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ARTYKUŁ ORYGINALNY / *ORIGINAL ARTICLE*

The effect of rosuvastatin and atorvastatin on erectile dysfunction in hypercholesterolaemic patients

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Abstract

Background and aim: The aim of this study was to evaluate the effect of atorvastatin and rosuvastatin on erectile dysfunction in hypercholesterolaemic patients.

Methods: Ninety consecutive male hypercholesterolaemic patients (mean age 50.4 ± 7.9 years) who were otherwise healthy were included into the study prospectively. None of the patients had any cardiovascular risk factors except hypercholesterolaemia. The patients were divided into two groups. One group received atorvastatin while the other group was given rosuvastatin. All patients were followed for six months and International Index of Erectile Function-5 (IIEF-5) score and blood samples were re-evaluated.

Results: Patients were in similar ages in both groups. There were also no statistical differences in terms of blood glucose levels, total cholesterol, low density lipoprotein, high density lipoprotein, triglyceride and mean IIEF score in both groups at the beginning. After six months, no IIEF score changes were observed in the rosuvastatin group after the medication. However, the IIEF score was significantly lower in the atorvastatin group ($p = 0.019$).

Conclusions: Rosuvastatin showed no effect on erectile dysfunction, while we observed increased erectile dysfunction with atorvastatin. Our study reveals that different statin types may have different effects on erectile dysfunction.

Key words: statin, erectile dysfunction, hypercholesterolaemia, atherosclerosis

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INTRODUCTION

Erectile dysfunction (ED) is a major health problem affecting 52% of men between 40 and 70 years [1]. It has been shown that ED is highly related to vascular diseases like hypertension, diabetes and heart disease [1]. ED and vascular disease are thought to have a similar aetiology at the level of endothelium. The association between ED and hypercholesterolaemia has also been shown in a group of healthy male subjects [2]. Statins are one of the major prescribed drugs worldwide which have been proven to be effective in preventing major coronary events, coronary revascularisation and stroke, irrespective of the initial lipid profile [3]. This class of drugs shares a common mechanism to inhibit cholesterol synthesis in the liver that involves blocking conversion of 3-hydroxy-3-methylglutharyl coenzyme A to mevalonate [4]. It has been suggested that statin therapy may worsen ED. Two different mechanisms of action have been proposed to explain this. One of them was the lipophilicity of statins [5]. Statins also up-regulate endothelial nitric oxide synthase activity and improve nitric-oxide-dependent vasodilatation in various vascular beds, and show this effect even before altering the lipid profile [6, 7].

METHODS

Ninety consecutive male hypercholesterolaemic patients (mean age 50.4 ± 7.9 years) who were otherwise healthy were included into the study prospectively. Hypercholesterolaemia was defined as low density lipoprotein cholesterol (LDL-C) > 160 mg/dL. All the patients presented with ED. None of the patients had any cardiovascular risk factors except hypercholestrolaemia. All patients were evaluated for coronary artery disease using treadmill exercise testing. Patients with hormonal

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Table 1. Baseline patient characteristics

Characteristics	Rosuvastatin group (n = 44)	Atorvastatin group (n = 46)	P
Age [years]	49.3 ± 8.3	51.4 ± 7.4	0.211
Statin dosage [mg]	14.55 ± 6.27	25.65 ± 11.67	**0.001**
IIEF-5 score	17.23 ± 6.22	18.96 ± 4.80	0.143
Mild ED [%]	27 (61.4%)	31 (67.4%)	
Moderate ED [%]	11 (25.0%)	14 (30.4%)	0.125
Severe ED [%]	6 (13.6%)	1 (2.2%)	

ED — erectile dysfunction; IIEF-5 — International Index of Erectile Function

and neurological pathologies, an abnormal penile vasculature system, diabetes mellitus, coronary artery disease, smoking and any cardiovascular risk factors were excluded from the study. Presence and degree of ED was evaluated using the International Index of Erectile Function-5 (IIEF-5) score [8]. ED was considered when the IIEF-5 score was ≤ 21. Severe ED is defined as IIEF-5 score < 7, moderate ED is IIEF-5 score 8–16, and mild ED is IIEF-5 score > 16. Venous blood samples were taken from subjects after 12-h fasting. Total cholesterol (TC), LDL-C, high-density lipoprotein cholesterol (HDL-C), and triglyceride (TG) were measured using a commercial enzymatic colorimetric kit (Merk Ltd., Darmstadt, Germany). Patients were divided into two groups and randomised to atorvastatin (20–40 mg) or rosuvastatin (10–20 mg). Group 1 (44 patients, mean age 49.3 ± 8.3 years) received rosuvastatin while Group 2 (46 patients, mean age 51.4 ± 7.4 years) was given atorvastatin. Statin dosage was concluded according to the LDL-C levels of the patients. All patients were followed for six months and IIEF-5 score and blood samples were re-evaluated. During the study period, patients were informed not to take drugs improving erectile function so as not to influence the results of the study. The study was approved by the local ethics committee and all patients signed informed consent to participate.

Statistical analysis

Statistical analyses were conducted using Statistical Package for the Social Sciences 15.0 (SPSS, Chicago, IL, USA). All continuous variables were tested by the Kolmogorov-Smirnov test for normal distribution. Descriptive statistics are presented as mean ± standard deviation for continuous variables and as numbers and percentages for categorical variables. Quantitative parameters with normal distribution were tested with Student t test and without normal distribution tested using Mann Whitney U test to compare two groups. Paired sample T test and Wilcoxon sign test were used to compare parameters in between groups. The results were considered significant when the p value was less than 0.05.

RESULTS

A total of 90 patients, mean age 50.4 ± 7.9 years, were followed for six months. Patients were in similar ages in both groups (Table 1). Patients in Group 1 received 14.5 ± 6.2 mg of rosuvastatin while patients in Group 2 were given 25.6 ± 11.6 mg of atorvastatin. Of these patients, 58 (63.3%) patients had mild ED, 25 (27.7%) patients had moderate ED and seven (7.7%) patients had severe ED. The mean IIEF-5 score was similar in both groups (Table 1). There were also no statistical differences in terms of TC, LDL-C, HDL-C and TG in both groups at the beginning (Table 2). After six months, TC and LDL-C levels were lower compared to the beginning and there were no statistical differences in both groups. No difference was observed in HDL-C levels in the rosuvastatin group, but HDL levels were slightly increased in the atorvastatin group ($p = 0.033$). However, the difference in both groups was not statistically significant. There was a significant difference in both groups in terms of TG levels before and after the medications ($p < 0.001$ for both groups). But TG levels were lower with rosuvastatin therapy ($p = 0.037$).

No IIEF score change was observed in the rosuvastatin group after the medication. However, IIEF score was significantly lower in the atorvastatin group ($p = 0.019$) (Fig. 1). We also observed that after given statins in both groups, no severe ED patients remained. Additionally, there were no differences in IIEF-5 scores between the two groups after statin therapy. When patients were sub grouped into three groups, as mild, moderate and severe ED according to their IIEF-5 scores, no differences were observed in both groups following statin treatment (Table 3). During the study period, we did not determine other potential adverse effects of statins.

DISCUSSION

Erectile dysfunction shares similar risk factors with cardiovascular disease (e.g. lack of exercise, obesity, smoking, hypercholesterolaemia, metabolic syndrome). Hypercholesterolaemia is one of the most important cardiovascular risk factors. The association between hypercholesterolaemia and ED is evident according to preclinical, clinical and epidemiologic studies [9]. Multiple randomised, double-blind, placebo-controlled studies and observational studies have demonstrated that statins decrease mortality and major cardiovascular events in high-risk people with hypercholesterolaemia [10]. Statins interfere with an enzyme which affects de novo synthesis

Table 2. Mean International Index of Erectile Function-5 (IIEF-5) score and cholesterol levels of patients and before and after statin treatment

		Rosuvastatin group	Atorvastatin group	P
Mean IIEF-5 score	Before	17.23 ± 6.22	18.96 ± 4.80	**0.143**
	After	17.14 ± 6.48	17.33 ± 5.30	**0.879**
	P	0.896	**0.019***	
Total cholesterol [mg]	Before	229.73 ± 39.82	225.00 ± 47.01	0.610
	After	166.84 ± 34.32	170.89 ± 39.76	0.609
	P	**0.001**	**0.001**	
LDL-cholesterol [mg]	Before	157.41 ± 42.83	151.27 ± 48.33	0.528
	After	100.98 ± 32.91	100.82 ± 36.81	0.983
	P	**0.001**	**0.001**	
HDL-cholesterol [mg]	Before	45.02 ± 10.38	41.30 ± 9.85	0.090
	After	46.23 ± 10.26	43.43 ± 9.41	0.188
	P	0.294	**0.033**	
Triglyceride [mg]	Before	177.45 ± 101.88	189.82 ± 116.02	0.597
	After	123.55 ± 45.82	151.77 ± 75.47	0.037
	P	**0.001**	**0.001**	

*statistically significant; HDL — high density lipoprotein; LDL — low density lipoprotein

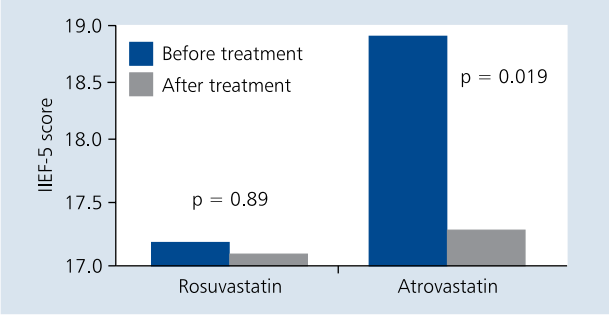

Figure 1. International Index of Erectile Function-5 (IIEF-5) score before and after treatment with rosuvastatin and atorvastatin

of cholesterol by inhibiting the rate-limiting step of the catalysis. This pathway generates a range of other products in addition to cholesterol, such as coenzyme Q10, heme-A, and isoprenylated proteins [11]. Additionally, cholesterol itself is not entirely a final product but also an intermediate to a suite of additional products such as sex steroids, corticosteroids, bile acids and vitamin D [12, 13]. A decrease in circulating levels of LDL-C is accompanied by increased hepatic LDL-C receptor activity, which causes an increased clearance of LDL-C from the bloodstream. In clinical trials, statins are beneficial in the primary and secondary prevention of coronary heart disease. However, the overall benefits observed with statins appear to be greater than expected from changes in lipid levels alone, suggesting effects beyond those of cholesterol lowering [14]. Recent studies have shown pleiotropic effects of statins such as reducing oxidative stress, inflammation, improving endothelial function, and enchancing the stability of atherosclerotic plaques [15]. Additionally, it has also been reported that statins may improve ED and phosphodiasterase type 5 inhibitors outcomes. This has been suggested as being related to pleitropic effects of statins [16, 17]. Atorvastatin, simvastatin, lovastatin, fluvastatin, cerivastatin and pitavastatin

Table 3. Erectile dysfunction (ED) after statin treatment

		Rosuvastatin group	Atorvastatin group	P
Before treatment	Mild ED	27 (61.4%)	31 (67.4%)	
	Moderate ED	11 (25.0%)	14 (30.4%)	0.125
	Severe ED	6 (13.6%)	1 (2.2%)	
After treatment	Mild ED	26 (59.1%)	27 (58.7%)	
	Moderate ED	18 (40.9%)	19 (41.2%)	0.970
	Severe ED	–	–	
	P	0.251	0.317	

are relatively lipophilic compounds [18]. Lipophilic statins are considered more likely to enter endothelial cells by passive diffusion than hydrophilic statins, such as pravastatin and rosuvastatin, which are primarily targeted at the liver. However, lipophilicity does not entirely predict the ability of statins to exert extrahepatic effects [19]. One possible mechanism for statin and ED relation is based on the possibility that statin lipophilicity might have an effect.

Lipophilic statins such as atorvastatin hence could act either centrally or induce a drug-induced peripheral neuropathy in the penile nerves [5]. However, in our study, we found that IIEF-5 score was significantly decreased following atorvastatin treatment, while there was no change with rosuvastatin therapy. Solomon et al. [5] revealed no association between statin therapy and the extent of ED in a small patient group with high cardiovascular risk. However, Corona et al. [20] studied 244 males with ED and found lower levels of free testosterone and reduced testis volume following statin treatment. It has been suggested that statins may cause ED secondary to the inhibition of testosterone synthesis. As we did not determine the concentration of sex hormone levels at baseline and follow up, we could not determine the effect on sexual function. However, we could not find any studies comparing different statin types in these patients. In our study, despite similar decreases in cholesterol levels with rosuvastatin and atorvastatin treatment, patients taking atorvastatin had worsening of ED. In addition, regarding IIEF-5 score in these patients, decreasing effect of lipophilic statins should be considered carefully.

Limitations of the study

The overall sample size of this study was small with short term follow up. Further studies with larger sample sizes and long term follow up are required to validate our findings. ED was only considered with IIEF-5 score, not with a qualitative method like penile vascular study or penile ultrasonography. And also other sexual functions such as sexual desire, frequency of sexual activity, orgasmic function, psychological state such as stress, intercourse satisfaction and overall satisfaction were not evaluated. We did not perform penile Doppler for the diagnosis ED because of ethical considerations and potential serious complications. Instead, we preferred IIEF score which is a practical method because it is noninvasive and reproducible [21, 22].

CONCLUSIONS

Our data suggests that statins might have different effects on ED in patients without cardiovascular risk factors except hypercholesterolaemia. However, the potential negative effects of lipophilic statins on ED should be validated with further studies. Larger placebo controlled longitudinal studies are needed to better clarify the relationship between the treatment with different statins types according to lipophilicity and ED.

Conflict of interest: *none declared*

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Wpływ rosuwastatyny i atorwastatyny na zaburzenia erekcji u chorych z hipercholesterolemią

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Streszczenie

Wstęp i cel: Celem niniejszej pracy była ocena wpływu atorwastatyny i rosuwastatyny na zaburzenia erekcji u chorych z hipercholesterolemią.

Metody: Do badania włączono prospektywnie kolejnych pacjentów z hipercholesterolemią (średnia wieku 50,4 ± 7,9 roku), u których nie występowały inne choroby. U żadnego z pacjentów nie występowały inne czynniki ryzyka sercowo-naczyniowego poza hipercholesterolemią. Uczestników badania podzielono na dwie grupy. Osoby z jednej grupy otrzymywały atorwastatynę, a osoby z drugiej grupy — rosuwastatynę. Wszystkich chorych obserwowano przez 6 miesięcy, po czym ponownie przeprowadzono ocenę zaburzeń erekcji z użyciem skali IIEF-5 oraz analizę próbek krwi.

Wyniki: Pacjenci z obu grup byli w podobnym wieku. Nie stwierdzono również statystycznych różnic między grupami pod względem wyjściowych wartości stężenia glukozy we krwi, cholesterolu całkowitego, lipoprotein frakcji LDL, lipoprotein frakcji HDL, triglicerydów i średniej punktacji w skali IIEF. Po 6 miesiącach leczenia nie zanotowano zmian w punktacji IIEF w grupie przyjmującej rosuwastatynę, natomiast w grupie stosującej atorwastatynę punktacja IIEF była istotnie niższa ($p = 0,019$).

Wnioski: Rosuwastatyna nie miała wpływu na zaburzenia erekcji, natomiast atorwastatyna spowodowała nasilenie tych zaburzeń. W badaniu wykazano, że różne rodzaje statyn mogą odmiennie wpływać na zaburzenia erekcji.

Słowa kluczowe: statyna, zaburzenia erekcji, hipercholesterolemia, miażdżyca

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