ABSTRACT

BACKGROUND: There is a lack of knowledge of those contemporary factors associated with modifying subtherapeutic treatments in hypercholesterolemic patients. The aim of this study was to assess determinants of treatment modification in patients not attaining their low-density lipoprotein cholesterol goals. METHODS: The CE ntralized Pan-Asian survey on tHE Under-treatment of hypercholesterolemia enrolled patients taking stable lipid-lowering medications. The study physicians then determined existing patient treatments, which were to be continued or modified when treatments failed. The patient questionnaire surveying patient attitudes and perceptions toward their hypercholesterolemia management was prospectively collected. The odds ratios (ORs) (95% confidence intervals) were calculated. RESULTS: Among the 420 patients included for analysis, 35.7% were designated for planned treatment modification. Those patients assigned to treatment modification were more likely to have a family history of premature coronary heart disease (40% vs. 19%), an indication for secondary prevention (76% vs. 61%), elevated triglyceride (60% vs. 48%) and fasting sugar (84% vs. 67%), and were less adherent to their medications (29% vs. 12%) than patients assigned to treatment continuation. Patient recognition of treatment failure [OR, 1.82 (1.13-2.94)], the lower frequency of cholesterol checkup [OR, 2.40 (1.41-4.08)], patient satisfaction with provided cholesterol information [OR, 2.30 (1.21-4.39)], and their feelings toward cholesterol management [OR, 0.25 (0.10-0.62) and 3.80 (2.28-6.32)] for confusion and no strong feeling, respectively were determinants of the treatment modification assignment. CONCLUSIONS: There was a large gap between evidence-based goals and modification of subtherapeutic treatments, particularly among patients with lower treatment satisfaction and better compliance. Our findings have emphasized the need to further reduce inertia in implementing hypercholesterolemia management.

ABSTRACT

RG7652 (MPSK3169A), a fully human immunoglobulin G1 (IgG1) monoclonal antibody directed against proprotein convertase subtilisin/kexin type 9 (PCSK9), blocks the interaction between PCSK9 and low-density lipoprotein (LDL) receptor. EQUATOR (ClinicalTrials.govNCT01609140), a randomized, double-blind, and dose-ranging phase 2 study, evaluated RG7652 in patients (1) at high risk for or (2) with coronary heart disease (CHD). The primary end point was change in LDL cholesterol (LDL-C) from baseline to day 169. Patients (n = 248; median age, 64 years; 57% men; 52% with established CHD; 82% on statins) with baseline LDL-C levels of 90 to 250 mg/dl (mean, 126 mg/dl) continuing on standard-of-care therapy were randomized to receive 1 of 5 RG7652 doses or placebo, subcutaneously every 4, 8, or 12 weeks for 24 weeks. Significant dose-dependent reductions in LDL-C levels from baseline to nadir (56 to 74 mg/dl [48% to 60%]) were
ABSTRACT

Background: Evidence from randomized controlled trials (RCTs) suggests the consumption of konjac glucomannan (KJM), a viscous soluble fiber, for improving LDL-cholesterol concentrations. It has also been suggested that the cholesterol-lowering potential of KJM may be greater than that of other fibers. However, trials have been relatively scarce and limited in sample size and duration, and the effect estimates have been inconsistent. The effect of KJM on new lipid targets of cardiovascular disease (CVD) risk is also unknown. Objective: This systematic review and meta-analysis aimed to assess the effect of KJM on LDL cholesterol, non-HDL cholesterol, and apolipoprotein B.

Design: Medline, Embase, CINAHL, and the Cochrane Central databases were searched. We included RCTs with a follow-up of $/\geq3$ wk that assessed the effect of KJM on LDL cholesterol, non-HDL cholesterol, or apolipoprotein B. Data were pooled by using the generic inverse-variance method with random-effects models and expressed as mean differences (MDs) with 95% CIs. Heterogeneity was assessed by the Cochrane Q statistic and quantified by the I² statistic.

Results: Twelve studies (n = 370), 8 in adults and 4 in children, met the inclusion criteria. KJM significantly lowered LDL cholesterol (MD: -0.35 mmol/L; 95% CI: -0.46, -0.25 mmol/L) and non-HDL cholesterol (MD: -0.32 mmol/L; 95% CI: -0.46, -0.19 mmol/L). Data from 6 trials suggested no impact of KJM on apolipoprotein B.

Conclusions: Our findings support the intake of approximately 3 g KJM/d for reductions in LDL cholesterol and non-HDL cholesterol of 10% and 7%, respectively. The information may be of interest to health agencies in crafting future dietary recommendations related to reduction in CVD risk. This study was registered at clinicaltrials.gov as NCT02068248.


ABSTRACT

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ABSTRACT
BACKGROUND AND AIMS: Patients with familial hypercholesterolemia (FH) are often characterized by premature coronary artery disease (CAD) with heterogeneity at onset. The aim of the present study was to investigate the associations of lipoprotein (a) [Lp(a)] with the FH phenotype, genotype and roles of Lp(a) in determining CAD risk among patients with and without FH. METHODS: We enrolled 8050 patients undergoing coronary angiography, from our Lipid clinic. Clinical FH was diagnosed using the Dutch Lipid Clinic Network criteria. Mutational analysis (LDLR, APOB, PCSK9) in definite/probable FH was performed by target exome sequencing. RESULTS: Lp(a) levels were increased, with a clinical FH diagnosis (unlikely, possible, definite/probable FH) independent of the patients status, with Lp(a)-hyperlipoproteinemia [Lp(a)-HLP] (median 517.70 vs. 570.98 vs. 604.65 mg/L, p < 0.001) or without (median 89.20 vs. 99.20 vs. 133.67 mg/L, p < 0.001). Patients with Lp(a)-HLP had a higher prevalence of definite/probable FH than those without (6.1% vs. 2.4%, p < 0.05). However, no significant difference in Lp(a) was observed in patients with definite/probable FH phenotype carrying LDLR or LDLR-independent (APOB, PCSK9) or neither mutations (p > 0.05). Multivariate analysis showed that Lp(a) and FH phenotype were both significant determinants in predicting the early onset and severity of CAD. Subsequently, patients with Lp(a)-HLP in definite/probable FH increased significantly the CAD risk (all p < 0.05). CONCLUSIONS: Lp(a) levels were higher in patients with FH phenotype than in those without, but no difference were found in FH patients of different mutated backgrounds. Moreover, Lp(a) and FH played a synergistic role in predicting the early onset and severity of CAD.


ABSTRACT

BACKGROUND AND AIMS: Atherosclerotic plaque molecular imaging with 18F-sodium fluoride (NaF) in positron emission tomography with computed tomography (PET-CT) provides potential discrimination between active unstable microcalcification and established dormant calcification. We aimed to study 18F-NaF atherosclerotic plaque uptake in high cardiovascular (CV) risk participants and its associations with CV risk factors, coronary calcium score and thoracic fat volume. METHODS: High CV risk hypertensive individuals from a single centre were prospectively scanned with 18F-NaF-PET-CT in the coronary, aortic and carotid arteries. Atherosclerotic plaque 18F-NaF uptake was expressed as Corrected Uptake per Lesion (CUL): maximum standard uptake value in each vascular territory subtracted by mean blood pool activity. RESULTS: Mean age was 64 years, 56% male and 96% Caucasian (n = 25). Ninety six per cent of the subjects showed 18F-NaF uptake in the aorta (CUL 0.9 +/- 0.3), 40% in the carotid arteries (median CUL 0.0, IQR 0.0-0.7) and 64% in the coronary arteries (0.4, IQR 0.0-0.6). Individuals with >/= five risk factors (60%) had increased overall 18F-NaF uptake (1.1 +/- 0.3 vs. 0.7 +/- 0.3, p < 0.01), which was positively correlated with predicted fatal CV risk - SCORE (r = 0.49, p = 0.01). There was no correlation between 18F-NaF uptake in the coronary arteries and calcium score (p = 0.87). Thoracic fat was moderately correlated with overall CUL (r = 0.41, p = 0.04). CONCLUSIONS: In a high CV risk group, 18F-NaF atherosclerotic plaque uptake was
related to the burden of CV risk factors and thoracic fat volume, but there was no association between coronary uptake and calcium score.


**ABSTRACT**

Objective. To investigate whether prior treatment of atorvastatin reduces the frequency of hospital acquired pneumonia (HAP). Methods. Totally, 492 patients with acute ischemic stroke and Glasgow Coma Scale $\leq 8$ were enrolled in this study. Subjects were assigned to prior atorvastatin treatment group (n = 268, PG) and no prior treatment group (n = 224, NG). All the patients were given 20 mg atorvastatin every night during their hospital stay. HAP frequency and 28-day mortality were measured. Levels of inflammatory biomarkers [white blood cell (WBC), procalcitonin (PCT), tumor necrosis factor-alpha (TNF-alpha), and interleukin-6 (IL-6)] were tested. Results. There was no significant difference in the incidence of HAP between PG and NG (25.74% versus. 24.55%, p > 0.05) and 28-day mortality (50.72% versus 58.18%, p > 0.05). However, prior statin treatment did modify the mortality of ventilator associated pneumonia (VAP) (36.54% versus 58.14%, p = 0.041) and proved to be a protective factor (HR, 0.564; 95% CI, 0.310~0.825, p = 0.038). Concentrations of TNF-alpha and IL-6 in PG VAP cases were lower than those in NG VAP cases (p < 0.01). Conclusions. Prior atorvastatin treatment in patients with ischemic stroke was associated with a lower concentration of IL-6 and TNF-alpha and improved the outcome of VAP. This clinical study has been registered with ChiCTR-ROC-17010633 in Chinese Clinical Trial Registry.


**ABSTRACT**

BACKGROUND: Few studies have been conducted that compared lipid levels and uric acid in CKD or End-Stage Renal Disease (ESRD) patients with most using animal models. The purpose of the study was to explore effects on lipids while controlling uric acid levels in CKD patients.

METHODS: Twenty-four CKD patients (N = 24) volunteered to participate in this study. The study was conducted using a double-blind, randomized, placebo controlled experimental protocol. The experimental group was prescribed 300 mg of allopurinol PO daily by their treating physician and followed prospectively for 8-weeks. The control group consumed a similar pill once a day for 8-weeks. RESULTS: ANCOVA revealed significant differences in total cholesterol (P = 0.009) and Apo B (P = 0.006) with lower levels in the allopurinol group. A trend emerged with LDL (P = 0.052) with lower levels in the allopurinol group. No significant differences were discovered in triglycerides (P = 0.403), HDL (P = 0.762) and total Cholesterol/HDL Ratio (P = 0.455). CONCLUSIONS: After statistically controlling for compliance and inflammation significant differences between groups were observed for total cholesterol and Apo B. In both instances the allopurinol group had lower concentrations than the placebo
group. Similarly, a trend was observed in LDL with the allopurinol group having lower concentrations than the placebo group.


ABSTRACT
BACKGROUND: Researchers have reported an independent direct relationship between lipid levels and hyperuricemia with MetS. The purpose of this study was to determine the relationship between serum uric acid levels and lipids among patients on allopurinol.

METHODS: A retrospective secondary data analysis was conducted on 66 adult patients from a family health clinic in Central Texas. Medical records used were recorded during a nine year period (2002 - 2010) ascertaining the relationship between uric acid and lipids. RESULTS: Spearman correlations revealed a weak correlation between uric acid and total cholesterol, a weak correlation between uric acid and triglycerides and LDL-C. A weak inverse correlation was discovered between uric acid and HDL-C. A moderate correlation was discovered when all lipid variables combined were compared to uric acid. CONCLUSIONS: We discovered LDL-C and triglycerides to be significant predictors of uric acid with weak correlations. Additionally, weak correlations existed between uric acid and total cholesterol and HDL-C with an inverse relationship discovered with HDL-C. These findings support the literature suggesting that uric acid is more likely to be associated with total cholesterol and triglycerides. In addition, new discoveries serve as an indication that LDL-C may also be associated with uric acids levels. The mechanism by which uric acid may regulate lipids is elusive but suggestions have included suppression of lipid peroxidase and decreases in critical lipase activity.


ABSTRACT
BACKGROUND: Matrix metalloproteinase (MMP)-9 is excessively expressed in frail region of atherosclerotic plaque and released in circulation following plaque rupture. High MMP-9 level associated with severity of occluded thrombus and subsequent myocardial infarction. MMP-9 (-1562C>T) polymorphism associated with acute myocardial infarction, however conflicting data present regarding impact of MMP-9 (-1562C>T) polymorphism on circulating MMP-9 level in acute myocardial infarction with ST-elevation (STEMI), clinical entity represents totally occluded coronary thrombus. METHODS: We enrolled consecutively subjects with acute coronary syndrome treated in intensive coronary care unit. Acute coronary syndrome diagnosis were classified into STEMI and non-ST-elevation acute coronary syndrome (NSTEMACS). Seventy consecutive subjects were enrolled for this study, 31 subjects with STEMI and 39 subjects with NSTEMACS. RESULTS: On admission serum MMP-9 level, measured with sandwich enzyme immunoassay, were higher in STEMI as compared with NSTEMACS (1,574.2 +/- 604.1 ng/mL vs. 1,104.4 +/- 591.5 ng/mL, P < 0.01). Proportion of subjects with MMP-9 (-1562C>T) polymorphism, analyzed with PCR-RFLP, were higher in STEMI as compared with NSTEMACS.
(66.7% vs. 33.3%, P = 0.15). T allele frequency was almost twice in STEMI as compared to in NSTEACS. Almost all (83%) subjects with MMP-9 (-1562C>T) polymorphism had high serum MMP-9 level (> 1,334.5 ng/mL) during STEMI, whereas in NSTEACS all subjects had low level. CONCLUSION: MMP-9 (-1562C>T) polymorphism associated with high serum MMP-9 level in patients with STEMI.


ABSTRACT
INTRODUCTION: As part of the CEPHEUS study, CEPHEUS I was conducted in 2010 and 2011 in Cairo and then the CEPHEUS II study was carried out in Alexandria and Delta Regions in Egypt between April 2014 and August 2015 to determine the proportion of dyslipidemic patients on lipid-lowering treatment reaching LDL-C treatment goals. METHODS: We conducted an open-label, observational, multicenter, cross-sectional survey where 90 investigators enrolled 1127 patients receiving lipid-lowering drugs for at least 3 months. After signing informed consent forms, the study questionnaires were completed by patients and investigators. Blood samples were taken for laboratory investigations. Patients with missing LDL-C data were excluded from the analysis and results from 896 patients were analyzed according to European Atherosclerosis Society and EAS/ESC 2011 guidelines. RESULTS: Out of 896 patients enrolled based on the risk stratification of EAS/ESC 2011 guidelines, 12.4% were classified as low risk, 20.0% as moderate risk, 2.5% as high risk, and 65.2% as very high risk. Achievement goals were 84.7, 44.7, 18.2, and 22.3% for low-risk, moderate-risk, high-risk, and very high risk patients, respectively, with an overall achievement goal of 34.4%. The study population included 50.2% diabetes, 64.4% hypertension, 54.9% metabolic syndrome, 32.2% family history of cardiovascular disease, 23.1% smokers, and 33.8% secondary prevention. Lipid-lowering agents were prescribed as a monotherapy to 90.1% and in combination in 9.9% with goal achievements of 34 and 38%, respectively (p > 0.05). Statins were prescribed to 86.9% of patients. The most frequent prescribed statins were rosuvastatin (47.1%) and atorvastatin (36.0%), followed by simvastatin (9.2%). Treatment goal was achieved in 34.2, 36.0, and 31.7% for rosuvastatin, atorvastatin, and simvastatin, respectively, with no significant difference in achievement goals (p > 0.05).
CONCLUSIONS: Hypercholesterolemia is still not being effectively managed in many at-risk patients in Egypt. The majority of patients enrolled in the study were being actively treated with lipid-lowering medications yet the percentage goal achievement was less when compared to CEPHEUS results.


ABSTRACT
Graves' disease (GD) may display uncommon manifestations. We report a patient with rare complications of GD and present a comprehensive literature review. A 35-year-old woman presented with a two-week history of dyspnea, palpitations, and edema. She had a raised
jugular venous pressure, goiter, and exophthalmos. Laboratory tests showed pancytopenia, a raised alkaline phosphatase level, hyperbilirubinemia (mainly direct bilirubin), and hyperthyroidism [TSH: <0.01 mIU/L (reference values: 0.45-4.5), fT4: 54.69 pmol/L (reference values: 9.0-20.0), and fT3: >46.08 pmol/L (reference values: 2.6-5.7)]. Her thyroid uptake scan indicated GD. Echocardiography showed a high right ventricular systolic pressure: 60.16 mmHg. Lugol's iodine, propranolol, cholestyramine, and dexamethasone were initiated. Hematologic investigations uncovered no reason for the pancytopenia; therefore, carbimazole was started. Workup for hepatic impairment and pulmonary hypertension (PH) was negative. The patient became euthyroid after 3 months. Leukocyte and platelet counts and bilirubin levels normalized, and her hemoglobin and alkaline phosphatase levels and right ventricular systolic pressure (52.64 mmHg) improved. This is the first reported single case of GD with the following three rare manifestations: pancytopenia, cholestatic liver injury, and PH with right-sided heart failure. With antithyroid drugs treatment, pancytopenia should resolve with euthyroidism, but PH and liver injury may take several months to resolve.

ABSTRACT

ABSTRACT
OBJECTIVES: Dyslipidaemia is common in patients with subclinical hypothyroidism (SCH). To date, there is no universal agreement regarding the lipid-lowering effect of substitution treatment with L-T4 in patients with SCH. We aimed to clarify the effect by conducting this systematic review and meta-analysis of randomized controlled trials (RCTs). DESIGN: We systematically searched PubMed, the Cochrane Library, ClinicalTrials.gov and EMBASE for RCTs comparing substitution treatment to placebo treatment or observation. We focused on the primary outcomes of changes from baseline of total, low-density lipoprotein, and high-density lipoprotein cholesterol (TC, LDL-C and HLD-C) and triglycerides. Subgroup analyses were performed, assessing the effect of treatment duration, disease severity, and ethnicity on the occurrence of discrepancy RESULTS: Twelve trials, with 940 participants, were eligible for analysis. Compared with the control group, levothyroxine substitution yielded a mean reduction in TC (-0.29mmol/l, [-0.42 to -0.16]) and LDL-C (-0.22mmol/l, [-0.36 to -0.09]), with no significant effects on HDL-C (-0.04mmol/l, [-0.08 to 0.01]) or triglycerides (-0.04mmol/l, [-0.08 to 0.00]). Trials in which only patients with mild SCH (thyrotropin <10 mIU/L) were enrolled showed equivalent effects. The lowering effects were weaker, but still significant, in long-term treatment (>6 months) compared with short-term treatment (</=6 months) for TC (-0.19mmol/l [-0.35, -0.03] vs. -0.50mmol/l [-0.68, -0.31], p = 0.047) and LDL-C (-0.09mmol/l [-0.16, -0.02] vs. -0.46mmol/l [-0.68, -0.25], p = 0.006). CONCLUSIONS: Levothyroxine treatment
has clear benefits on TC and LDL-C in SCH patients, including those with mild SCH. This article is protected by copyright. All rights reserved.


**ABSTRACT**

BACKGROUND & AIMS: While a recent meta-analysis of prospective studies reported that coffee consumption is associated with a lower risk of cardiovascular disease mortality, limited and inconsistent data are available on the relation of coffee intake with subclinical disease. Thus, the aim of the present study was to see the association of coffee consumption with the prevalence of atherosclerotic plaque in the coronary arteries in NHLBI Family Heart Study.

METHODS: In a cross-sectional design, we studied 1929 participants of the NHLBI Family Heart Study without known coronary heart disease. Coffee consumption was assessed by a semi-quantitative food frequency questionnaire and coronary-artery calcium (CAC) was measured by cardiac computed tomography. We defined prevalent CAC as an Agatston score of \( \geq 100 \) and used generalized estimating equations to calculate prevalence ratios of CAC as well as a sensitivity analysis at a range of cutpoints for CAC.

RESULTS: Mean age was 56.7 years and 59% of the study subjects were female. In adjusted analysis for age, sex, BMI, smoking, alcohol, physical activity, field center, and energy intake, prevalence ratio (95% CI) for CAC was 1.0 (reference), 0.92 (0.57-1.49), 1.34 (0.86-2.08), 1.30 (0.84-2.02), and 0.99 (0.60-1.64) for coffee consumption of almost never, \(<1/day\), \(1/day\), 2-3/day, and \( \geq 4 \) cups/day, respectively. In a sensitivity analysis, there was no evidence of association between coffee consumption and prevalent CAC when CAC cut points of 0, 50, 150, 200, and 300 were used. CONCLUSIONS: These data do not provide evidence for an association between coffee consumption and prevalent CAC in adult men and women.


**ABSTRACT**

BACKGROUND: Glucagon-like peptide-1 receptor agonists (GLP-1 RAs) for the treatment of type 2 diabetes mellitus are known to delay gastric emptying (GE). The potential effect of the GLP-1 RA dulaglutide on the pharmacokinetics (PK) of four orally administered drugs and on the pharmacodynamic (PD) effect of warfarin was investigated.

METHODS: In four separate clinical pharmacology studies, digoxin, warfarin, atorvastatin and Ortho-Cyclen(R) were orally administered to healthy subjects with and without a subcutaneous dose of dulaglutide 1.5 mg. The effect of dulaglutide coadministration was assessed based on the PK parameters of key analytes. For warfarin PD, the effect of dulaglutide on the international normalized ratio (INR) was evaluated.

RESULTS: Areas under the concentration-time curves (AUCs) with and without dulaglutide were similar for all analytes except atorvastatin, where it was reduced by 21%. Maximum concentrations (C max) were generally lower following coadministration with
dulaglutide, with statistically significant reductions (90% confidence intervals of geometric least squares means ratios outside 0.80-1.25) for all analytes except R-warfarin. For all analytes, there was a general trend for the time to C max (t max) to increase following coadministration with dulaglutide. For warfarin, dulaglutide coadministration had no statistically significant effect on the maximum INR (INRmax); however, a 2% increase in area under the INR curve (AUCINR) was observed. CONCLUSIONS: Dulaglutide did not affect the absorption of the tested medications to a clinically relevant degree. Based on the PK and PD evaluations, no dose adjustments for digoxin, warfarin, atorvastatin and Ortho-Cyclen(R) are recommended when coadministered with dulaglutide. CLINICAL TRIAL REGISTRATION NUMBERS: NCT01458210, NCT01436201, NCT01432938, and NCT01250834.


ABSTRACT

BACKGROUND AND OBJECTIVE: Semaglutide is a glucagon-like peptide-1 analogue in development for the once-weekly treatment of type 2 diabetes mellitus. Its effect on the rate and extent of absorption of concomitant oral medications (metformin, warfarin, atorvastatin and digoxin) was evaluated in healthy subjects. METHODS: Subjects received metformin (500 mg twice daily for 3.5 days), warfarin (25 mg, single dose), atorvastatin (40 mg, single dose) or digoxin (0.5 mg, single dose) before and with subcutaneous semaglutide treatment at steady state (1.0 mg). Lack of drug-drug interaction was concluded if the 90% confidence intervals for the area under the plasma concentration-time curve ratio before and with semaglutide were within a pre-specified interval (0.80-1.25). RESULTS: Overall, metformin, warfarin, atorvastatin and digoxin pharmacokinetics were not affected to a clinically relevant degree with semaglutide co-administration. Estimated area under the plasma concentration-time curve ratios for all concomitant medications before and with semaglutide treatment were within the pre-specified interval. In addition, semaglutide did not affect maximum plasma concentration of concomitant medications to a relevant degree. Furthermore, no clinically relevant change in international normalised ratio response to warfarin was observed with semaglutide co-administration. Most adverse events with semaglutide treatment were mild or moderate. Adverse events with semaglutide and co-administered medication were comparable to those reported during treatment with semaglutide alone, and were mostly gastrointestinal related. CONCLUSIONS: No clinically significant pharmacokinetic or pharmacodynamic interactions were identified and no new safety issues observed with combined treatment with semaglutide. This suggests that no dose adjustments should be required when semaglutide is administered concomitantly with these medications.


ABSTRACT
The chemical structure of polyphenols consisting of aromatic rings, capable of quenching free radicals, makes them ideal candidates to protect against oxidation. Polyphenols are present in a variety of foods including grapes, berries, dark chocolate, coffee and tea to mention a few. A number of studies have shown that dietary polyphenols exert a protective effect against hypertension, dyslipidemias, inflammation, endothelial function and atherosclerosis, conditions associated with increased risk for cardiovascular disease. Studies indicate that by decreasing cholesterol absorption, polyphenols alter hepatic cholesterol homeostasis resulting in decreases in plasma lipids and reduction in atherogenic lipoproteins thus having a protective effect against atherosclerosis; polyphenols have also been shown to decrease the activity of enzymes involved in the renin-angiotensin-aldosterone system and improve blood pressure. Further, they have been recognized to increase nitric oxide production and to improve endothelial function. In this review we will present some of the evidence derived from epidemiological studies, clinical interventions as well as animal and cell studies supporting the cardioprotective effects of dietary polyphenols.


ABSTRACT
AIMS: The coadministration of alirocumab, a PCSK9 inhibitor for treatment of hypercholesterolaemia, and insulin in diabetes mellitus (DM) requires further study. Described here is the rationale behind a phase-IIIb study designed to characterize the efficacy and safety of alirocumab in insulin-treated patients with type 1 (T1) or type 2 (T2) DM with hypercholesterolaemia and high cardiovascular (CV) risk. METHODS: ODYSSEY DM-INSULIN (NCT02585778) is a randomized, double-blind, placebo-controlled, multicentre study that planned to enrol around 400 T2 and up to 100 T1 insulin-treated DM patients. Participants had low-density lipoprotein cholesterol (LDL-C) levels at screening >/=70mg/dL (1.81mmol/L) with stable maximum tolerated statin therapy or were statin-intolerant, and taking (or not) other lipid-lowering therapy; they also had established CV disease or at least one additional CV risk factor. Eligible patients were randomized 2:1 to 24 weeks of alirocumab 75mg every 2 weeks (Q2W) or a placebo. Alirocumab-treated patients with LDL-C >/=70mg/dL at week 8 underwent a blinded dose increase to 150mg Q2W at week 12. Primary endpoints were the difference between treatment arms in percentage change of calculated LDL-C from baseline to week 24, and alirocumab safety. RESULTS: This is an ongoing clinical trial, with 76 T1 and 441 T2 DM patients enrolled; results are expected in mid-2017. CONCLUSION: The ODYSSEY DM-INSULIN study will provide information on the efficacy and safety of alirocumab in insulin-treated individuals with T1 or T2 DM who are at high CV risk and have hypercholesterolaemia not adequately controlled by the maximum tolerated statin therapy.


ABSTRACT
Literature update week 13 (2017)

Niacin, as an antidysslipidemic drug, elicits a strong flushing response by release of prostaglandin (PG) D2. However, whether niacin is beneficial for inflammatory bowel disease (IBD) remains unclear. Here, we observed niacin administration-enhanced PGD2 production in colon tissues in dextran sulfate sodium (DSS)-challenged mice, and protected mice against DSS or 2,4,6-trinitrobenzene sulfonic acid (TNBS)-induced colitis in D prostanoid receptor 1 (DP1)-dependent manner. Specific ablation of DP1 receptor in vascular endothelial cells, colonic epithelium, and myeloid cells augmented DSS/TNBS-induced colitis in mice through increasing vascular permeability, promoting apoptosis of epithelial cells, and stimulating pro-inflammatory cytokine secretion of macrophages, respectively. Niacin treatment improved vascular permeability, reduced apoptotic epithelial cells, promoted epithelial cell update, and suppressed pro-inflammatory gene expression of macrophages. Moreover, treatment with niacin-containing retention enema effectively promoted UC clinical remission and mucosal healing in patients with moderately active disease. Therefore, niacin displayed multiple beneficial effects on DSS/TNBS-induced colitis in mice by activation of PGD2/DP1 axis. The potential efficacy of niacin in management of IBD warrants further investigation.


ABSTRACT
BACKGROUND: Evolocumab (AMG 145), a PCSK9 inhibitor, has been shown to decrease low-density lipoprotein cholesterol (LDL-C) levels. Doses of 140mg administered every 2weeks (Q2W) and 420mg administered every 4weeks (Q4W) are widely used, and both dosing schedules were effective in clinical trials. However, some researchers have speculated that 140mg Q2W administration has equal or even greater efficacy. This meta-analysis was performed to assess the differences in efficacy and safety between the two doses. METHODS: We searched the PubMed, EMBASE, and Web of Science databases to identify relevant clinical trials published before January 2016. A total of 2403 patients from 8 randomized controlled trials were identified and included in the analysis. RESULTS: Evolocumab administered at 140mg Q2W resulted in a greater percent change from baseline in LDL-C concentration (-7.27; 95% confidence interval (CI), -10.36 to -4.18) and had greater efficacy in achieving the treatment goal of LDL-C <1.8mmol/L with an relative risk (RR) of 1.09 (95% CI, 1.00 to 1.18) compared with 420mg Q4W in patients who were concomitantly treated with statins. These findings were not significantly different between the 140mg Q2W and 420mg Q4W groups when evolocumab was administered as monotherapy. There was no difference in the rate of occurrence of the main treatment-related adverse events between the two doses. CONCLUSIONS: Evolocumab administered at 140mg Q2W was more effective than the 420mg Q4W dosage at lowering lipid concentrations, especially in patients who concomitantly received stable statin therapy.

**ABSTRACT**

PURPOSE: Our aim was to assess whether 18F-NaF PET/CT is able to predict progression of the CT calcium score. METHODS: Between August 2007 and November 2015, 34 patients (18 women, 16 men; age, mean +/- standard deviation, 57.5 +/- 13.9 years; age range 19-78 years) with malignancy or orthopaedic disease were enrolled in this study, with approximately 1-year follow-up data. Baseline and follow-up CT images were retrospectively evaluated for the presence of calcification sites in major vessel walls. The maximum and mean CT values (CTmax and CTmean, in Hounsfield units), calcification volumetric score (CVS, in cubic millimetres) and Agatston units score (AU) were evaluated for each site. Subsequent changes in CTmax, CTmean, CVS and AU were calculated and expressed as DeltaCTmax, DeltaCTmean, DeltaCVS and DeltaAU, respectively. We then evaluated the relationship between 18F-NaF uptake (using the maximum target-to-background ratio, TBRmax, and the maximum blood-subtracted 18F-NaF activity, bsNaFmax, which was obtained by subtracting the SUVmax of each calcified plaque lesion and NaF-avid site from the SUVmean in the right atrium blood pool) and the change in calcified plaque volume and characteristics obtained after 1 year. RESULTS: We detected and analysed 182 calcified plaque sites and 96 hot spots on major vessel walls. 18F-NaF uptake showed very weak correlations with CTmax, CTmean, CVS, CVS after 1 year, AU and AU after 1 year on both baseline and follow-up PET/CT scans for each site. 18F-NaF uptake showed no correlation with DeltaCTmax or DeltaCTmean. However, there was a significant correlation between the intensity of 18F-NaF uptake and DeltaCVS and DeltaAU. CONCLUSION: 18F-NaF uptake has a strong correlation with calcium score progression which was a predictor of future cardiovascular disease risk. PET/CT using 18F-NaF may be able to predict calcium score progression which is known to be the major characteristic of atherosclerosis.


**ABSTRACT**

Background Familial hypercholesterolaemia is a common autosomal dominant disease, caused by mutations leading to elevated low-density lipoprotein (LDL) cholesterol and, if untreated, to premature cardiovascular disease. Methods Patients (young adults with a family history of hypercholesterolaemia or premature cardiovascular disease) with LDL cholesterol concentration >/=4.9 mmol/l, after excluding Familial Combined Hyperlipidaemia, were evaluated for causative mutations, Dutch Lipid Clinic Network score calculation and non-invasive ultrasound examination of carotid arteries. Results Of the 263 patients, 210 were heterozygotes for LDL receptor (LDLR) mutations, four had APOB gene mutations, one PCSK9 gene mutation, while 48 had no evidence of mutations. Among 194 unrelated index cases 149 had mutations (77%). Among patients with LDLR mutations (n = 145), there were five compound heterozygotes, 75 patients with null mutations and 65 with missense mutations. As many as 178 patients underwent a follow-up and treatment (statin +/- ezetimibe), achieving a mean reduction of 49% in LDL cholesterol, with 21% of patients reaching the LDL goal of 2.6 mmol/l. In a multivariate analysis, carotid plaques, at ultrasound examination, were associated with the presence of genetic mutation (p = 0.001), LDL cholesterol (p < 0.001), Dutch Lipid
Clinic Network score ($p < 0.001$), independently of age, gender, smoking habits and systolic blood pressure. The presence of carotid plaque ($p = 0.017$), LDL cholesterol ($p < 0.003$), Dutch Lipid Clinic Network score ($p < 0.001$) were independently associated with premature cardiovascular disease. Conclusions We identified patients with causative mutations in 82% of the cases under study. In addition to LDL cholesterol and Dutch Lipid Clinic Network score, carotid plaques in ultrasound evaluation provide direct evidence of premature vascular disease and are associated with high risk for cardiovascular events.


**ABSTRACT**
The pancreas is a centralized organ vital for whole body metabolic control. Recent advances in the field of metabolism have reinforced its importance for orchestrating endocrine hormone secretion in response to several nutrients including glucose, lipids and amino acids, in addition to hormones and inflammatory signals. Cell types within the pancreas, in particular the insulin-producing beta cells, control nutrient breakdown and energy production and are essential to maintain not only efficient hormone secretion, but also cell integrity, survival, and the ability to sense and adapt to changing metabolic environments. The present review highlights recent research advances on how glucolipotoxicity, mitochondrial dysfunction, and systemic inflammation affects pancreatic metabolism, and how new technologies and more advanced research models are improving our ability to study this organ system. Taken together, careful characterization and understanding of the importance of nutrient metabolism within this important, yet complex organ, will help us to better understand pathologies intimately associated with the pancreas and possibly discover new and more effective therapeutic strategies.


**ABSTRACT**
INTRODUCTION: Non-fasting plasma triglyceride (TG) and remnant cholesterol levels, cholesterol content of triglyceride-rich lipoproteins, have been suggested to be an additional cause of cardiovascular diseases; thus, pharmacological TG-lowering with fibrates, activators of PPAR-alpha system, has been linked to risk reduction. Areas covered: This manuscript reviews available evidence on clinical trials involving highly selective PPAR-alpha agonists (i.e., pemafibrate) and drugs used in the pre-clinical and experimental setting (e.g., WY14,643). Original publications in English were selected, as well as Abstracts of international meetings' presentations. Clinical trials were identified using the clinicaltrial.gov database and the EU Clinical Trials Register (clinicaltrialsregister.eu). Expert opinion: In addition to the aim of improving lipid profile with fibrates, the interest in new PPAR-alpha activators stems from the need to overcome some of the clinical problems encountered with dose-dependent adverse events; a rise of plasma creatinine, gallstone formation, drug-drug interactions (i.e. gemfibrozil), and myopathy. New PPAR-alpha agonists improved TG and HDL-C levels as well as
other parameters related to TG metabolism (remnant cholesterol and apoB), without raising liver enzymes. Although the use of fibrates is rated "second choice" by many clinicians, new PPAR-alpha agonists may offer a more accessible route to the management of hypertriglyceridemia, a frequent clinical condition.


ABSTRACT

Reactive oxygen species (ROS) have emerged as important molecules in cardiovascular function. Nicotinamide-adenine dinucleotide phosphate (NADPH) oxidase is the major source of ROS in phagocytic and vascular cells. Several lines of evidence indicate that quercetin contributes to protecting against atherosclerosis. Herein, we investigated the effect of quercetin on alleviating atherosclerosis by regulating NADPH oxidase subunits expression in vivo, and explored the mechanism of quercetin suppressing the ROS overproduction stimulated by ox-LDL in mouse peritoneal macrophages (MPMs). Model ApoE KO mice were fed with either a normal chow diet or a high fat diet (HFD) supplemented with or without dosed quercetin for 24 weeks. Quercetin significantly reduced the atherosclerotic plaque area, alleviated the systemic oxidative stress, and suppressed aortic p47phox, p67phox expressions but partially reversed the NOX4 expression as compared to those in the HFD group. In vitro, quercetin effectively inhibited the ox-LDL induced ROS formation in MPMs, and blocked the vital step in activation of NADPH oxidase - membrane translocation of p47phox. Our findings suggest that regular consumption of dietary quercetin plays a role in preventing atherosclerosis giving its evident regulatory effect on subunits of NADPH oxidase.


ABSTRACT

Inflammatory mechanisms may be involved in atherosclerotic plaque rupture. By using a novel histology-based method to quantify plaque instability here, we assess whether lectin pathway (LP) of complement activation, a major inflammation arm, could represent an index of plaque instability. Plaques from 42 consecutive patients undergoing carotid endarterectomy were stained with hematoxylin-eosin and the lipid core, cholesterol clefts, hemorrhagic content, thickness of tunica media, and intima, including or not infiltration of cellular debris and cholesterol, were determined. The presence of ficolin-1, -2, and -3 and mannose-binding lectin (MBL), LP initiators, was assessed in the plaques by immunofluorescence and in plasma by ELISA. LP activation was assessed in plasma by functional in vitro assays. Patients presenting low stenosis (<75%) had higher hemorrhagic content than those with high stenosis (>75%), indicating increased erosion. Increased hemorrhagic content and tunica media thickness, as well as decreased lipid core and infiltrated content were associated with vulnerable plaques.
and therefore used to establish a plaque vulnerability score that allowed to classify patients according to plaque vulnerability. Ficolins and MBL were found both in plaques' necrotic core and tunica media. Patients with vulnerable plaques showed decreased plasma levels and intraplaque deposition of ficolin-2. Symptomatic patients experiencing a transient ischemic attack had lower plasma levels of ficolin-1. We show that the LP initiators are present within the plaques and their circulating levels change in atherosclerotic patients. In particular, we show that decreased ficolin-2 levels are associated with rupture-prone vulnerable plaques, indicating its potential use as marker for cardiovascular risk assessment in atherosclerotic patients.


**PM:** http://www.ncbi.nlm.nih.gov/pubmed/?term=28343238

**ABSTRACT**

En-face fat staining is frequently used to visualize atherosclerotic lesions. This method, however, is not suitable to visualize endothelial barrier damage prior to microscopically detectable morphological alterations of the arterial wall such as sub-endothelial lipid deposition. To enable the investigation of early endothelial barrier damage and in particular the initial steps of atherosclerosis, a new method has to fulfill three requirements: (i) easy and fast to perform, (ii) low cost of applicability without requirement for highly sophisticated technical equipment, and (iii) reliable reproducibility of valid results. To this end, we used intracardial Evans blue dye injection after washout of blood and measured dye deposition within the aortic wall as a parameter of endothelial barrier leakiness, which is recognized as one of the earliest signs of atherosclerotic plaque formation. These analyses were performed in ApoE -/-, LDL receptor -/- and Cc1 -/- mouse models which have been reported to develop aortic plaques with or without high cholesterol diet. Our data show that sub-endothelial dye deposition is a reliable and reproducible readout parameter to assess endothelial barrier damage. Along these lines, measurements of aortic intima areas with Evans blue deposition in relation to total intima circumference enabled quantitative assessments of the results. Our technique enables the imaging of endothelial barrier damage prior to detectable aortic lipid deposition and plaque development. Thus, it will facilitate the detection of the initial vascular pathogenic processes that lead to cardiovascular diseases. It will also enable the testing of new drugs and therapeutic procedures to prevent these disorders.


**PM:** http://www.ncbi.nlm.nih.gov/pubmed/?term=28352986

**ABSTRACT**

A recent genome-wide association study associated 62 single nucleotide polymorphisms (SNPs) from 43 genomic loci, with fasting lipoprotein subfractions in European-Americans (EAs) at genome-wide levels of significance across three independent samples. Whether these associations are consistent across ethnicities with a non-European ancestry is unknown. We analyzed 15 lipoprotein subfraction measures, on 1677 African-Americans (AAs), 1450 Hispanic-
Americans (HAs), and 775 Chinese-Americans (CHN) participating in the multi-ethnic study of atherosclerosis (MESA). Genome-wide data were obtained using the Affymetrix 6.0 and Illumina HumanOmni chips. Linear regression models between genetic variables and lipoprotein subfractions were adjusted for age, gender, body mass index, smoking, study center, and genetic ancestry (based on principal components), and additionally adjusted for Mexican/Non-Mexican status in HAs. A false discovery rate correction was applied separately within the results for each ethnicity to correct for multiple testing. Power calculations revealed that we did not have the power for SNP-based measures of association, so we analyzed phenotype-specific genetic risk scores (GRSs), constructed as in the original genome-wide analysis. We successfully replicated all 15 GRS-lipoprotein associations in 2527 EAs. Among the 15 significant GRS-lipoprotein associations in EAs, 11 were significant in AAs, 13 in HAs, and 1 in CHNs. Further analyses revealed that ethnicity differences could not be explained by differences in linkage disequilibrium, lipid lowering drugs, diabetes, or gender. Our study emphasizes the importance of ethnicity (here indexing genetic ancestry) in genetic risk for CVD and highlights the need to identify ethnicity-specific genetic variants associated with CVD risk.


ABSTRACT

BACKGROUND: Previous studies from our group demonstrated the anti-inflammatory properties of statins on cardiopulmonary bypass (CPB), through inhibition of neutrophil transendothelial migration. We sought to determine the utility of preoperative statin on patients undergoing cardiac surgery, to investigate any moderating effects on the systemic inflammatory response (SIRS) with CPB, and to evaluate any clinical impact on our patients.

METHODS: This is a prospective, randomised controlled trial with national regulatory body approval. Eligible patients were already on oral statin therapy. They were then randomly assigned to either investigation arm (n = 15, atorvastatin 80 mg for 2 weeks before surgery) or control arm (n = 15, no change to current statin therapy). Blood and urine samples were collected at 3 timepoints. Postoperative clinical measures were documented. RESULTS: Patients in the investigation arm have significantly lower troponin level (p = 0.016), and lower level of urine neutrophil gelatinase-associated lipocalin (NGAL; p = 0.002); thus demonstrating a lesser degree of cardiac and renal injury in these patients. Higher level of Interleukin-8 (IL-8) at baseline (p = 0.036) and 4 h post cross-clamp removal (p = 0.035) in the investigation arm. A similar trend is also observed in Matrix Metalloproteinase-9 (MMP-9; p > 0.05). There were however no differences in clinical outcomes. CONCLUSIONS: Maximizing the dose of statin in patients waiting for cardiac surgery has measurable biological effects. There is evidence of less cardiac and renal damage. The use of preoperative statins and in particular, high dose preoperative statin therapy, may prove a useful new tool for optimal preparation of patients for cardiac surgery. TRIAL REGISTRATION: EudraCT no. 2012-003396-20 . Registered 05 November 2012.


ABSTRACT

CONTEXT: Atorvastatin calcium (ATV), a cholesterol-lowering agent, suffers from poor systemic availability (14%) after oral administration in addition to other side effects on the gastrointestinal tract, liver and muscle. OBJECTIVE: The goal of the present investigation was to improve ATV bioavailability and overcome complications attendant with peroral administration by developing a new nanovesicular system encapsulating ATV for its delivery via the transdermal route. METHODS: The vesicular systems were prepared by incorporating different polyethylene glycol fatty acid esters such as Labrasol, Cremophor EL, Gelucire 44/14 and Tween 80 as edge activators (EAs) in the lipid bilayer. The effect of the phosphatidylcholine (PC):EA molar ratio on the physicochemical properties of the vesicles was investigated. The pharmacokinetic studies of the optimized formulation were evaluated in rats. The optimized formulation was tested in poloxamer 407-induced hyperlipidemic rats. The plasma lipid profile, activity of liver enzymes, and oxidative stress parameters were measured using commercially available kits. RESULTS: The results revealed high ATV entrapment efficiency (EE%) ranging from 55.62 to 83.91%. The formulations that contained Labrasol showed the highest EE%. The mean diameter of the vesicles was in the range of 186-583nm. T8 containing Gelucire 44/14 as an EA in the molar ratio of 15:1 (PC:EA) gave the smallest size and exhibited the best permeation parameters across the skin. The pharmacokinetic studies revealed that about three times statistically significant (p<0.05) improvement in bioavailability, after transdermal administration of nanotransfersomal ATV gel compared to oral ATV suspension. The transdermal vesicular system exhibited a significant decrease in plasma total cholesterol, triglycerides and LDL cholesterol comparable to oral ATV. Additionally, it lowered the malondialdehyde levels in plasma and abolished the increase in liver enzyme activity. CONCLUSION: The results obtained suggest that the proposed transdermal vesicular system can serve as a promising alternative means for delivery of ATV.


ABSTRACT

BACKGROUND: High-density lipoproteins (HDL) have athero-protective biological properties: antioxidative, anti-apoptotic, anti-inflammatory, and they have the efflux capacity of cellular cholesterol. Plasma mRNA analysis can be used to investigate statin pleiotropy in vivo as a new analytical tool for non-invasive assessment of gene expression in vascular beds. The aim of this study was to assess the pleiotropic effects of atorvastatin in stable angina patients with high-risk values (group A) as compared with patients who had borderline and desirable HDL-cholesterol (HDL-C) values (group B). METHODS: The atorvastatin therapy (20 mg/day) was given to forty-three patients with stable angina for 10 weeks. We investigated three statin pleiotropy-targeted genes: inter-cellular adhesion molecule-1, chemokine (C-C motif) ligand 2 and cathepsin S and assessed by gel electrophoresis gradient the effects of atorvastatin on HDL
size and subclasses. RESULTS: In group A, after therapy, HDL-C concentration was significantly increased but not in group B. Atorvastatin lowered plasma chemokine (C-C motif) ligand 2 and intercellular adhesion molecule-1 mRNA levels in both groups, but did not change the plasma cathepsin S mRNA levels. In group A only, baseline total bilirubin showed negative correlations with the genes of cathepsin S ($r=0.506; p=0.023$) and significantly increased after therapy. CONCLUSIONS: HDL-C and bilirubin can be promising therapeutic targets in the treatment of cardiovascular diseases. Analysis of cell-free mRNA in plasma might become a useful tool for estimating statin pleiotropy.


ABSTRACT
Hypercholesterolaemia remains one of the leading risk factors for the development of cardiovascular disease. Many large double-blind studies have demonstrated that lowering LDL-cholesterol using a statin can reduce the risk of having a cardiovascular event by ~30%. However, despite the success of statins, some patient populations are unable to lower their LDL-cholesterol to meet the targeted lipid levels, due to compliance or potency issues. This is especially true for heterozygous familial hypercholesterolaemia (heFH) patients who may require additional upregulation of the Low-Density Lipoprotein Receptor (LDLR) to reduce LDL-cholesterol levels below those achievable with maximal dosing of statins. Here we identify a series of small molecules from a genomic DNA reporter screen which upregulate the LDLR in mouse and human liver cell lines at nanomolar potencies (EC50: 39 nM). Structure-activity relationship studies carried out on the lead compound (compound OX03771) led to the identification of compound OX03050, which had similar potency (EC50: 26 nM), but a much-improved pharmacokinetic profile and showed in vivo efficacy. Compound OX03050 and OX03771 were found to inhibit squalene synthase, the first committed step in cholesterol biosynthesis. These squalene synthase inhibitors were shown to act cooperatively with statins to increase LDLR expression in vitro. Overall, we have demonstrated here a novel series of small molecules with the potential to be further developed to treat patients either alone, or in combination with statins.


ABSTRACT
Myocardial infarction (MI) is an acute event characterized by myocardial necrosis. Thrombotic MI is caused by spontaneous atherosclerotic plaque disruption that results in a coronary thrombus; non-thrombotic MI occurs secondary to oxygen supply-demand mismatch. We sought to characterize the differential metabolic perturbations associated with these subtypes utilizing a systems approach. Subjects presenting with thrombotic MI, non-thrombotic MI and stable coronary artery disease (CAD) were included. Whole blood was collected at two acute
OBJECTIVES: This study sought to evaluate whether a panel of biomarkers improved prognostication in patients with heart failure (HF) and reduced ejection fraction of ischemic origin using a systematized approach according to suggested requirements for validation of new biomarkers. BACKGROUND: Modeling combinations of multiple circulating markers could potentially identify patients with HF at particularly high risk and aid in the selection of individualized therapy. METHODS: From a panel of 20 inflammatory and extracellular matrix biomarkers, 2 different biomarker panels were created and added to the Seattle HF score and the prognostic model from the CORONA (Controlled Rosuvastatin Multinational Trial in Heart Failure) study (n = 1,497), which included conventional clinical characteristics and C-reactive protein and N-terminal pro-B-type natriuretic peptide. Interactions with statin treatment were also assessed. RESULTS: The two models-model 1 (endostatin, interleukin 8, soluble ST2, troponin T, galectin 3, and chemokine [C-C motif] ligand 21) and model 2 (troponin T, soluble ST2, galectin 3, pentraxin 3, and soluble tumor necrosis factor receptor 2)-significantly improved the CORONA and Seattle HF models but added only modestly to their Harrell’s C statistic and net reclassification index. In addition, rosuvastatin had no effect on the levels of a wide range of inflammatory and extracellular matrix markers, but there was a tendency for patients with a lower level of biomarkers in the 2 panels to have a positive effect from statin treatment. CONCLUSIONS: In the specific HF patient population studied, a multimarker approach using the particular panel of biomarkers measured was of limited clinical value for identifying future risk of adverse outcomes.
Background/Aims: To define the effect of statins on interleukin 1beta (IL-1beta)-induced osteoclastogenesis and elucidate the underlying mechanisms. Methods: Bone marrow cells were obtained from 5-week-old male ICR (Institute for Cancer Research) mice, and they were cultured to differentiate them into osteoclasts with macrophage colony-stimulating factor and the receptor activator of nuclear factor (NF)-kappaB ligand in the presence or absence of IL-1beta or atorvastatin. The formation of osteoclasts was evaluated by tartrate-resistant acid phosphatase (TRAP) staining and resorption pit assay with dentine slice. The molecular mechanisms of the effects of atorvastatin on osteoclastogenesis were investigated using reverse transcription polymerase chain reaction and immunoblotting for osteoclast specific molecules. Results: Atorvastatin significantly reduced the number of TRAP-positive multinucleated cells as well as the bone resorption area. Atorvastatin also downregulated the expression of the NF of activated T-cell c1 messenger RNA and inhibited the expression of osteoclast-specific genes. A possible underlying mechanism may be that atorvastatin suppresses the degradation of the inhibitors of NF-kappaB and blocks the activation of the c-Jun N-terminal kinase, extracellular signal-regulated kinase, and p38; thus, implicating the NF-kappaB and mitogen-activated protein kinases pathway in this process. Conclusions: Atorvastatin is a strong inhibitor of inflammation-induced osteoclastogenesis in inflammatory joint diseases.


ABSTRACT
Degenerative disc disease is a worldwide problem, however, conservative treatment and surgical treatment can only partly relieve symptoms, but do not have therapeutic effect on the degenerated intervertebral disc (IVD) itself. The use of stem cell transplantation has become one of the most popular treatments. With gradually understanding of the endogenous mechanism of stem cells migration and movement in vivo, endogenous IVD stem cells can be activated to repair and reconstruct the degenerated IVD. Nucleus pulposus mensenchymal stem cells exhibit more potent biological activity in the hypoxic environment of the IVD. Hypoxia inducible factor can regulate the energy metabolism of IVD cells by activating Glucose transporter 1 pathway. The simvastatin can enhance the theraprutic effect of many kinds of stem cells by increasing number and function of the stem cell. Herein we postulate that simvastatin can regulate the differentiation of nucleus pulposus mensenchymal stem cells into nucleus pulposus cell by promoting expression of hypoxia inducible factor to repair and reconstruct degenerated IVD.


ABSTRACT
In this study, we investigated the distribution of vitamin D and its association with carotid atherosclerotic plaque (CP) in Chinese type 2 diabetic (T2D) patients. We performed a cross-sectional study in 210 T2D and 94 age- and gender-matched nondiabetic patients during winter months, by determining serum 25-hydroxyvitamin D (25(OH)D) levels in both diabetic and nondiabetic controls. We carried out measurements of B-mode ultrasonography of carotid arteries in each T2D patient. The 25(OH)D concentration was 26.25 nmol/L among the T2D patients. About 93.3% T2D patients suffered from hypovitaminosis D. First, we found a clear inverse correlation between the 25(OH)D concentration and CP (P <0.001). Second, an association between 25(OH)D and macrovascular disease was significant (P = 0.005). In multivariate logistic regression analysis, decreasing 25(OH)D concentration was markedly associated with CP in T2D patients. Third, after adjusting for the confounding factors, we also observed a positive correlation between low levels of 25(OH)D in T2D patients with CP, when the following parameters were measured: old age (odds ratio [OR] = 2.533, P = 0.013); smoking (OR = 3.872, P = 0.001); and high level of low-density lipoprotein (LDL) cholesterol (OR = 2.776, P = 0.009). Thus, we concluded that high prevalence of hypovitaminosis D exists in Chinese T2D patients. Further, we found a significant association between low concentration of serum 25(OH)D and the existence of high body mass index, and high circulating LDL to be substantially positive predictors of patients with CP in T2D.


**ABSTRACT**

Atherosclerosis (AS) remains the leading cause for global cardiovascular disease morbidity and mortality, and a major cause of cardiopathy, myocardial infarction and peripheral vascular diseases. Macrophages serve a critical role in atherosclerotic plaque stabilization and rupture, and the selective removal of macrophages may be beneficial in improving plaque stability. Autophagy is a process of selffeeding, during which cytoplasmic proteins or organelles are packaged into vesicles and fused with the lysosome to form an autophagosome. The newly formed autophagosome can degrade internalized proteins, and this process may be used to serve the metabolic and selfrenewal requirements of the cell. Autophagy serves an important role in maintaining cell homeostasis and promoting cell survival, and therefore an imbalance in autophagy is closely associated with multiple diseases.


**ABSTRACT**

The production of magnetic nanoparticles of utmost quality for biomedical imaging requires several steps, from the synthesis of highly crystalline magnetic cores to the attachment of the different molecules on the surface. This last step probably plays the key role in the production of clinically useful nanomaterials. The attachment of the different biomolecules should be performed in a defined and controlled fashion, avoiding the random adsorption of the components that could lead to undesirable byproducts and ill-characterized surface
composition. In this work, we review the process of creating new magnetic nanomaterials for imaging, particularly for the detection of atherosclerotic plaque, in vivo. Our focus will be in the different biofunctionalization techniques that we and several other groups have recently developed. Magnetic nanomaterial functionalization should be performed by chemoselective techniques. This approach will facilitate the application of these nanomaterials in the clinic, not as an exception, but as any other pharmacological compound.


**ABSTRACT**

(1) Background: Marine n-3 polyunsaturated fatty acids (PUFA) and -linolenic acid (GLA) are well-known anti-inflammatory agents that may help in the treatment of inflammatory disorders. Their effects were examined in patients with rheumatoid arthritis; (2) Methods: Sixty patients with active rheumatoid arthritis were involved in a prospective, randomized trial of a 12 week supplementation with fish oil (group I), fish oil with primrose evening oil (group II), or with no supplementation (group III). Clinical and laboratory evaluations were done at the beginning and at the end of the study; (3) Results: The Disease Activity Score 28 (DAS 28 score), number of tender joints and visual analogue scale (VAS) score decreased notably after supplementation in groups I and II (p < 0.001). In plasma phospholipids the n-6/n-3 fatty acids ratio declined from 15.47 +/- 5.51 to 10.62 +/- 5.07 (p = 0.005), and from 18.15 +/- 5.04 to 13.50 +/- 4.81 (p = 0.005) in groups I and II respectively. The combination of n-3 PUFA and GLA (group II) increased -linolenic acid (0.00 +/- 0.00 to 0.13 +/- 0.11, p < 0.001), which was undetectable in all groups before the treatments; (4) Conclusion: Daily supplementation with n-3 fatty acids alone or in combination with GLA exerted significant clinical benefits and certain changes in disease activity.


**ABSTRACT**


**ABSTRACT**

In Estonia, HMG-CoA reductase inhibitors are widely used to modify lipid levels but there are no current data on additional medicines prescribed alongside the statins. The aim of this study was to identify the frequency of potential clinically relevant interactions at a national level among an outpatient population treated with statins between January and June 2008, based on the prescription database of the Estonian Health Insurance Fund. This retrospective prevalence study included 203,646 outpatients aged 50 years or older, of whom 29,367 received statin therapy. The study analysed individuals who had used at least one prescription medicine for a minimum of 7 days concomitantly with statins. Potential drug interactions were analysed using
Epocrates online, Stockley's Drug Interactions, and the drug interaction database developed in Estonia. Statins metabolised by the CYP3A4 isoenzyme were prescribed to 64% of all statin users. Medicines known to have potentially clinically significant interactions with statins were prescribed to 4.6% of patients. The drugs prescribed concomitantly most often with simvastatin were warfarin (5.7%) and amiodarone (3.9%), whereas digoxin (1.2%) and ethinylestradiol (2%) were prescribed with atorvastatin. Potential interactions were not detected in the treatment regimens of rosuvastatin, pravastatin, and fluvastatin users.


ABSTRACT

AIM: To investigate the combined effects of SLCO1B1 and ABCB1 genotypes on the pharmacokinetics of simvastatin and its active metabolite simvastatin acid, in relation to CYP3A4 inhibition. METHODS: We conducted a single-dose pharmacokinetic study of simvastatin in 26 healthy volunteers screened for their SLCO1B1 c.521T>C and ABCB1 c.1236C>T-FPP genotypes, with and without amlodipine pretreatment. The genetic effects and drug-interaction effect on simvastatin pharmacokinetic parameters were analyzed using a linear-mixed model. RESULTS: The SLCO1B1 c.521T>C variant significantly increased exposure to simvastatin acid by around 40% (p < 0.05), similar to that caused by the amlodipine pretreatment. The ABCB1 gene showed no influence on exposure to simvastatin or simvastatin acid. CONCLUSION: Only SLCO1B1, not ABCB1 genotype, is likely to be associated with simvastatin-induced myopathy. SLCO1B1 genotyping may be particularly beneficial in simvastatin users who are co-administered CYP3A4 inhibitors.


ABSTRACT

The mevalonate (MEV) cascade is responsible for cholesterol biosynthesis and the formation of the intermediate metabolites geranylgeranylpyrophosphate (GGPP) and farnesylpyrophosphate (FPP) used in the prenylation of proteins. Here we show that the MEV cascade inhibitor simvastatin induced significant cell death in a wide range of human tumor cell lines, including glioblastoma, astrocytoma, neuroblastoma, lung adenocarcinoma, and breast cancer. Simvastatin induced apoptotic cell death via the intrinsic apoptotic pathway. In all cancer cell types tested, simvastatin-induced cell death was not rescued by cholesterol, but was dependent on GGPP- and FPP-depletion. We confirmed that simvastatin caused the translocation of the small Rho GTPases RhoA, Cdc42, and Rac1/2/3 from cell membranes to the cytosol in U251 (glioblastoma), A549 (lung adenocarcinoma) and MDA-MB-231(breast cancer). Simvastatin-induced Rho-GTP loading significantly increased in U251 cells which were reversed with MEV, FPP, GGPP. In contrast, simvastatin did not change Rho-GTP loading in A549 and MDA-MB-231. Inhibition of geranylgeranyltransferase I by GGTi-298, but not
farnesyltransferase by FTI-277, induced significant cell death in U251, A549, and MDA-MB-231. These results indicate that MEV cascade inhibition by simvastatin induced the intrinsic apoptosis pathway via inhibition of Rho family prenylation and depletion of GGPP, in a variety of different human cancer lines.


ABSTRACT

5-Fluorouracil has been considered as a cornerstone therapy for colorectal cancer; however, it suffers from low therapeutic response rate and severe side effects. Therefore, there is an urgent need to increase the clinical efficacy of 5-fluorouracil. Recently, fish oil rich in n-3 polyunsaturated fatty acids has been reported to chemosensitize tumor cells to anti-cancer drugs. This study is designed to understand the underlying mechanisms of synergistic effect of fish oil and 5-fluorouracil by evaluation of tumor cell-associated markers such as apoptosis and DNA damage. The colon cancer was developed by administration of N,N-dimethylhydrazine dihydrochloride and dextran sulfate sodium salt. Further these animals were treated with 5-fluorouracil, fish oil, or a combination of both. In carcinogen-treated animals, a decrease in DNA damage and apoptotic index was observed. There was also a decrease in the expression of Fas, Fasl, caspase 8, and Bax, and an increase in Bcl-2. In contrast, administration of 5-fluorouracil and fish oil as an adjuvant increased both DNA damage and apoptotic index by activation of both extrinsic and intrinsic apoptotic pathways as compared to the other groups. The increased pro-apoptotic effect by synergism of 5-fluorouracil and fish oil may be attributed to the incorporation of n-3 polyunsaturated fatty acids in membrane, which alters membrane fluidity in cancer cells. In conclusion, this study highlights that the induction of apoptotic pathway by fish oil may increase the susceptibility of tumors to chemotherapeutic regimens.


ABSTRACT

BACKGROUND: The aim of this study was to assess the knowledge and attitude of medical students in relation to cardiovascular disease (CVD) risk factors as well as to assess the impact of medical education on their knowledge and recognition of the importance of implementation of preventive measures. METHODS: This cross-sectional study included 514 students in the second year of studying at the Faculty of Medicine in Belgrade, Serbia (younger students response rate 79.57%) and 511 students in the last year of education (older students response rate 90.21%). For data collection, an anonymous self-administered questionnaire was used, which included two types of questions about CVD risk factors and questions about the student’s attitude. RESULTS: Older students knew significantly more about CVD risk factors than students who were at the beginning of their medical studies; however, more than half of the older students did not know the correct answers about CVD risk factors. The only exceptions were
questions about "bad" and "good" cholesterol, metabolic syndrome (MSy) and lipid lowering therapy in high risk subjects. Physical inactivity, obesity, type 2 diabetes, smoking and hypertension were not ranked highly enough as important CVD risk factors. Compared groups of students did not significantly differ in attitude scores. The majority of them recognized CVD as the leading cause of death, had normal weight and knew their own blood pressure. CONCLUSION: Knowledge of medical students from Belgrade about CVD risk factors should be improved.