharmacokinetics.


ABSTRACT
This review summarizes the current data on the interleukin (IL)-17A pathway in experimental atherosclerosis and clinical data. IL-17A is a prominent cytokine for early T cell response produced by both innate and adaptive leukocytes. In atherosclerosis, increased total IL-17A levels and expression in CD4+ T helper and gammadelta T cells have been demonstrated. Cytokines including IL-6 and TGFbeta that increase IL-17A expression are elevated. Many other factors such as lipids, glucose and sodium chloride concentrations as well as vitamins and arylhydrocarbon receptor agonists that promote IL-17A expression are closely associated with cardiovascular risk in the human population. In acute inflammation models, IL-17A mediates innate leukocyte recruitment of both neutrophils and monocytes. In atherosclerosis, IL-17A increased aortic macrophage and T cell infiltration in most models. Secondary recruitment effects via the endothelium and according to recent data also pericytes have been demonstrated. IL-17 receptor A is highly expressed on monocytes and direct effects have been reported as well. Beyond leukocyte accumulation, IL-17A may affect other factors of plaque formation such as endothelial function, and according to some reports, fibrous cap formation and vascular relaxation with an increase in blood pressure. Anti-IL-17A agents are now available for clinical use. Cardiovascular side effect profiles are benign at this point. IL-17A appears to be a differential regulator of atherosclerosis and its effects in mouse models suggest that its modulation may have contradictory effects on plaque size and possibly stability in different patient populations.


ABSTRACT
BACKGROUND: Type 2 diabetes is a major healthcare problem. Glucose-, lipid-, and blood pressure-lowering strategies decrease the risk of micro- and macrovascular complications. However, a substantial residual risk remains. To unravel the etiology of type 2 diabetes and its complications, large-scale, well-phenotyped studies with prospective follow-up are needed. This is the goal of the DiaGene study. In this manuscript, we describe the design and baseline characteristics of the study. METHODS: The DiaGene study is a multi-centre, prospective, extensively phenotyped type 2 diabetes cohort study with concurrent inclusion of diabetes-free individuals at baseline as controls in the city of Eindhoven, The Netherlands. We collected
anthropometry, laboratory measurements, DNA material, and detailed information on medication usage, family history, lifestyle and past medical history. Furthermore, we assessed the prevalence and incidence of retinopathy, nephropathy, neuropathy, and diabetic feet in cases. Using logistic regression models, we analyzed the association of 11 well known genetic risk variants with type 2 diabetes in our study. RESULTS: In total, 1886 patients with type 2 diabetes and 854 controls were included. Cases had worse anthropometric and metabolic profiles than controls. Patients in outpatient clinics had higher prevalence of macrovascular (41.9% vs. 34.8%; P = 0.002) and microvascular disease (63.8% vs. 20.7%) compared to patients from primary care. With the exception of the genetic variant in KCNJ11, all type 2 diabetes susceptibility variants had higher allele frequencies in subjects with type 2 diabetes than in controls. CONCLUSIONS: In our study population, considerable rates of macrovascular and microvascular complications are present despite treatment. These prevalence rates are comparable to other type 2 diabetes populations. While planning genomics, we describe that 11 well-known type 2 diabetes genetic risk variants (in TCF7L2, PPARG-P12A, KCNJ11, FTO, IGF2BP2, DUSP9, CENTD2, THADA, HHEX, CDKAL1, KCNQ1) showed similar associations compared to literature. This study is well-suited for multiple omics analyses to further elucidate disease pathophysiology. Our overall goal is to increase the understanding of the underlying mechanisms of type 2 diabetes and its complications for developing new prediction, prevention, and treatment strategies.


ABSTRACT

INTRODUCTION: Lipid-lowering therapy effectively decreases cardiovascular risk on a population level, but it remains difficult to identify an individual patient’s personal risk reduction while following guideline directed medical therapy, leading to overtreatment in some patients and cardiovascular events in others. Recent improvements in cardiac CT technology provide the ability to directly assess an individual's atherosclerotic disease burden, which has the potential to personalize risk assessment for lipid-lowering therapy. Areas Covered: We review the current unmet need in identifying patients at elevated residual risk despite guideline directed medical therapy, the evidence behind plaque regression as a potential marker of therapeutic response, and highlight state-of-the-art advances in coronary computed tomographic angiography (CCTA) for measurement of quantitative and qualitative changes in coronary atherosclerosis over time. Literature search was performed using PubMed and Google Scholar for literature relevant to statin therapy and residual risk, coronary plaque regression measurement, and CCTA assessment of quantitative and qualitative change in coronary atherosclerosis. Expert Commentary: We discuss the potential ability of CCTA to guide lipid-lowering therapy as a bridge between population and personalized medicine in the future, as well as the potential barriers to its use.

ABSTRACT


ABSTRACT

Objective: The link between metabolic derangement of the gut-liver-visceral white adipose tissue (v-WAT) axis and gut microbiota was investigated. Methods: Rats were fed a fructose-rich diet and treated with an antibiotic mix. Inflammation was measured in portal plasma, ileum, liver, and v-WAT, while insulin signalling was analysed by measuring levels of phosphorylated kinase Akt. The function and oxidative status of hepatic mitochondria and caecal microbiota composition were also evaluated. Results: Ileal inflammation, increase in plasma transaminases, plasma peroxidised lipids, portal concentrations of tumour necrosis factor alpha, lipopolysaccharide, and non-esterified fatty acids, were induced by fructose and were reversed by antibiotic. The increased hepatic ceramide content, inflammation and decreased insulin signaling in liver and v-WAT induced by fructose was reversed by antibiotic. Antibiotic also blunted the increase in hepatic mitochondrial efficiency and oxidative damage of rats fed fructose-rich diet. Three genera, Coprococcus, Ruminococcus, and Clostridium, significantly increased, while the Clostridiaceae family significantly decreased in rats fed a fructose-rich diet, and antibiotic abolished these variations. Conclusions: When gut microbiota modulation by fructose is prevented by antibiotic, inflammatory flow from the gut to the liver and v-WAT are reversed.

[24] Nejm MB, Haidar AA, Hirata AE et al. Fish Oil Supplementation Reduces Heart Levels of Interleukin-6 in Rats with Chronic Inflammation due to Epilepsy. Frontiers in neurology 2017; 8:263.

ABSTRACT

Sudden unexpected death in epilepsy (SUDEP) is a major cause of premature death related to epilepsy. The causes of SUDEP remain unknown, but cardiac arrhythmias and asphyxia have been suggested as a major mechanism of this event. Inflammation has been implicated in the pathogenesis of both epilepsy and ventricular arrhythmia, with interleukin-6 (IL-6) being recognized as a crucial orchestrator of inflammatory states. Our group previously reported that levels of IL-6 were increased in the hearts of epileptic rats. In this scenario, anti-inflammatory actions are among the beneficial effects of fish oil dietary supplementation. This investigation revealed that elevated levels of IL-6 in the heart were markedly reduced in epileptic rats that were treated in the long-term with fish oil, suggesting protective anti-inflammatory actions against dangerously high levels of IL-6. Based on these findings, our results suggest beneficial effects of long-term intake of fish oil in reducing the inflammation associated with chronic epilepsy.
BACKGROUND: Heterozygous familial hypercholesterolemia increases the risk of adverse cardiovascular events. Whether affected relatives of probands are at increased risk remains unknown. We aimed to evaluate the long-term cardiovascular risk in heterozygous familial hypercholesterolemia relatives with a low-density lipoprotein receptor (LDLR) mutation who were all recommended statin therapy. METHODS AND RESULTS: Participants were identified by cascade screening at Aarhus University Hospital during 1992-1994. A comparison cohort from the Danish general population was matched 10:1 to relatives by birth year and sex. Using medical registries, participants were followed until the event of interest, migration, death, or end of follow-up on December 31, 2014. The primary end point was all-cause mortality and major adverse cardiovascular events comprising myocardial infarction, ischemic stroke, transient ischemic attack, peripheral artery disease, and coronary revascularization. We included 220 relatives. Median age was 37 years (interquartile range: 27-52 years) of which 118 (54%) had an LDLR mutation. By 2004, when prescription data became available, 89% of mutation-carrying participants were taking statins during their follow-up period. Despite frequent use of lipid-lowering medication, the adjusted hazard ratio of the primary end point was 1.65 (95% confidence interval, 1.17-2.33) in mutation-carrying relatives compared with the general population cohort. The risk in non-mutation-carrying relatives was not different from that of the general population cohort (adjusted hazard ratio: 0.85; 95% confidence interval, 0.56-1.29). Comparing mutation-carrying relatives with non-mutation-carrying relatives, the adjusted hazard ratio was 1.94 (95% confidence interval, 1.14-3.31). Results were driven by nonfatal events. CONCLUSION: Heterozygous familial hypercholesterolemia relatives with an LDLR mutation had an increased long-term risk of adverse cardiovascular events.


ABSTRACT


ABSTRACT

BACKGROUND: The 2008 Ezetimibe and Simvastatin in Hypercholesterolemia Enhances Atherosclerosis Regression (ENHANCE) study demonstrated ezetimibe + simvastatin vs simvastatin alone had a neutral effect on the surrogate endpoint of carotid intima-media thickness. Subsequent media portrayal of the study prompted ezetimibe discontinuation in many patients. OBJECTIVE: The objective of the study was to assess the impact of ENHANCE
reporting on ezetimibe discontinuation, low-density lipoprotein cholesterol (LDL-C) changes, and potential cardiovascular disease (CVD) risk. METHODS: This analysis used claims data in a retrospective, observational study of patients receiving ezetimibe + statin and compared LDL-C for patients who discontinued ezetimibe (n = 970) vs those who continued ezetimibe + statins (n = 3706) after ENHANCE results disclosure. Change in relative CVD risk was estimated from the absolute LDL-C difference between groups per the Cholesterol Treatment Trialists' meta-analysis of statin trials. RESULTS: The rate of ezetimibe discontinuation was 2% in the 6 months before and 21% in the 6 months after reporting of ENHANCE results. Among patients who ultimately discontinued vs continued ezetimibe, respective mean LDL-C levels were 79.8 and 78.3 mg/dL 6 months before reporting of the ENHANCE results and 93.5 and 78.1 mg/dL 6 months after reporting of ENHANCE. Predictive application of the Cholesterol Treatment Trialists' meta-analysis suggested the 13.9 mg/dL increase in mean LDL-C translated to a 9.4% increase in relative CVD risk for those who discontinued ezetimibe. CONCLUSION: After reporting of the neutral ENHANCE results, ezetimibe discontinuation rate increased, LDL-C levels increased, and predicted CVD risk increased among those who discontinued ezetimibe. Characterization of clinical outcomes regarding lipid-altering agents based on surrogate biomarker studies not designed to assess CVD outcomes may be misleading, potentially placing patients at increased CVD risk.


ABSTRACT

BACKGROUND: It remains unclear whether treatment of dyslipidemia with 3-hydroxy-3-methyl-glutaryl-coenzyme A reductase inhibitors (statins) reduces the risk of developing hypertension. OBJECTIVE: In this post-hoc analysis of the Management of Elevated Cholesterol in the Primary Prevention Group of Adult Japanese (MEGA) Study, a large-scale primary prevention trial with pravastatin, we examined the preventive effect of pravastatin on the future development of hypertension in patients with hypercholesterolemia. METHODS: Of the overall (MEGA) Study population, 3397 nonhypertensive patients at baseline were enrolled in this study. The patients were randomly assigned to either the diet alone group (n = 1722) or the diet plus pravastatin group (n = 1675) and then were followed-up for a median of 36 months to determine new-onset hypertension. RESULTS: During the follow-up period, 1595 patients developed hypertension (49.1% in the diet alone group and 44.7% in the diet plus pravastatin group). After adjusting for multiple covariates, the diet plus pravastatin group showed a 10% reduction in the risk of developing hypertension (hazard ratio 0.90, 95% confidence interval 0.81-0.998), compared with the diet alone group. Subgroup analyses revealed that the preventive effect of pravastatin on the development of hypertension was pronounced in patients aged >/=60 years, men, those with chronic kidney disease or diabetes mellitus and those without obesity. CONCLUSIONS: Pravastatin reduced the risk of developing hypertension in Japanese patients with hypercholesterolemia. The risk reduction of cardiovascular disease with statins could be partly explained by their preventive effect on the development of hypertension.
ABSTRACT

Objective The present study was performed to explore the therapeutic potential of simvastatin in subarachnoid hemorrhage (SAH) in the context of the Simvastatin in Aneurysmal Subarachnoid Hemorrhage (STASH) trial. Methods MEDLINE, EMBASE, and the Cochrane Library were searched for all randomized controlled trials (RCTs) investigating the therapeutic effect of simvastatin on aneurysmal SAH. We applied a random-effects model to calculate the data. Results Five RCTs involving 951 patients met the eligibility criteria. We found no statistically significant effects on vasospasm detected by transcranial Doppler (relative risk [RR], 0.91; 95% confidence interval [CI], 0.55-1.49), delayed cerebral ischemia (DCI) (RR, 0.85; 95% CI, 0.63-1.14), or all-cause mortality (RR, 1.02; 95% CI, 0.67-1.54). Subgroup analysis showed that these consolidated results were stable at different doses, different times to start of treatment, and different courses of treatment in all included RCTs. Sensitivity analysis showed that the STASH trial, which had a large population, did not influence the consolidated results of all three outcomes. Conclusions Simvastatin showed no benefits in decreasing the incidence of vasospasm, DCI, or all-cause mortality after aneurysmal SAH. We conclude that patients with SAH should not be treated routinely with simvastatin during the acute stage.


ABSTRACT

PURPOSE: The aim of this study was to evaluate the effects of fish oils, including eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA), on ventricular tachyarrhythmic episodes (VTEs) in implantable cardioverter defibrillator (ICD) recipients with ischemic cardiomyopathy. METHODS: One hundred five ICD recipients with ischemic cardiomyopathy received 3.6 g of EPA and DHA and placebo for 6 months, each at a random order, with a 4-month washout period between treatments. Eighty-seven patients completed the 16-month study protocol. The primary end point was any VTE (including sustained and non-sustained ventricular tachycardias at a rate of >150 bpm) as recorded by the ICDs. Secondary end points included device therapy (anti-tachycardia pacing (ATP) or shocks). RESULTS: During treatment with fish oils, there was a significant increase in EPA and DHA concentrations in red blood cells (RBCs) and subcutaneous fat tissue. Among 87 patients who completed the study protocol, the mean number of VTEs was significantly lower during treatment with fish oil (1.7) vs. placebo (5.6; p = 0.035). Appropriate device therapy for VTE occurred in 18 (21%) patients. Fish oil therapy was associated with a trend toward fewer VTEs terminated with ATP (2.8 +/- 13.7 vs. 0.5 +/- 2.1, respectively; p = 0.077). VTE terminated by ICD shocks, however, was rare, and rates were similar between both groups (0.11 +/- 0.6 vs. 0.10 +/- 0.4, p = not significant,
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respectively). CONCLUSIONS: Our data suggest that fish oil therapy may be associated with a reduction in the frequency of VTE in ICD recipients with ischemic cardiomyopathy.


ABSTRACT
Blood eosinophil counts and serum periostin levels are biomarkers of type 2 inflammation. Although serum levels of HDL (high-density lipoprotein) and apolipoprotein A-I have been associated with less severe airflow obstruction in asthma, it is not known whether serum lipids or lipoprotein particles are correlated with type 2 inflammation in asthmatics. Here, we assessed whether serum lipids and lipoproteins correlated with blood eosinophil counts or serum periostin levels in 165 atopic asthmatics, and 163 non-asthmatic subjects with and without atopy. Serum lipids and lipoproteins were quantified using standard laboratory assays and nuclear magnetic resonance (NMR) spectroscopy. Absolute blood eosinophils were quantified by complete blood counts. Periostin levels were measured using the Elecsys Periostin assay. In atopic asthmatics, blood eosinophils negatively correlated with serum HDL-cholesterol and total HDL particles measured by NMR spectroscopy (HDLNMR). Serum periostin levels negatively correlated with total HDLNMR. In contrast, blood eosinophil counts positively correlated with serum triglyceride levels. This study demonstrates for the first time that HDL particles were negatively correlated, whereas serum triglycerides were positively correlated, with blood eosinophils in atopic asthmatics. This supports the concept that serum levels of HDL and triglycerides may be linked to systemic type 2 inflammation in atopic asthma.


ABSTRACT
Plasma lipids have been extensively studied in sedentary and in subjects practicing exercise training, but not in extreme inactivity as occurs in bedridden patients. This is important for the care of bedridden patients and understanding the overall plasma lipid regulation. Here, we investigated plasma lipids, lipid transfers to HDL and inflammatory markers in bedridden patients. Fasting blood samples were collected from 23 clinically stable bedridden patients under long-term care (>90 days) and 26 normolipidemic sedentary subjects, paired for age and gender. In vitro transfer of four lipids to HDL was performed by incubating plasma with donor nanoparticles containing radioactive lipids. Total (193 +/- 36 vs 160 +/- 43, p = 0.005), LDL (124 +/- 3 vs 96 +/- 33 p = 0.003) and HDL-cholesterol (45 +/- 10 vs 36 +/- 13, p = 0.008), apolipoprotein A-I (134 +/- 20 vs 111 +/- 24, p = 0.001) and oxidized LDL (53 +/- 13 vs 43 +/- 12, p = 0.011) were lower in bedridden patients, whereas triglycerides, apolipoprotein B, CETP and LCAT were equal in both groups. Transfers of all lipids, namely unesterified cholesterol, cholesterol esters, triglycerides and phospholipids, to HDL were lower in bedridden patients, probably due to their lower HDL-cholesterol levels. Concentrations of IL-1beta, IL-6, IL-8, HGF...
and NGF were higher in bedridden patients compared to sedentary subjects. In conclusion, inactivity had great impact on HDL, by lowering HDL-cholesterol, apolipoprotein A-I and thereby cholesterol transfers to the lipoprotein, which suggests that inactivity may deteriorate HDL protection beyond the ordinary sedentary condition.


ABSTRACT
BACKGROUND: Lowering cholesterol levels decreases the risk of atherosclerotic diseases. Effective ways to stably reduce LDL-C level are warranted in type 2 diabetic patients, a high-risk population for CVD, with various anti-diabetic therapeutic background. The RESEARCH study focuses on LDL-C reduction in this population along with modifications of the lipid profiles. We evaluated long-term ezetimibe add-on therapy in T2DM patients with hypercholesterolemia. METHODS: In a randomized, multicenter, open-label, prospective study, a total of 109 T2DM patients not attaining LDL-C target value despite first-line dose statin (10 mg of atorvastatin or 1 mg of pitavastatin) therapy in Japan were recruited. We investigated the difference in cholesterol lowering effect between ezetimibe (10 mg) add-on statin (EAT) group and double-dose statin (DST) group. Changes of parameters related to atherosclerotic event risks were assessed. RESULTS: The reduction of LDL-C was larger in the EAT group (28.3%) than in the DST group (9.2%) at 52 weeks as well as the primary endpoint of 12 weeks. EAT achieved significant lower levels of TC and apo B, respectively. Both treatments attained significant reduction in sd-LDL-C or hsCRP on this long-term basis. Notably, sd-LDL-C in EAT reduced as low as 36.1 +/- 14.9 mg/dl to reach near the threshold (35.0 mg/dl) for atherosclerosis with significantly higher achievement rate (55.6%) than DST treatment. Simultaneously, hsCRP reduction by EAT attained as low value as 0.52 +/- 0.43 mg/l. CONCLUSIONS: In the present 52-week long-term period, ezetimibe add-on therapy showed a robust advantage in lowering LDL-C and in attaining target LDL-C values compared with the doubling of statin dose. Moreover, it's meaningful that sd-LDL, powerfully atherogenic lipoprotein, exhibited prominent decrease consistently prominently by ezetimibe add-on therapy. DM patients with hypercholesterolemia are at high risk for CAD, and adding ezetimibe onto usual-dose statin treatment in Japan has been suggested as the first-line therapy for those DM patients who failed to attain the target LDL-C value (UMIN000002593).


ABSTRACT
BACKGROUND: The high recurrent rate of chronic subdural hematoma (CSDH) has consistently confused the neurosurgeons, and the role of atorvastatin in the management of CSDH has remained unclear over past decade, and atorvastatin seems to be a safe and cost-effective treatment to CSDH. Therefore, it is necessary to conduct a systematic review to discuss the effect of atorvastatin in CSDH. METHOD: We searched the PubMed, EMBASE, Cochrane Library,
and the China Biology Medicine disc, up to March 2017, for published studies on the effects of atorvastatin in the management of CSDH, and reviewers performed a brief qualitative descriptive analysis of atorvastatin's efficacy in the management of CSDH. RESULTS: Three eligible studies were included in this systematic review. Results indicated that atorvastatin accelerated hematoma absorption, decreased recurrence risk, and surgical requirement. CONCLUSION: Limited evidence suggests that oral atorvastatin may be beneficial in the management of CSDH. Further high-quality studies focused on dosage, duration, hematoma size are needed to further elucidate the role of atorvastatin in the management of CSDH.


ABSTRACT
Folate receptor beta (FR-beta) is overexpressed on activated, but not resting, macrophages involved in a variety of inflammatory and autoimmune diseases. A pivotal step in atherogenesis is the subendothelial accumulation of macrophages. In nascent lesions, they coordinate the scavenging of lipids and cellular debris to define the likelihood of plaque inflammation and eventually rupture. In this study, we determined the presence of FR-beta-expressing macrophages in atherosclerotic lesions by the use of a fluorine-18-labeled folate-based radiotracer. Human endarterectomized specimens were used to measure gene expression levels of FR-beta and CD68. Increased FR-beta and CD68 levels were found in atherosclerotic plaques compared to normal artery walls by quantitative real-time polymerase chain reaction. Western blotting and immunohistochemistry demonstrated prominent FR-beta protein levels in plaques. FR-beta-positive cells colocalized with activated macrophages (CD68) in plaque tissue. Carotid sections incubated with 3'-aza-2'-[18F]fluorofolic acid displayed increased accumulation in atherosclerotic plaques through in vitro autoradiography. Specific binding of the radiotracer correlated with FR-beta-expressing macrophages. These results demonstrate high FR-beta expression in atherosclerotic lesions of human carotid tissue correlating with CD68-positive macrophages. Areas of high 3'-aza-2'-[18F]fluorofolic acid binding within the lesions represented FR-beta-expressing macrophages. Selectively targeting FR-beta-positive macrophages through folate-based radiopharmaceuticals may be useful for noninvasive imaging of plaque inflammation.


ABSTRACT
The present study aimed to explore the direct toxicity of proprotein convertase subtilisin/kexin type 9 (PCSK9) to atherosclerosis (AS) and its association with apoptotic endothelial cells. Apolipoprotein E/ mice were randomly divided into two groups, control and experimental. The control group was administered a normal diet and the experimental group was administered a highfat diet. After 20 weeks, the aorta was isolated and dissected. Hematoxylin and eosin staining, and immunohistochemical analysis were performed. Human umbilical vein endothelial
cells were incubated with varied concentrations of oxidized lowdensity lipoprotein (oxLDL) for different times. The apoptotic rate was detected by flow cytometry. Western blotting and reverse transcriptionquantitative polymerase chain reaction analysis were conducted to detect the expression of PCSK9, Bcell lymphoma 2 (Bcl2), bcl2like protein 4 (Bax) and caspase-3. Short hairpin (sh) RNAPCSK9 was transfected into endothelial cells using lentiviral transfection. The expression levels of PCSK9, Bax, Bcl2, caspase-3 and the mitogenactivated protein kinase (MAPK) pathway proteins were detected. The highfat group was successfully established as an AS model and PCSK9 was highly expressed in the AS plaque. Treatment with oxLDL induced apoptosis and increased mRNA and protein levels of PCSK9. PCSK9 mRNA and proteins levels were downregulated by shRNAPCSK9. The deficiency of PCSK9 markedly inhibited the expression of proapoptotic proteins and promoted antiapoptotic proteins. In addition, phosphorylation of p38 and cJun Nterminal kinases was altered by shRNAPCSK9. Targeting of PCSK9 by shRNAPCSK9 may repress endothelial cell apoptosis through MAPK signaling in AS, providing a novel direction for understanding the mechanism and treatment of AS.


ABSTRACT

Alopecia areata can affect the entire scalp (alopecia totalis) or cause loss of all body hair (alopecia universalis). Ciclosporin (CsA) has been suggested for its treatment, with controversial results. Concomitant use of statins and CsA may increase the risk of rhabdomyolysis due to drug-drug interactions. Here we report the case of a 45-year-old woman treated with CsA for alopecia universalis, who presented a severe myoglobinuric acute kidney injury following the concomitant use of simvastatin. Upon admission to our unit, she was oligo-anuric. Her serum creatinine level was 13.8 mg/dl. CsA and simvastatin therapy were stopped, and haemodialysis treatment was started (eight daily dialysis sessions) until sufficient kidney function was regained. After 1 month, her serum creatinine level was 3.5 mg/dl; after 2 months and onwards (follow-up of 4 months), her serum creatinine level was 1.4 mg/dl and creatinine clearance was 43.2 ml/min. In conclusion, physicians should be aware of the potential risks of the combined use of CsA and statins. Patients should be advised to report any muscle symptoms when they are on statins and CsA. The laboratory follow-up should include the monitoring of serum creatinine and muscle enzyme levels, blood CsA levels and liver function tests.


ABSTRACT

The present systematic review with meta-analysis of randomized controlled trials (RCTs) aimed to analyze the effectiveness of omega-3 fatty acids on the frequency, severity, and duration of migraine. This systematic review was performed by searching several databases for controlled clinical trials. Of the 13 trials, five, two, and three RCTs met the eligibility criteria to evaluate the
efficacy of omega-3 on the frequency, duration, and severity of migraine attacks, respectively. The Jadad scale was used to evaluate the risk of bias analysis. Overall estimates of the intervention effect were obtained from random-effect meta-analysis. The studies' heterogeneity was evaluated using the chi-squared test (chi2) (Cochran's test (Q test)) and I2 Index. Potential sources of heterogeneity among the trials were investigated by meta-regression analyses. The results showed that omega-3 intake had no effect on frequency (WMD = -0.20; 95%CI -0.67, 0.27; P = 0.401, and I2 = 4.6%; P = 0.380) and severity (SMD = -0.59; 95%CI -1.85, 0.66; P = 0.35, and I2 = 88.8%; P = 0.000) of migraine but had a reduction effect on the duration of migraine attacks (WMD = -3.44; 95%CI -5.70, -1.19; P = 0.003, and I2 = 0.0%; P = 0.926). In conclusion, omega-3 intake leads to a significant reduction of approximately 3.44 hours in the duration of migraine. Further randomized controlled trials of high methodological quality with adequate sample sizes are required to confirm the results of the meta-analyses.


ABSTRACT

BACKGROUND: Statins and benzodiazepines are widely used drugs, especially in ischemic heart disease, where exacerbation caused by anxiety can even lead to cardiac death. There have not been any reports of statin drug interaction with anxiolytics so far, but it is possible that these drugs interact with each other. We examined the effect of chronic oral administration of simvastatin on the anxiolytic activity and pharmacokinetics of diazepam in rats. METHODS: Studies were conducted on male Wistar Han rats treated with simvastatin (2.5, 5, 10, 20mg/kg) for 4-6 weeks, and/or diazepam (2.5, 5, 10mg/kg) administered once on the day of the study. Evaluation of potential pharmacodynamic interaction was based on the behavioral tests: elevated plus maze (EPM) test and the Vogel conflict test (VCT). The assessment of the potential pharmacokinetic interaction was based on measurements of concentrations of diazepam and its metabolites in the blood of animals. RESULTS: Diazepam 5 and 10mg/kg given together with simvastatin 10 and 20mg/kg showed no anxiolytic effect in the EPM test. In the VCT diazepam combinations with simvastatin did not produce any anxiolytic effect either, with an exception of the co-administration of diazepam 10mg/kg and simvastatin 10mg/kg. Simvastatin (20mg/kg) significantly reduced the area under curve (AUC) of diazepam by 51.6% and temazepam by 54.6%. CONCLUSIONS: Abolition of diazepam anxiolytic effect during concomitant use of simvastatin is probably caused by diminished bioavailability of diazepam, although pharmacodynamic interaction between these drugs cannot be excluded.


ABSTRACT

It has been reported that changes in cytokine levels affect mitochondrial functions, levels of hypoxia-inducible factor alpha (HIF-1alpha), and tissue damage during sepsis. We aimed to investigate the effects of simvastatin pretreatment on mitochondrial enzyme activities, and on levels of ghrelin, HIF-1alpha, and thiobarbituric acid reactive substances (TBARS) in kidney
tissue during sepsis. Rats were separated into four groups, namely, control, lipopolysaccharides (LPS) (20 mg/kg), simvastatin (20 mg/kg), and simvastatin + LPS. We measured the levels of mitochondrial enzyme activities and TBARS in the kidney using spectrophotometry. The histological structure of the kidney sections was examined after staining with hematoxylin and eosin. Tumor necrosis factor alpha (TNF-alpha), IL-10, HIF-1alpha, and ghrelin immunoreactivity were examined using proper antibodies. In tissue, TNF-alpha (p < 0.01) and HIF-1alpha (p < 0.05) levels were increased in the simvastatin + LPS and LPS groups. TBARS levels were higher in the LPS group than in the other groups (p < 0.01), but they were similar in the simvastatin + LPS and control groups (p > 0.05). Ghrelin immunoreactivity was lower in the LPS group (p < 0.05) and higher in the simvastatin + LPS group than in the LPS group (p < 0.01). We observed tubular damage in the sections of the LPS group. There were no differences in mitochondrial enzyme activities between the groups (p > 0.05). We observed that pretreatment of simvastatin caused favorable changes on ghrelin and TBARS levels in rats with sepsis.


**ABSTRACT**

Alzheimer's disease (AD) is the most common cause of dementia and one of the most important causes of morbidity and mortality among the aging population. AD diagnosis is made post-mortem, and the two pathologic hallmarks, particularly evident in the end stages of the illness, are amyloid plaques and neurofibrillary tangles (NFT). Currently, there is no curative treatment for AD. Additionally, there is a strong relation between oxidative stress, metabolic syndrome (MetS) and AD. The high levels of circulating lipids and glucose imbalances amplify lipid peroxidation that gradually diminishes the antioxidant systems, causing high levels of oxidative metabolism that affects cell structure, leading to neuronal damage. Accumulating evidence suggests that AD is closely related to a dysfunction of both insulin signaling and glucose metabolism in the brain, leading to an insulin-resistant brain state. Four drugs are currently used for this pathology: Three FDA-approved cholinesterase inhibitors and one NMDA receptor antagonist. However, wide varieties of antioxidants are promissory to delay or prevent the symptoms of AD and may help in treating the disease. Therefore, therapeutic efforts to achieve attenuation of oxidative stress could be beneficial in AD treatment, attenuating Abeta-induced neurotoxicity and improve neurological outcomes in AD. The term inflammaging characterizes a widely accepted paradigm that aging is accompanied by a low-grade chronic up-regulation of certain pro-inflammatory responses in the absence of overt infection, and is a highly significant risk factor for both morbidity and mortality in the elderly. This article is protected by copyright. All rights reserved.