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Original research article

The effect of ezetimibe-statin combination on steroid hormone production in men with coronary artery disease and low cholesterol levels

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ABSTRACT

Background: Aggressive statin treatment was found to slightly reduce testosterone production. The aim of this study was to compare the effects of ezetimibe-statin combination and high-dose statin therapy on testicular and adrenal cortex function in men with LDL cholesterol levels below 70 mg/dL.
Methods: The study included 26 adult men with coronary artery disease. Twelve of these patients did not tolerate high-dose statin therapy and were treated with lower doses of a statin plus ezetimibe. Fourteen patients tolerating high-dose simvastatin or rosuvastatin treatment continued high-dose statin therapy throughout the study period. Plasma lipids, glucose homeostasis markers and plasma levels of testosterone, cortisol, dehydroepiandrosterone sulphate, sex hormone-binding globulin, gonadotropins and ACTH, as well as urine free cortisol were assessed at baseline and after 16 weeks of treatment.
Results: Replacing high-dose statin therapy with ezetimibe/statin combination therapy reduced plasma levels of LH by 32% ($p = 0.043$), as well as increased plasma levels of testosterone by 20% ($p = 0.038$). Ezetimibe/statin combination did not induce any significant changes in plasma levels or urine excretion of the remaining hormones. At the end of the study, plasma LH levels were higher, while plasma testosterone levels were lower in patients receiving the combination therapy than in those treated only with high-dose statin.
Conclusions: Our results indicate that ezetimibe combined with moderate statin dose exerts a less pronounced effect on testicular function in comparison with high-dose statin therapy.

Introduction

The results of four large clinical studies: TNT [1], IDEAL [2], PROVE IT-TIMI-22 [3] and A-to-Z [4], including patients with stable coronary artery disease, myocardial infarction and acute coronary syndromes, showed that intensive lipid-lowering high-dose statin therapy was associated with an improvement in clinical outcomes, particularly non-fatal cardiovascular events, compared with less aggressive therapy. Based on these results, the European Society of Cardiology/European Atherosclerosis Society [5] and the American Association of Clinical Endocrinologists [6] recommend that the treatment target for low-density lipoprotein (LDL) cholesterol in patients at very high cardiovascular risk (established or recent hospitalization for coronary, carotid, and peripheral vascular disease, diabetes plus one or more additional risk factors type, or type 1 diabetes with target organ damage, moderate to severe chronic kidney disease and SCORE level at least 10%) should be less than 70 mg/dL. The most recent American College of Cardiology/American Heart Association guidelines on the treatment of blood cholesterol to reduce atherosclerotic cardiovascular risk recommend intensive statin treatment (not treatment to LDL cholesterol targets) [7].

Most steroid hormones are produced from cholesterol contained in LDL, which is uptaken by the gonads and adrenal cortex, and used as a substrate for steroidogenesis [8]. At least

Abbreviations: ACTH, adrenocorticotropic hormone; DHEA-S, dehydroepiandrosterone sulphate; FSH, follicle-stimulating hormone; HDL, high-density lipoprotein; HMG-CoA, 3-hydroxy-3-methylglutaryl-CoA; HOMA-IR, the homeostasis model assessment of insulin resistance index; LDL, low-density lipoprotein; LH, luteinizing hormone; SCORE, systematic coronary risk estimation; SD, standard deviation; SHBG, sex hormone-binding globulin.

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theoretically, in states associated with very low LDL cholesterol levels, cholesterol conversion to steroid hormones may be impaired. Interestingly, a marked reduction or absence of plasma apolipoprotein B-containing lipoproteins, including chylomicrons, very low-density lipoproteins and LDL [9], observed in abetalipoproteinemia, resulted in a deterioration of adrenocortical and gonadal functions [10,11]. In our previous study, we observed that a rosuvastatin-induced reduction in plasma LDL cholesterol levels below 70 mg/dL was associated with a small decrease in plasma testosterone levels, a small increase in plasma gonadotropins and adrenocorticotropic hormone (ACTH) levels, but not with changes in plasma cortisol, plasma dehydroepiandrosterone sulphate (DHEA-S) and urine free cortisol [12]. These findings were in agreement with the results of a recent meta-analysis of randomized controlled studies conducted by Schooling et al. [13] which suggested that statins, being 3-hydroxy-3-methylglutaryl-CoA (HMG-CoA) reductase inhibitors, may slightly reduce plasma testosterone levels in both men and women. To the best of our knowledge, no previous study has investigated the impact of the remaining hypolipidemic agents on testicular function. In our study, we have compared the effects of ezetimibe-statin combination and high-dose ezetimibe on adrenal and testicular androgen production in patients with coronary artery disease and LDL cholesterol levels below 70 mg/dL.

Materials and methods

All participants ($n = 27$) provided written consent as approved by the local ethics committee. Men (35–65 years old), recruited between April and June, were eligible for enrollment if they (1) had stable coronary artery disease with a history of cardiovascular events, (2) had been treated with atorvastatin (20–40 mg daily) or rosuvastatin (5–10 mg daily) for at least 12 weeks and this treatment had been well tolerated, (3) because of LDL cholesterol levels in the range of 70–100 mg/dL required doubling of the dose of the previously used HMG-CoA reductase inhibitor and a higher dose of atorvastatin or rosuvastatin was administered for at least four weeks and (4) high-dose statin treatment reduced LDL cholesterol to below 70 mg/dL. We compared two groups of patients who met these inclusion criteria. The first group included 12 patients in whom the increase in statin dose led to an asymptomatic rise in the levels of aminotransferases (>3 times above the normal limit) and of creatine kinase (>5 times above the normal limit). In these patients statin dose was reduced by half (to the initial dose) and they started treatment with ezetimibe (10 mg daily). The second group included 15 age- and weight-matched men with coronary artery disease, in whom doubling of statin dose did not result in any adverse effects and high-dose statin therapy was continued throughout the study. The sample size needed for the study was calculated using Sample Power software (SPSS, Chicago, IL, USA) based on data from our previous studies. A power calculation using 80% power and type I error of 0.05 indicated that a minimum of 12 patients in each group would need to be included in the study to detect a difference between the groups

The exclusion criteria included unstable coronary artery disease, myocardial infarction or stroke within 6 months preceding the study, symptomatic congestive heart failure, any acute and chronic inflammatory processes, diabetes, hyperprolactinemia, thyroid or any other endocrine disorders, uncontrolled hypertension, chronic pancreatitis, impaired renal or hepatic function, concomitant treatment with drugs affecting hypothalamic-pituitary-gonadal axis and/or hypothalamic-pituitary-adrenal axis activities (androgens and antiandrogens, gonadotropins, gonadotropin-releasing hormone agonists and antagonists, glucocorticoids, somatostatin analogs and steroid synthesis inhibitors), concomitant treatment with agents known to interact with statins or ezetimibe (potent CYP3A4 inhibitors or inducers, ciclosporin, verapamil, diltiazem, amiodarone, bile acid sequestrants, gemfibrozil and coumarin anticoagulants), participation in our previous studies and poor patient compliance.

Hypolipidemic agents were administered once daily at bedtime for 16 weeks without any changes in dosage, and throughout the entire study period both groups of patients complied with dietary recommendations (total fat intake <30% of total energy intake, saturated fat intake <7% of energy consumed, cholesterol intake <200 mg per day, an increase in fiber intake to 15 g per 1000 kcal), as well as were encouraged to take moderate to vigorous exercise for at least 30 min per day.

The investigation of possible treatment-induced adverse effects was performed fortnightly. Compliance was investigated during each visit by tablet counts and was considered satisfactory when the number of tablets taken by a patient ranged from 90% to 100%. At the end of the study, the target LDL cholesterol levels (below 70 mg/dL) were achieved by all patients treated with the combination therapy as well as 14 patients treated with high-dose statin therapy, and only data of these patients were included in the final analyses.

All measurements (plasma lipids, fasting glucose, and hormones) were performed at baseline and after 16 weeks of therapy. Lipid profiles and plasma glucose were assessed by routine laboratory techniques (bioMerieux France; Beckman, Palo Alto, CA, USA). To avoid any error resulting from the Friedewald formula, LDL-cholesterol was determined directly. Plasma insulin, cortisol, DHEA-S, testosterone and sex hormone-binding globulin (SHBG) as well as 24-h urine free cortisol were determined by enzyme-linked immunosorbent assay (DRG Instruments GmbH, Marburg, Germany; R&D, McKinley Place N.E. Minneapolis, MN, USA). LH, FSH and ACTH levels were measured by the immunochemiluminescence method (Siemens Healthcare Diagnostics, Inc., Deerfield, IL, USA). Insulin resistance was assessed using the homeostasis model assessment of insulin resistance index (HOMA-IR) by the following formula: insulin resistance = plasma insulin [mIU/L] × plasma glucose [mg/dL]/405.

The normality of the quantitative variables was verified using the Kolmogorov-Smirnov test. In order to reach normality, log transformation was used for the non-normal variables (HOMA-IR and hormones). Comparisons between both groups were made by the *t*-test for independent samples. The differences between the means of variables within the same treatment group were analyzed with Student's paired *t*-test. Categorical variables were compared using χ^2 test. Correlations were assessed using Kendall's tau test. Values of $p < 0.05$ were considered statistically significant.

Results

At baseline, both groups were comparable with respect to age, body weight and medical background (Table 1). No serious adverse events were observed throughout the study and all patients completed the study protocol. In both groups of patients, lipid profile and glucose homeostasis markers remained at the similar level throughout the study (Table 2). No changes in plasma levels or urine excretion of all investigated hormones were observed in patients who continued high-dose statin therapy. Replacing statin therapy with ezetimibe/statin combination decreased plasma levels of LH, tended to reduce plasma levels of FSH, increased plasma levels of testosterone, but did not cause any changes in plasma levels of ACTH, cortisol and DHEA-S as well as urine free cortisol. At the end of the study, plasma LH levels were higher, while plasma testosterone levels were lower in the patients treated with high-dose statin therapy than in the patients receiving a combination of a lower dose of a statin plus ezetimibe. At entry,