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The effects of statin treatment on adrenal and sexual function and nitric oxide levels in hypercholesterolemic male patients treated with a statin

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Hypercholesterolemia;
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ACTH;
Cortisol;
Testosterone;
Erectile dysfunction;
Somatosensory evoked potential

BACKGROUND: Erectile dysfunction complaints among men treated with a statin are not uncommon.

OBJECTIVES: To evaluate the effect of lowering low-density lipoprotein cholesterol (LDL-C) to target levels using varying doses of atorvastatin therapy in hypercholesterolemic male patients on adrenocortical hormones, sexual functions, and serum nitric oxide (NO) levels.

METHODS: Eleven hypercholesterolemic male patients who had LDL-C levels greater than 160 mg/dL were included in the study and 11 healthy male individuals served as controls. Following basal hormone measurements, 1-and 250-mcg adrenocorticotropic hormone stimulation tests were performed in both groups, and blood sampling was performed at 0, 30, and 60 minutes for the determination of blood levels of cortisol, total testosterone (TT), free testosterone (FT), 11-deoxycortisol, and dehydroepiandrostenedione. Depending on baseline LDL-C concentrations, atorvastatin therapy was given to patients with daily doses of 5 or 10 mg and the study procedures were repeated once patients reached risk stratified goal LDL-C levels. LDL-C values after treatment were classified into 3 groups as LDL-C $>$ 160 mg/dL, LDL-C 100 to 130 mg/dL and LDL-C $<$ 100 mg/dL. NO levels were measured at baseline and after statin therapy. Erectile function was assessed both objectively and subjectively by using penile somatosensory evoked potential (SEP) and the International Index of Erectile Function-5 Questionnaire, respectively, at 3 different LDL-C levels.

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RESULTS: With regard to adrenocorticotropic hormone stimulation test (1 or 250 mcg) results, peak cortisol levels before and after statin treatment among 3 LDL-C groups and among controls did not differ significantly. However, peak TT and FT hormone levels decreased in conjunction with decreasing levels of LDL-C among the statin-treated patients, whereas dehydroepiandrostenedione and 11-11-deoxycortisol peak values did not change. N1 latency obtained during SEP, which is the first negative deflection, was prolonged with decreasing levels of LDL-C and a significant decrease in International Index of Erectile Function-5 scores were observed. When LDL-C levels of ≥ 160 mg/dl was reduced to 100 to 130 mg/dl, maximal NO elevations were noted.

CONCLUSIONS: Our results suggest that decreased LDL-C levels caused by different doses of atorvastatin treatment did not associate with significant changes in adrenal hormone levels. In contrast, there was a significant relationship between attained LDL-C on statin therapy and TT and FT levels. Electrophysiologically, abnormal SEP responses obtained in the patient group with LDL-C levels below 100 indicate a negative impact on the integrity of the somatosensory pathway, which plays a role in erectile function. Reducing LDL-C with a statin was associated with both decreased testosterone levels and erectile dysfunction.

Introduction

Hypercholesterolemia is a major cardiovascular risk factor. Statins are the most efficacious and widely used drug for treating hypercholesterolemia. Statins decrease the mortality and morbidity of cardiovascular disease.[1–4] Atorvastatin is the most commonly used statin and has been evaluated in a broad range of clinical trials.[5]

Cholesterol is an important regulator of cell membrane fluidity and is a precursor to bile acids and steroid hormones. Currently available lipid-lowering medications, especially when used in combination, can induce considerable reductions in circulating levels of low-density lipoprotein cholesterol (LDL-C). LDL particles are believed to be an important delivery vehicle of cholesterol to steroidogenic tissues. There is some lingering concern that LDL-C lowering may adversely impact the capacity of steroidogenic tissues to produce adrenocortical hormones and sex steroids such as testosterone. Some studies have shown a correlation of statin use with increased risk for erectile dysfunction (ED).[6,7] The role of endothelial dysfunction is well known in atherosclerosis development and nitric oxide (NO) plays a crucial role in endothelial dysfunction.[8,9] Statins potentiate increased NO production and improved endothelial function by a pleiotropic mechanism independent from lipid-lowering effects.[10]

We investigated the effects of lipid-lowering treatment with atorvastatin on (1) adrenocortical and androgen hormones and (2) sexual function at different levels of LDL-C in hypercholesterolemic male patients. To evaluate erectile function, we performed penile somatosensory evoked potential (SEP) measurements, to assess the impact of statin therapy on the sensorimotor component of penile erection. To our knowledge, penile SEP has not been previously studied in hypercholesterolemic patients having different levels of LDL-C. We also explored the effect of statin treatment on serum NO levels as a pleiotropic effect.

Materials and methods

Study population

Eleven male patients diagnosed with hypercholesterolemia were enrolled in the study. Eleven age-matched healthy men without hypercholesterolemia were included as a control group. The following inclusion criteria were used: (1) age of 18 to 65 years and body mass index < 30 kg/m^2; (2) presence of hypercholesterolemia (morning fasting serum LDL-C $>$ 160 mg/dL); (3) absence of malignant hypertension (especially diastolic blood pressure $>$ 95 mm/Hg); (4) absence of diabetes mellitus; (5) absence of chronic drug use (except some drugs not affecting the basal hormone levels and without interaction with statins); and (6) absence of smoking. Inclusion criteria for the control group were the same as the study group except for fasting lipid levels.

Physical examinations were normal in both study and control groups. Liver function tests, thyroid function tests, and other biochemical tests were normal. Sexual, psychosocial, and medical histories were assessed in both groups. The quality of sexual function was evaluated by using the International Index of Erectile Function-5 (IIEF-5) Questionnaire.[11]

LDL-C values in the control and patient groups before and after treatment were classified into 3 groups as LDL-C $>$ 160 mg/dL, LDL-C 100 to 130 mg/dL, and LDL-C $<$ 100 mg/dL.

Atorvastatin therapy

Daily 5- or 10-mg atorvastatin was initiated in all patients according to risk stratified goal LDL-C level to be reached. At the end of the first 10-day treatment period, patients were evaluated for myalgia symptoms. aspartate aminotransferase, alanine aminotransferase, and creatinine