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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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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

phosphokinase levels were measured. Patients were evaluated on a monthly basis to assess treatment compliance and treatment-related adverse events until an LDL-C level of 100 to 130 mg/dL was reached. Pretreatment investigations (steroid hormone levels, 1- and 250-mcg adrenocorticotropic hormone (ACTH) stimulation test, SEP, and questionnaires) were repeated in patients after reaching target LDL-C level of 100 to 130 mg/dL and <100 mg/dL.

ACTH stimulating testing

Study and control groups were subjected to hormone testing in an endocrinology clinic. ACTH stimulation tests were performed in both groups by administering 1- and 250-mcg ACTH. The 2 tests were performed 48 hours apart. Tetracosactrin (1-24, Synacthen; Novartis, Switzerland) was used for the ACTH 250-mcg test. For the 1-mcg ACTH test, tetracosactrin (1-24, Synacthen; Novartis) was diluted in 250 mL of saline and stored at +4°C in the refrigerator up to 6 months. Tests were carried out at 8:00 to 9:00 after fasting about 8 to 10 hours. After taking blood samples for cortisol, total testosterone (TT), free testosterone (FT), 11-deoxycortisol (11-DOC), and dehydroepiandrostenedione (DHEAS) baseline measurements, 1-mcg ACTH was given by intravenous bolus for stimulation test. Blood samples were obtained at 30 and 60 minutes and assayed for changes in corticosteroid levels. The same procedure was performed for the 250-mcg ACTH test. Sera were stored at −80°C until assayed.

Penile SEP study

A number of clinical neurophysiological tests have been used in the evaluation of ED.[12,13] SEP is a method to demonstrate integrity of the somatosensory pathway from peripheral nerve to a relevant region in the brain. Latencies of the deflections obtained during SEP study is the most important output. The dorsal penile nerve is one of the 3 major branches of the pudendal nerve and plays a crucial role in male sexual function. The dorsal penile nerve SEP study has been frequently used to evaluate ED in previous investigations.[14,15] In the present study, we used penile SEP to assess ED in hypercholesterolemic patients treated with atorvastatin.

Penile SEP studies were performed in a neurophysiology laboratory during afternoon hours between 3 PM and 5 PM, at room temperature of 23°C. SEP testing was applied only once in members of the healthy control group, whereas it was repeated 3 times in the treatment group: LDL-C > 160 mg/dL (basal measurement), 100 to 130 mg/dL, and <100 mg/dL. All subjects abstained from sexual activity for 24 hours before testing. Before SEP, nerve conduction studies were done on all study subjects to exclude peripheral neuropathy. For SEP studies, stimuli were applied with penile ring electrodes according to guidelines of the International Federation of Clinical Neurophysiology.[16] Cutaneous stimulus parameters were set at 0.1-ms duration, square wave pulse, and a frequency of 4 Hz.

Before the SEP recordings, sensory thresholds were determined in each subject. This procedure was defined as the lowest stimulus intensity necessary to evoke a sensory perception. An initial electrical stimulus, which is 1 mA in intensity and 0.1 ms in duration is applied to patient and control via stimulus electrodes. The stimulus intensity is increased gradually by 1 mA until the participant feels the stimulus sensation. This stimulus level is described as a sensory threshold. For the SEP study, stimulus intensity was determined as 2 times sensory threshold. An average of 300 stimuli were recorded, and the test repeated 3 times to ensure reproducibility. Latency of N1 was defined as the first negative (upward) deflection of the W-shaped averaged cortical waveform. If the response could not be reproduced at least twice or if the cortical response could not be clearly identified, the N1 was classified as not evocable.

Erectile dysfunction

The IIEF-5 questionnaire was used to assess ED in patients (Figure 1).[11] The IIEF-5 questionnaire consists of 5 questions and responses scored from 0 to 5 points and has been shown to be a good diagnostic tool in making the diagnosis of ED. Patients having scores ≤21 should be evaluated for ED.[17]

Biochemical procedures

Measurements of lipid and steroid hormone levels were performed in the Nuclear Medicine and Clinical Biochemistry Laboratories of Erciyes University Medical Faculty. Serum levels of cortisol (IM1841; Prague, Czech Republic), TT (Diasource, Nivelles, Belgium), FT (DSL4900, Prague, Czech Republic), DHEAS (KIP0481; Louvain-la-Neuve, Belgium), and 11-DOC (KIPI20000; Louvain-la-Neuve, Belgium) were measured by radioimmunoassay methods. Reference values for cortisol, TT, FT, DHEAS, and 11-DOC were 5 to 26 mcg/dL, 134 to 625 ng/dL, 8.69 to 54.6 pg/mL, 300 to 3330 ng/dL and 0 to 8 ng/dL, respectively. Serum lipid levels were measured by an autoanalyzer (Architect c16000; Abbott Laboratories, Abbott Park, IL) with original kits. Serum NO levels were measured using Cayman (Catalog No. 780001) commercial enzyme-linked immunosorbent assay, according to the manufacturer's instructions.

Statistical analysis

In statistical analysis, for normal distribution suitability of the data histogram q-q graphs and the Shapiro-Wilk test were used. In group comparisons, the Student t test and Mann-Whitney U test were used for independent samples and one-sided variation analysis (repeated measures analysis of variance) was used for dependent samples with multiple measurements. A $P < .05$ was considered significant. Data were expressed as mean ± standard deviation or median (25th and 75th percentiles). IBM SPSS analysis Statistics 20.0 (IBM Inc, Armonk, NY) software package was used.

Over the past 6 months:					
	Very low	Low	Moderate	High	Very high
1. How do you rate your confidence that you could get and keep an erection?	1	2	3	4	5
2. When you had erections with sexual stimulation, how often were your erections hard enough for penetration?	Almost never or never	A few times (much less than half the time)	Sometimes (about half the time)	Most times (much more than half the time)	Almost always or always
	1	2	3	4	5
3. During sexual intercourse, how often were you able to maintain your erection after you had penetrated your partner?	Almost never or never	A few times (much less than half the time)	Sometimes (about half the time)	Most times (much more than half the time)	Almost always or always
	1	2	3	4	5
4. During sexual intercourse, how difficult was it to maintain your erection to completion of inter course?	Extremely difficult	Very difficult	Difficult	Slightly difficult	Not difficult
	1	2	3	4	5
5. When you attempted sexual intercourse, how often was it satisfactory for you?	Almost never or never	A few times (much less than half the time)	Sometimes (about half the time)	Most times (much more than half the time)	Almost always or always
	1	2	3	4	5

Total Score:_____

1-7: Severe ED **8-11**:Moderate ED **12-16:** Mild-moderate ED **17-21:** Mild ED **22-25:** No ED

Figure 1 International Index of Erectile Function-5 (IIEF-5) Questionnaire.

The Fisher's least significant difference test was used for multiple comparisons. Also, Bonferroni correction was applied for multiple testing adjustments. A value of $P < .01$ was considered significant for Bonferroni correction analysis.

Results

As shown in Table 1, there was no statistically significant difference in age between treatment and control groups ($P = .532$). The mean baseline LDL-C levels in treatment and control groups were 200.5 ± 26.3 and 100.2 ± 16.3 mg/dL, respectively, and there was a statistically significant difference between groups ($P < .001$). Although high-density lipoprotein cholesterol and triglyceride levels were not different from the controls, total cholesterol levels were significantly higher in the treatment group ($P < .001$).

Table 2 summarizes 1-mcg ACTH stimulation test results for the control and treatment groups at 0, 30, and 60 minutes with peak values and area under the curve values of TT, FT, DHEAS, 11-DOC, and cortisol, before and after statin treatment. When we compared the treatment group to the control group, we observed that TT and FT levels were significantly lower in patients with LDL-C<100 mg/dL at 0, 30, and 60 minutes.

Table 1 Pretreatment lipid levels of treatment and control groups

Parameters	Control group (n = 11)	Treatment group (n = 11)	*P*
Age (y)	35.1 ± 6.8	37.6 ± 11.4	.532
LDL-C (mg/dL)	100.2 ± 16.3	200.5 ± 26.3	<.001
HDL-C (mg/dL)	37.7 ± 6.4	42.3 ± 5.5	.089
Triglyceride (mg/dL)	111.0 (89.0–171.0)	154.0 (106.0–234.0)	.300
Total cholesterol (mg/dL)	171.0 (157.0–176.0)	289.0 (247.0–304.0)	<.001

LDL-C, low-density lipoprotein cholesterol; HDL-C, high-density lipoprotein cholesterol.
The data are expressed as mean ± standard deviation or median (25th or 75th percentiles).

Table 3 shows 250-mcg ACTH stimulation test results of control and treatment groups at 0, 30, and 60 minutes with peak values and area under the curve values of TT, FT, DHEAS, 11-DOC, and cortisol, before and after statin treatment. Similar to the 1-mcg ACTH stimulation test results, the 250-mcg ACTH stimulation test TT and FT levels were significantly lower in patients with LDL-C < 100 mg/dL than control and other study groups with LDL-C > 160 mg/dL and LDL-C 100–130 mg/dL. Comparison of steroid hormone levels of groups according to 1- and 250-mcg ACTH stimulation tests are summarized in Tables 2 and 3.

There was a significant difference between patients having LDL-C > 160 mg/dL and the control group in terms of basal N1 latency ($P = .029$). In the patient group, a second measurement of N1 latency was performed when LDL-C 130 to 160 mg/dL and a third was done when LDL-C < 100 mg/dL. There was no significant difference between first and second measurements or between second and third measurements. However, when comparing the first to the last measurement, when LDL-C < 100 mg/dL, N1 latency was prolonged ($P = .029$). In addition, severity of sensory threshold in patients having LDL-C < 100 mg/dL was higher than in healthy controls ($P = .039$). SEP data of study subjects are summarized in Table 4. Table 5 summarizes IIEF-5 scores in the control and patient groups. Baseline IIEF-5 scores in control and treatment groups with LDL-C > 160 mg/dL were 23.7 ± 1.4 and 24.1 ± 1.5, respectively, and there was no statistically significant difference. IIEF-5 scores in the treatment groups before and after statin treatment (LDL-C with 160 mg/dL, LDL-C 100–130 mg/dL, and LDL-C < 100 mg/dL) were 24.1 ± 1.5, 16.1 ± 3.0, 9.73 ± 3.0, respectively. The difference between groups was statistically significant ($P < .05$).

As shown in Table 6, NO levels in patients with LDL-C 100 to 130 mg/dL increased significantly compared with baseline. NO levels in the treatment group with LDL-C < 100 mg/dL was significantly higher compared with baseline, but it was lower than in patients with LDL-C between 100–130 mg/dL.

Discussion

LDL particles are a potential reservoir of cholesterol for adrenal and gonadal steroidogenesis.[7] For this reason, it is possible that low LDL-C levels may correlate with reduced production of adrenal and gonadal hormones, but the threshold level of LDL-C that might induce this effect is unknown. Studies on this issue in the literature are scarce and available data are conflicting.[18,19]

Our study investigating the relationship between statin therapy and ED by using SEP has not been previously performed, although some studies suggested that statin therapy does not have any effect on erectile function.[20,21] In a study conducted by Santini et al,[22] diabetic patients were treated with daily 20-mg atorvastatin for 3 months. No statistically significant difference was found between pretreatment and posttreatment levels of cortisol, DHEAS, TT, and androstenedione. Stanworth et al[23] conducted a study in which 355 patients with diabetes were treated with atorvastatin or simvastatin. Statistically significant decreases in TT levels were found in the atorvastatin group but not the simvastatin group. Medras et al[24] assessed the effect of treatment with statins on testosterone levels in men. They studied 189 men, 38 of whom were treated with simvastatin or atorvastatin and the study demonstrated that men treated with statins had significantly lower TT and FT levels. A meta-analysis of placebo-controlled randomized trials that assessed the effect of statins on testosterone among men suggested statins reduce testosterone.[25]

To evaluate adrenal function, Sezer et al[26] performed a 1-mcg ACTH stimulation test in their study conducted with 41 patients (mean LDL-C level 58 mg/dL on statin treatment) and 38 healthy controls (mean LDL-C level 131 mg/dL). They found no difference in cortisol levels between patient and control groups, consistent with our study. But in contrast to our study they did not analyze sex steroids, especially testosterone. In a 2-year study conducted by Kanat et al,[27] 98 diabetic patients from 4 centers in Turkey were divided into 2 groups. Patients in group 1 were treated with 10-mg ezetimibe and 10-mg atorvastatin daily for the first 3 months and 80 mg atorvastatin daily for the next 3 months. Patients in group 2 were treated with 80-mg atorvastatin daily for the first 3 months and 10-mg ezetimibe plus 10-mg atorvastatin daily for the next 3 months. DHEAS, FT, and cortisol levels were measured. DHEAS and FT decreased significantly in both groups. Cortisol levels decreased to below normal range during the daily 80-mg atorvastatin but increased to previous levels during

Table 2 Steroid hormone levels in controls and statin-treated groups in response to 1-mcg ACTH

Variable	Control (n = 11)	LDL-C > 160 mg/dL (n = 11)	*P*1	LDL-C, 100–130 mg/dL (n = 11)	*P*2	LDL-C < 100 mg/dL (n = 11)	*P*3	*P*4
TT								
0′	780.4 ± 295.9	659.4 ± 229.1	.296	589.0 ± 204.3	.093	435.1 ± 169.6	.003	<.001
30′	767.2 ± 277.5	602.4 ± 212.8	.134	491.1 ± 133.9	.008	379.6 ± 115.2	<.001	<.001
60′	697.3 ± 281.9	652.6 ± 235.9	.691	547.7 ± 136.1	.129	399.5 ± 133.4	.005	.005
Peak	864.4 ± 290.8	761.4 ± 226.6	.365	666.0 ± 165.6	.063	497.4 ± 155.6	.001	<.001
AUC	45,180.0 ± 15,108.6	37,750.9 ± 11,061.9	.203	31,783.6 ± 6946.0	.015	23,907.2 ± 6804.0	<.001	<.001
FT								
0′	13.8 ± 4.2	12.8 ± 3.5	.558	10.0 ± 2.5	.019	7.9 ± 1.9	<.001	<.001
30′	14.6 ± 3.0	12.5 ± 4.4	.189	8.8 ± 1.7	<.001	7.4 ± 2.3	<.001	<.001
60′	13.9 ± 4.6	11.61 ± 3.9	.224	9.76 ± 2.5	.016	7.05 ± 2.5	<.001	<.001
Peak	15.97 ± 3.9	13.9 ± 4.2	.249	10.7 ± 2.4	.001	8.4 ± 2.2	<.001	<.001
AUC	853.9 ± 187.2	739.5 ± 218.0	.202	561.4 ± 109.0	<.001	446.1 ± 125.9	<.001	<.001
DHEAS								
0′	2565.6 ± 946.9	2630.4 ± 1078.4	.882	1992.9 ± 878.9	.157	2101.6 ± 1078.4	.296	.033
30′	2494.1 ± 708.6	2491.9 ± 1153.6	.996	2129.0 ± 822.1	.278	1904.0 ± 827.6	.088	.109
60′	2494.5 ± 712.3	2552.0 ± 1195.4	.892	2102.3 ± 909.2	.273	2065.0 ± 974.5	.252	.124
Peak	2730.9 ± 829.9	2818.4 ± 1145.1	.840	2284.6 ± 867.0	.232	2259.6 ± 1048.3	.256	.055
AUC	150,722.7 ± 44,625.3	152,492.7 ± 67,497	.943	125,297.7 ± 49,831.4	.222	119,619.5 ± 53,254.3	.153	.068
11-DOC								
0	1.6 ± 0.3	1.9 ± 0.7	.099	1.8 ± 0.7	.332	1.7 ± 0.7	.634	.410
30	2.1 ± 0.7	3.24 ± 0.56	<.001	2.67 ± 0.82	.077	2.87 ± 0.9	.030	.148
60	1.7 ± 0.4	2.6 ± 0.7	<.001	2.2 ± 1.0	.087	1.9 ± 0.7	.193	.149
Peak	2.2 ± 0.6	3.3 ± 0.6	<.001	3.1 ± 0.9	.012	2.9 ± 0.8	.020	.525
AUC	109.9 ± 24.4	165.5 ± 26.7	<.001	140.4 ± 29.6	.016	140.6 ± 33.7	.024	.044
Cortisol								
0′	10.7 ± 2.3	12.8 ± 3.7	.123	11.4 ± 3.6	.592	10.6 ± 1.8	.859	.219
30′	23.8 ± 5.8	20.7 ± 3.9	.153	20.9 ± 6.8	.294	19.5 ± 5.6	.094	.705
60′	17.8 ± 3.8	13.7 ± 2.4	.007	14.4 ± 3.8	.046	15.8 ± 3.2	.203	.048
Peak	24.5 ± 5.2	20.7 ± 3.8	.066	21.6 ± 5.8	.226	19.9 ± 5.2	.055	.564
AUC	1141.9 ± 187.3	1017.5 ± 126.2	.083	1014.0 ± 266.7	.208	982.0 ± 212.3	.076	.786

ACTH, adrenocorticotropic hormone; AUC, area under the curve; DHEAS, dehydroepiandrostenedione; 11-DOC, 11-deoxycortisol; FT, free testosterone; TT, total testosterone.

*P*1 shows the somatosensory evoked potential data comparison with the Student *t* test between control group and patients with low-density lipoprotein cholesterol > 160 mg/dL. *P*2 shows the somatosensory evoked potential data comparison with the Student *t* test between control group and patients with low-density lipoprotein cholesterol 100–130 mg/dL. *P*3 shows the somatosensory evoked potential data comparison with the Student *t* test between control group and patients with low-density lipoprotein cholesterol < 100 mg/dL. *P*4 shows the participant somatosensory evoked potential values at different low-density lipoprotein cholesterol values comparison with the 1-way analysis of variance in repeated measurements.

Adjusted *P* values less than .01 was considered statistically significant.

Table 3 Steroid hormone levels in controls and statin treatment groups in response to 250-mcg ACTH

Variable	Control (n = 11)	LDL-C > 160 mg/dL (n = 11)	*P*1	LDL-C, 100–130 mg/dL (n = 11)	*P*2	LDL-C < 100 mg/dL (n = 11)	*P*3	*P*4
TT								
0′	730.3 ± 207.0	592.6 ± 237.6	.163	554.7 ± 203.3	.059	416.7 ± 169.5	.001	.022
30′	755.5 ± 261.2	542.9 ± 167.0	.034	413.3 ± 176.3	.002	384.7 ± 147.3	.001	.001
60′	727.3 ± 246.6	589.8 ± 278.1	.234	435.8 ± 158.0	.004	344.3 ± 141.4	<.001	<.001
Peak	829.4 ± 245.2	702.2 ± 236.6	.230	579.4 ± 191.4	.015	441.6 ± 158.4	<.001	.002
AUC	44,526.8 ± 13,591.6	34,022.7 ± 11,360.6	.063	27,256.3 ± 9070.9	.002	22,956.8 ± 8566.5	<.001	<.001
FT								
0′	13.7 ± 3.9	11.2 ± 3.0	.116	9.7 ± 2.8	.012	7.6 ± 2.3	<.001	<.001
30′	14.7 ± 3.2	12.1 ± 3.3	.078	9.6 ± 2.7	.001	7.4 ± 2.1	<.001	<.001
60′	14.7 ± 3.9	10.4 ± 3.5	.013	8.3 ± 1.4	<.001	7.4 ± 2.4	<.001	.003
Peak	16.1 ± 3.2	12.7 ± 3.1	.018	10.4 ± 2.8	<.001	8±2.2	<.001	<.001
AUC	865.5 ± 183.2	688.4 ± 185.1	.036	557.8 ± 133.3	<.001	448.3 ± 126.7	<.001	<.001
DHEAS								
0	2422.7 ± 673.1	2568.4 ± 1208.3	.731	2168.6 ± 986.9	.489	1832.7 ± 833.8	.083	.043
30	2357.2 ± 606.0	2583.8 ± 1073.8	.549	2104.3 ± 894.5	.448	1835.8 ± 780.9	.096	.012
60	2492.7 ± 657.7	2759.1 ± 1335.3	.559	2175.9 ± 891.9	.354	1955.0 ± 610.2	.061	.060
Peak	2578.6 ± 674.7	2922.4 ± 1388.5	.469	2358.6 ± 1006.9	.555	2150.9 ± 717.6	.165	.074
AUC	144,447.2 ± 37,181.4	157,426.3 ± 68,301.8	.586	128,296.3 ± 53,735.5	.423	111,890.4 ± 42,353.4	.070	.021
11-DOC								
0′	1.7 ± 0.4	2.0 ± 0.5	.066	1.6 ± 0.5	.918	1.3 ± 0.3	.020	.002
30′	2.6 ± 0.9	3.4 ± 1.0	.090	2.9 ± 0.8	.496	2.5 ± 0.9	.731	.054
60′	2.5 ± 0.9	3.8 ± 1.2	.008	4.0 ± 1.4	.006	3.7 ± 1.4	.020	.738
Peak	3.1 ± 0.9	4.1 ± 1.1	.024	4.1 ± 1.3	.036	3.8 ± 1.3	.166	.558
AUC	140.8 ± 32.6	188.8 ± 45.3	.010	171.5 ± 37.6	.054	150.0 ± 44.1	.585	.007
Cortisol								
0′	12.5 ± 3.4	11.7 ± 4.2	.630	11.9 ± 3.4	.699	12.3 ± 3.0	.917	.872
30′	20.8 ± 5.3	18.7 ± 5.3	.365	22.2 ± 5.1	.528	21.2 ± 3.2	.824	.137
60′	27.2 ± 7.3	27.3 ± 7.2	.980	25.3 ± 5.2	.483	26.8 ± 7.2	.897	.646
Peak	27.6 ± 6.6	27.4 ± 6.9	.957	25.9 ± 5.4	.516	27.5 ± 6.4	.974	.668
AUC	1219.1 ± 241.3	1145.1 ± 246.9	.486	1224.4 ± 218.1	.957	1223.5 ± 203.1	.963	.482

ACTH, adrenocorticotropic hormone; AUC, area under the curve; DHEAS, dehydroepiandrostenedione; 11-DOC, 11-deoxycortisol; FT, free testosterone; LDL-C, low-density lipoprotein cholesterol; TT, total testosterone.

*P*1 shows the somatosensory evoked potential data comparison with the Student *t* test between control group and patients with LDL-C > 160 mg/dL. *P*2 shows the somatosensory evoked potential data comparison with the Student t test between control group and patients with LDL-C 100–130 mg/dL. *P*3 shows the somatosensory evoked potential data comparison with the Student *t* test between control group and patients with LDL-C < 100 mg/dL. *P*4 shows the participant somatosensory evoked potential values at different LDL-C values comparison with the 1-way analysis of variance in repeated measurements.

Adjusted *P* values less than .01 were considered statistically significant.

Table 4 Variables obtained from SEP comparison among patients with different LDL-C value and control group

Variable	Control (n = 11)	LDL-C > 160 mg/dL (n = 11)	*P*1	LDL-C, 100–130 mg/dL (n = 11)	*P*2	LDL-C < 100 mg/dL (n = 11)	*P*3	*P*4
Warning threshold	12.3 ± 2.8	14.6 ± 4.9	.217	15.7 ± 5.7	.115	18.0 ± 7.3	.039	.275
N1 latency	26.2 ± 2.1	27.20 ± 2.41	.443	31.8 ± 6.7	.070	33.3 ± 6.7	.029	.029

SEP, somatosensory evoked potential; LDL-C, low-density lipoprotein cholesterol.

*P*1 shows the SEP data comparison with the Student t test between control group and patients with LDL-C > 160 mg/dL. *P*2 shows the SEP data comparison with the Student t test between control group and patients with LDL-C 100–130 mg/dL. *P*3 shows the SEP data comparison with the Student t test between control group and patients with LDL-C < 100 mg/dL. *P*4 shows participant SEP values at different LDL-C values comparison with the 1-way analysis of variance in repeated measurements.

daily combination atorvastatin and ezetimibe therapy. However, patients were not evaluated with sexual scoring or ACTH stimulation tests.

In our study, although TT, FT, DHEAS, and 11-DOC levels decreased by lowering LDL-C levels, no significant reduction in cortisol levels was detected. Patients reported libido reduction after lowering LDL-C levels. Contrary to the aforementioned studies, we evaluated not only baseline hormone levels but also hormone levels after standard and low-dose ACTH stimulation tests. Therefore, this is the first study evaluating hormonal changes in high, moderate, and low LDL-C levels with 1- and 250-mcg ACTH stimulation tests. The aforementioned studies are generally short-term studies in which the duration of treatment might affect hormonal levels. In our study, patients used statins for approximately 9 months.

The number of studies investigating ED caused by low LDL-C levels on statin treatment by using the ACTH stimulation test and IIEF-5 questionnaire are negligible. Solomon et al[28] treated 93 patients with cardiovascular risk factors with a statin for 6 months and reported that the mean IIEF-5 score decreased from 21 (normal value) to 6.5 after statin treatment.

Theoretically, statins seem to be a double-edged therapy for patients with ED. Kostis et al[29] examined the effect of statin therapy on ED using the IIEF; the average age of participants and the degree of LDL cholesterol lowering did not alter the effect on IIEF. In contrast to our work, they found that statins caused a clinically relevant improvement of erectile function. Other studies have shown that statin therapy may reduce levels of testosterone and aggravate ED.[30] However, Nurkalem et al[31] suggest that different statins may have different effects on ED.

In the present study, IIEF-5 scores decreased significantly from 24.1 at baseline decreased to 16.1 and 9.7 in patients treated to LDL-C levels of 100 to 130 mg/dL and <100 mg/dL, respectively. Our study is the only study investigating ED caused by low LDL-C level on statin treatment by using not only IIEF-5 but also the SEP test. There is clinical evidence that peripheral somatosensory input to the central nervous system contributes to the male sexual response. The primary source of somatosensory information for sexual reflexes is mediated through the dorsal penile nerve. Our study demonstrates that N1 latency is prolonged when LDL-C < 100 mg/dL compared with other measurements and healthy controls. Consequently, abnormal penile SEP responses are an indicator of the presence of ED.

Penile SEP measurements were repeated 3 times during this study and the latency of N1 was found to be prolonged when the levels of LDL-C were reduced progressively more by statin therapy. The most prominent prolongation of N1

Table 5 Comparison of IIEF-5 scores among patients in different LDL-C groups and patient and control groups

Group	LDL-C > 160 mg/dL (n = 11)	LDL-C between 100 and 130 mg/dL (n = 11)	LDL-C < 100 mg/dL (n = 11)	*P**
Patient	24.1 ± 1.5	16.1 ± 3.0	9.7 ± 3.0	<.001
Control	23.7 ± 1.4	—	—	—
P†	.549	—	—	—

IIEF-5, International Index of Erectile Function-5; LDL-c, low-density lipoprotein cholesterol.

Data are expressed as mean ± standard deviation.

*The comparison between LDL groups.

†The comparison between patient and control.

Table 6 Comparison of nitric oxide levels among patients in different LDL-C groups and patient and control groups

Group	LDL-C > 160 mg/dL (n = 11)	LDL-C = 100–130 mg/dL (n = 11)	LDL-C < 100 mg/dL (n = 11)	$P^{\star}$
Patient	42.3 ± 10.7[a]	54.3 ± 16.6[b]	47.9 ± 11.5[ab]	.016
Control	35.1 ± 7.2	35.1 ± 7.2	35.1 ± 7.2	—
$P^{\dagger}$	.078	.004	.005	—

LDL-c, low-density lipoprotein cholesterol.

Data are expressed as mean ± standard deviation. Different letters in the same row refers to differences between groups, the same letters in the same row refers to the similarity between the groups.

*The comparison between LDL groups.

†The comparison between patient and control.

latency was observed in patients with the lowest LDL-C levels (below 100 mg/dL). The prolongation in the N1 latency was consistent with the alteration of serum testosterone and the complaints related to ED, which was assessed by using a questionnaire. The clinical importance of the elevation in the sensory threshold is unknown and further studies are necessary.

There is some evidence that penile SEP may be used to assess integrity of the sensorimotor pathway, which is essential for the maintenance of penile erection during sexual intercourse,[32] although the literature is controversial.[33] Based on our study results, it is clear that the SEP response is a useful diagnostic tool for the definition of ED development during statin use in hypercholesterolemic patients. Another very important finding from our study is the observation that high LDL-C levels did not interrupt the central response to dorsal penile nerve stimulation, suggesting that hypercholesterolemia (in the absence of significant pudendal artery atherosclerosis) in and of itself is not etiologic for ED.

The role of endothelial dysfunction is established in atherogenesis and NO plays a crucial role in normal vascular function.[8,34] In the setting of endothelial dysfunction, increased NO modification by oxidative mechanisms is activated in patients with hypercholesterolemia. Unlike other cholesterol-lowering agents, statins in vitro increase NO production by inducing and regulating endothelial nitric oxide synthase.[35] NO is an important vasodilator produced by arterial endothelial cells. Smooth muscle cells of penile cavernous tissue relax and blood vessels dilate in response to NO during penile erection.

There are studies showing the effect of statin therapy on NO in the literature, but studies showing NO levels according to different serum LDL-C levels and the relationship with libido are scarce. In a study conducted by Basarılı et al,[36] 50 patients with an acute myocardial infarction (42 males; mean age: 59.7 years; mean LDL-C 126.34 mg/dL) were treated with atorvastatin (10-80 mg/day) for 3 months and plasma NO was significantly increased. In the present study, increased NO levels with statin treatment were found but NO levels decreased when LDL-C decreased to <100 mg/dL. SEP indicated prolonged latency at LDL-C < 100 mg/dL. In addition, the IIEF-5 questionnaire score decreased at levels of LDL-C < 100 mg/dL. In this context, reductions in NO levels at low LDL-C concentrations could potentiate ED.

The small number of cases we evaluated is a limitation of this study. But the present study is an exploratory study. SEP was performed 3 times for each patient and patients were followed for 3 years. Long study duration and the testing required proved difficult for many patients and precluded us from including more patients in the study.

In conclusion, 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. We also found decreased IIEF-5 scores in response to LDL-C lowering. SEP data support the conclusion that the development of ED correlates with low LDL-C and testosterone levels. This will need to be studied further in a larger number of patients.

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