



The effect of atorvastatin on penile intracavernosal pressure and cavernosal morphology in normocholesterolemic rats

Mustafa Suat Bolat¹ , Mustafa Bakırtaş² , Fatih Fırat³ , Ekrem Akdeniz⁴ , Önder Çınar⁵ , Fikret Erdemir⁶

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ORCID IDs of the authors:

M.S.B. 0000-0002-4650-2271;
M.B. 0000-0003-3185-6947;
F.F. 0000-0003-4283-1374;
E.A. 0000-0002-0666-9579;
Ö.Ç. 0000-0002-0107-5843;
F.E. 0000-0002-3744-1681.

¹Department of Urology,
Ministry of Health, Samsun Gazi
State Hospital, Samsun, Turkey

²Department of Pathology,
University of Health Sciences,
Samsun Training and Research
Hospital, Samsun, Turkey

³Department of Urology,
Ministry of Health, Tokat State
Hospital, Tokat, Turkey

⁴Department of Urology,
University of Health Sciences,
Samsun Training and Research
Hospital, Samsun, Turkey

⁵Department of Urology, Bülent
Ecevit University School of
Medicine, Zonguldak, Turkey

⁶Department of Urology,
Gaziosmanpaşa University School
of Medicine, Tokat, Turkey

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Corresponding Author:
Mustafa Suat Bolat
E-mail:
msbolat@gmail.com

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ABSTRACT

Objective: A debate is open on the effects of lipid-lowering drugs on sexual function. We aimed to investigate the effect of atorvastatin use on penile intracavernosal pressure (ICP) and cavernosal morphology.

Material and methods: Fourteen mature male Sprague-Dawley-rats were randomly assigned to either the control group (which received standard food and water ad libitum) or the atorvastatin group (which received standard food, water, and statin) for twelve weeks. At the end of the study, ICPs were measured with cavernosometry. Penectomy specimens were histologically examined.

Results: The following mean values were obtained for the control and atorvastatin groups, respectively: pre-study body weights (350±16.9 g and 331.4±24.9 g); post-study body weights (356±18 g and 368±22.5 g (p>0.05); ICPs at 5 V (5.96±5.16 mmHg and 2.11±1.22 mmHg (p=0.07)); ICPs at 10 V (18.28±14.1 mmHg and 5.56±5.58 mmHg) (p=0.09); testosterone (1.23±0.78 and 0.78±0.58 mmol/dL) (p=0.39); blood glucose (151±22 mg/dL and 168.6±16.2 mg/dL) (p=0.12); triglyceride (93.4±19.8 mg/dL and 52.1±18.6 mg/dL) (p=0.01); total cholesterol (50.2±7.2 mg/dL and 47.7±6.6 mg/dL) (p=0.51); and low-density lipoprotein (LDL) cholesterol (10.0±4.4 mg/dL and 3.5±2.1 mg/dL) (p=0.01). The mean collagen thickness was similar (p=0.09); but the mean elastin thickness increased in the atorvastatin group (p=0.01).

Conclusion: The present study showed that the use of atorvastatin reduced the intracavernosal pressure in 10 V stimulation, and minimally decreased testosterone levels in rats, within a short period of time. When statin treatment is considered for its protective properties on cardiovascular system or for its lipid-lowering effect. It should be kept in mind that atorvastatin may also adversely contribute to erectile dysfunction.

Keywords: Collagen; elastin; intracavernosal pressure; penis; statin.

Introduction

Erectile function is the ability to achieve or maintain a penile erection sufficient for sexual performance. Erection involves smooth muscle relaxation as a result of central, hormonal, and peripheral factors.^[1] Parasympathetic stimuli originating from the intermediolateral column of the sacral spinal cord at the segments II and IV induce release of neurogenic nitric oxide synthase (nNOS) from cavernosal nerve endings and endothelial nitric oxide synthase (eNOS) from the cavernosal endothelium.^[2] Synthesized NO enters into the cavernosal

smooth muscle cells and mediates cyclic guanosine monophosphate (cGMP) synthesis that reduces Ca²⁺ levels through various mechanisms in the smooth muscle cells, induces and sustains smooth muscle relaxation.^[3] Numerous neurotransmitters affect the erection, and disruption at any stage may result in erectile dysfunction. Erectile dysfunction (ED) may develop due to psychogenic, hormonal, neurogenic, arterial pathologies; drugs, systemic and chronic diseases and drugs.^[4] Another significant, though indirect, risk factor for ED is cholesterol which is a major component of both the cell membrane and the cytosol. Alterations

in cholesterol metabolism can disrupt the intracellular signaling system, and subsequently may cause ED. Statins, and 3-hydroxy-3-methyl glutaryl coenzyme A (HMG-CoA) reductase inhibitors reduce the levels of total cholesterol and low density lipoprotein (LDL) cholesterol in serum. Use of atorvastatin for this purpose has been consistently increasing all over the world. Statins have anti-inflammatory and apoptotic features, and through these features, they may affect erectile function.^[5] However, there are conflicting reports regarding the impact of statins on sexual function. The negative effects of many drugs on male sexual function are well-known.^[6] However, the relationship between statins and male sexual function is not clear. A number of studies have hypothesized that statins were associated with ED, whereas some others advocated that statins improve ED.^[7,8]

In the present study, we aimed to investigate the specific effect of lipid-lowering agent statin in normocholesterolemic rats on penile intracavernosal pressure (ICP) and cavernosal morphology which are among the most important components of sexual function.

Material and methods

This study complies with the guidelines of the Institutional Animal Care and Use Committee at Gaziosmanpasa University vivarium sources (Ethics Approval no: 2016-HADYEK-33). Since this study was designed as an experimental study, no consent was needed. Fourteen mature male Sprague-Dawley rats between the ages of 9 and 12 weeks with mean body weights of $340.7 \text{ g} \pm 22.6$ (306-378) were selected for this study. The duration of atorvastatin administration was adjusted to correspond to its use for 8-10 years in humans.^[9] All procedures and protocols were conducted in accordance with the NIH (National Institutes of Health) guide for the care and use of laboratory animals. The rats were housed in a room controlled for temperature (295.15°K) and humidity ($60 \pm 5\%$) and with a 12 h light/dark cycle.

Following one week adaptation period, 14 rats were randomly assigned into 2 groups of 7. Rats were weighed at both the beginning and end of the study. The control group received standard food and water ad libitum for twelve weeks. The atorvastatin group received standard food and water, as well as atorvastatin in a dose of 25 mg/kg/day delivered with a pipette.^[10] The rats were weighed at the end of 12 week, and received general anesthesia with 2.5% isoflurane in N_2O (70%) / O_2 (30%). The cavernosal nerve was identified as previously described and an electronic stimulator with a bipolar hook was placed (Figure 1).^[11] In order to measure the rigid erection-which is one of the five phases of erection-, the ICP measurement technique was applied. Because the distal part of the rat's penis was structured with osseous tissue, the middle third of the penis was used both for cavernosal pressure measurement using a 26-gauge needle. Following ICP assessment, middle part of penis was retrieved for histopathologi-

cal examination. A computer-assisted program analyzed the data using an MP 45 pressure transducer system. Major pelvic ganglion nerve stimulation was performed using 5 V at a frequency of 20 Hz with a pulse width of 2 milliseconds, for 30 sec every 3 minutes. Following measurement of cavernosal pressure, the rats were sacrificed via cervical dislocation and penectomy was performed. Blood samples were taken for later assessment of 12 hours fasting testosterone and plasma lipid profile which were measured by using an automatic biochemical analyser.

Specimens in both groups were obtained and transferred in 10% neutral formalin solution after a few days for histopathological examination using Olympus BX55 light microscope and DP72 microscope digital camera system and software. Five micrometer thick longitudinal sections were obtained on coronal plane from the paraffin embedded tissue samples and collagen fibers were stained with Masson's trichrome stain (X100). The diameters of the thinnest and the thickest bulks of the collagen fibers were measured, and the mean diameters of the collagen bulk were calculated. Any change in cellular variation of the penile morphology was analyzed. The Verhoeff's elastic tissue stain was used for the evaluation of the elastic fibers of corpora cavernosa, and similarly the diameters of the thinnest and the thickest bulks of the elastic fibers were measured, the mean diameters of the elastic fiber bulk were calculated. The mean rates of collagen-to-elastic fiber diameters were calculated in both groups.

Statistical analysis

Data analyses were performed using GraphPad InStat software (Ver. 3.0) (GraphPad, USA). All data were expressed as the mean \pm standard deviation. Friedman and Wilcoxon tests were used to assess the changes in values. The results of this experiment were tested by Student-t test for the differences between two groups. A $p < 0.05$ was considered statistically significant.

Results

Mean pre-study body weights in the control, and atorvastatin groups were $350 \pm 16.9 \text{ g}$ (318-366 g) and $331.4 \pm 24.9 \text{ g}$ (306-378 g), respectively ($p=0.24$). At the end of the study the mean body weights of the control and atorvastatin groups were $356 \pm 18 \text{ g}$ (342-396 g) and $368 \pm 22.5 \text{ g}$ (338-406 g), respectively ($p=0.30$). In both groups, mean body weights were not statistically significant in either the pre- ($p=0.24$) or post-study assessments ($p=0.30$).

Mean ICPs at 5 V for the atorvastatin and control groups were $2.11 \pm 1.22 \text{ mmHg}$ and $5.96 \pm 5.16 \text{ mmHg}$ ($p=0.07$), whereas these values at 10 V were $5.56 \pm 5.58 \text{ mmHg}$ and $18.28 \pm 14.1 \text{ mmHg}$ ($p=0.04$), respectively. There was no statistically significant difference between two groups at 5 V electrical stimulation. However, 10 V stimulation resulted in the decrease in the mean ICP in atorvastatin group compared to the control group (Table 1).

Table 1. The mean body weights and the intracavernosal pressure measurements of the groups

	Control Group (n=7)		Study Group (n=7)		p	
	At the beginning	At the end	At the beginning	At the end	At the beginning	At the end
Body weight (mean±SD, min-max)	350±16.9 g (318-366 g)	356±18 g (342-396)	331.4±24.9 g (306-378)	368±22.5 g (338-406)	0.24	0.30
ICP (mmHg) [5V/30 sec, mean±SD]	5.96±5.16		2.11±1.22		0.07	
ICP (mmHg) [10V/30 sec, mean±SD]	18.28±14.1		5.56±5.58		0.04	

ICP: intracavernosal pressure; SD: standard deviation

Table 2. Biochemical and hormonal variables of the groups

Variable	Control group (n=7)	Study group (n=7)	p
Blood glucose (mg/dL)	151±22	168.6±16.2	0.12
Triglyceride (mg/dL)	93.4±19.8	52.1±18.6	0.01
Total cholesterol (mg/dL)	50.2±7.2	47.7±6.6	0.51
HDL cholesterol (mg/dL)	41.6±7.8	41.2±3.7	0.91
LDL cholesterol (mg/dL)	10±4.4	3.5±2.1	0.01
Total testosterone (mmol/dL)	1.23±0.78	0.78±0.58	0.39

HDL: high-density lipoprotein; LDL: low-density lipoprotein

Table 3. Collagen, Elastin, and collagen/elastin ratios in penile corpora cavernosa of the groups

	Control group (n=7)	Study group (n=7)	p
Collagen (micron) (mean±SD)	1.740±391.2	2.209±551.2	0.09
Elastin (micron) (mean±SD)	167.0±69.6	305.6±106.6	0.01
Collagen/elastin ratio	12.5±6.7	7.9±3.0	0.12

SD: standard deviation



Figure 1. Electrical stimulation of the penis to achieve artificial erection (Intracavernosal transducer is introduced)

For the control and atorvastatin groups respective mean testosterone [1.23±0.78 vs. 0.78±0.58 mmol/dL (p=0.39)]; glucose [151±22 mg/dL vs 168.6±16.2 mg/dL (p=0.12)]; triglyceride [93.4±19.8 mg/dL vs. 52.1±18.6 mg/dL (p=0.01)]; total cholesterol [50.2±7.2 mg/dL vs. 47.7±6.6 mg/dL (p=0.51)]; high-density lipoprotein (HDL) cholesterol [41.6±7.8 mg/dL vs. 41.2±3.7 mg/dL (p=0.91)] and LDL levels [10±4.4 mg/dL vs. 3.5±2.1 mg/dL (p=0.01)] levels were measured as indicated (Table 2).

For the control and atorvastatin groups, the mean collagen thicknesses of the penile corpora cavernosa were 1.740±391.2 and 2.209±551.2 μ (p=0.09), and the mean bulk of elastic fiber thicknesses were 167.0±69.6 and 305.6±106.6 μ, respectively (p=0.01) (Table 3, Figure 2a-c, and Figure 3a-c). The collagen-to-elastic fiber ratios were 12.5±6.7 and 7.9±3.0 for the control and statin groups, respectively (p=0.12).

Discussion

Present study is the first in the literature investigating the effects of statin on elastic and collagen fibers of penile corpora cavernosa and its association with penile intracavernous pressures.

In Massachusetts Male Aging Study (MMAS) mild, moderate, and severe ED were demonstrated in 17%, 25%, and 10% of men aged 40-70 years, respectively. It has been estimated that by 2025, ED will affect around 322 million men worldwide.^[12] Significant increases in obesity have resulted in a high prevalence of metabolic syndrome (MetS) in up to 45% of the population.^[13] Insulin resistance and dyslipidemia accompany metabolic syndrome, which is characterized with hypertriglyceridemia, LDL hypercholesterolemia, and atherogenic dyslipidemia. Since few people maintain lifestyle changes, bariatric surgery and anti-hyperlipidemic agents are frequently being used in the treatment of patients with MetS. Statins are among the most widely used drug categories for the prevention of cardiovascular disease. In a study, 23.4% of 2.171 in-hospital patients used lipid-lowering agents^[14] and, an estimated 11.9% of the US population is using statins.^[15] Oxidized LDL increases endothelial dysfunction by

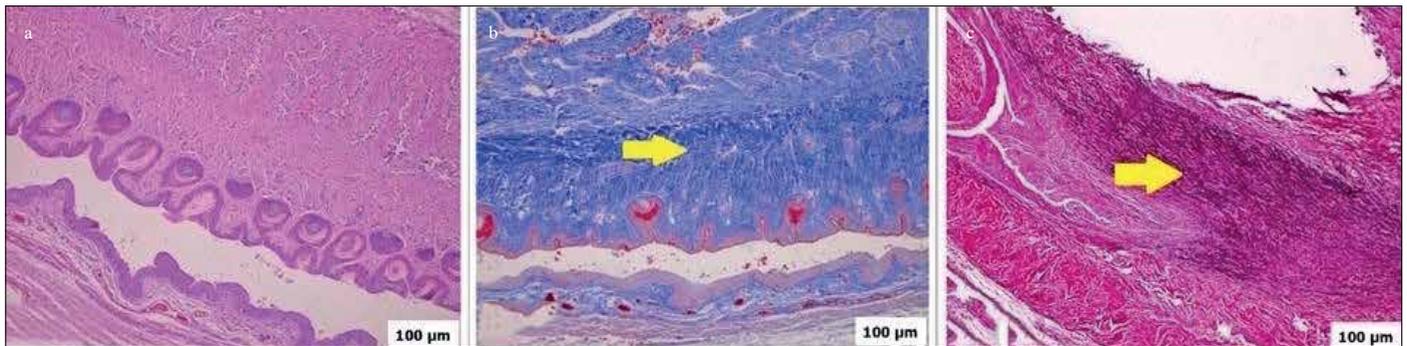


Figure 2. a-c. (a) Penile corpora cavernosa in the atorvastatin group. 100X magnification with hematoxylin&eosine. (b) Appearance of collagen fibers of the penile corpora cavernosa in the statin group (yellow arrow). X100 magnification with Masson's trichrome stain. (c) Appearance of elastic fibers of the penile corpora cavernosa in the statin group (black fibers) (yellow arrow). X100 magnification with Verhoeff's elastic tissue stain

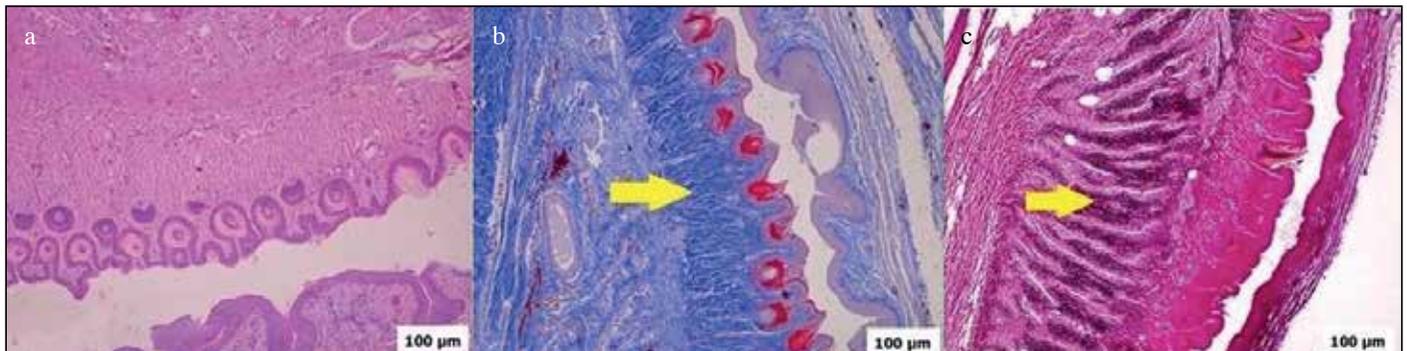


Figure 3. a-c. (a) Penile corpora cavernosa in the control group. 100 X magnification with hematoxylin&eosine. (b) Appearance of collagen fibers of the penile corpora cavernosa in the statin group (yellow arrow). X100 magnification with Masson's trichrome stain. (c) Appearance of elastic fibers of the penile corpora cavernosa in the statin group (black fibers) (yellow arrow). X100 magnification with Verhoeff's elastic tissue stain

decreasing the amount of bioavailable NO. Lowering cholesterol levels using HMG-CoA reductase inhibitors restores endothelial function.^[16] Statins improve chronic inflammation not only in hyperlipidemics, but also in normocholesterolemic patients due to its antihypercholesterolemic and pleiotropic effects.^[17] Statins have been shown to reduce both the frequency of cardiovascular episodes and mortality rates.^[18] Endothelial-NOS is an important molecule which improves vascular relaxation, platelet aggregation, and vascular smooth muscle proliferation, and prevents the development of atheromatous plaques.^[19] In addition to its lipid-lowering effects, statins also have positive effects on endothelial function, nitric oxide bioavailability, antioxidant properties, stabilization of atherosclerotic plaques, and vascular inflammation.^[20] In our study, statin was given in rats with normal lipid profiles. However our results revealed significant decrease in LDL cholesterol and triglyceride levels in the statin group. This finding can be explained with inhibition of HMG-CoA reductase.

Conflicting reports still exist regarding the role of statin use on sexual function. In a study of 20,731 patients, no association

was reported between statin use and gonadal or sexual function.^[21] whereas another systematic review reported decreases in testosterone levels. Baspinar et al.^[22] found that atorvastatin may cause a decrease in testosterone levels, resulting in ED in hyperlipidemic middle-aged males. Various negative effects of statin use have been reported in clinical studies including myositis, myalgia, and rhabdomyolysis. These effects are most likely due to statin's direct toxicity on mitochondria and muscle stem cells, which are responsible for regeneration and repair after injury as well as the elevation of creatinine kinase, alanine or aspartate aminotransferase levels, and proteinuria.^[23] Contrary to these reports, our findings regarding serum testosterone levels were not compatible with these reports, probably due to short observational period.

A study on lipid-lowering medications showed an association between statin use and increased risk of ED among participants younger than 55 years who had chronic diseases, whereas older men remained potent.^[24] McEniery et al.^[25] reported that elastic fibers undergo degradation and fragmentation with increas-

ing age and severity of the disease, accelerating cardiovascular mortality parallel to collagen accumulation. Our results showed that atorvastatin administration resulted in statistically nonsignificant increase in collagen accumulation, whereas the volume of elastic fibers significantly increased in the statin group. In this present study, the reduction in mean total testosterone level by 35.5% seemed to cause ED in the statin group. Although it was statistically nonsignificant, hypoandrogenemia may be a reasonable cause. Rearrangement of the two different types of fibers in penis may be associated with decrease in the intracavernosal pressure. However further comprehensive experimental studies investigating the effect of cavernosal collagen and elastic fibers on erection with longer follow-up periods are needed to judge this hypothesis.

A criticism may arise whether the ICP/mean arterial pressure (MAP) ratio is better than the ICP measurement only for the evaluation of full erection phase. Although the ICP/MAP parameter has been applied in most of the studies.^[26] Some other researchers have assessed ICP only. It has been shown that full erection phase occurs when the mean MAP value is achieved, and the ICP rises above the MAP only during ischiocavernous and bulbocavernous muscle contractions.^[27] Because of this and unavailability of computerized equipment and instruments, we measured ICP only.

The limitations of this study are the lack of comparable animal model with hypercholesterolemia and normocholesterolemia, and that statin administration was maintained for only a short period of 12 weeks.

In conclusion, the present study showed that the use of atorvastatin reduced the intracavernosal pressure in 10 V stimulation, and minimally decreased testosterone levels in rats within a short period of time. When atorvastatin treatment is considered for its cardiovascular protective or lipid-lowering effects, it should be kept in mind that atorvastatin may also contribute to ED.

Ethics Committee Approval: Ethics committee approval was received for this study from the ethics committee of Gaziosmanpasa University School of Medicine (Ethics Approval no: 2016-HADYK-33).

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