The Association Between Dyslipidemia and Its Treatment with Erectile Dysfunction

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13.1 Introduction

Low-density lipoprotein cholesterol (LDL-C) plays a vital role in the atherosclerotic process, and currently dyslipidemia is considered to be one of the most important risk factors for CV events [1]. The introduction of statins in treatment protocols for patients with dyslipidemia was a major advance for the treatment of CV disease and effectively reduces LDL-C levels and CV events [2, 3]. Because of their effectiveness, 30 million individuals in the USA and up to 200 million individuals worldwide are currently on statin therapy. In addition, the role of statin therapy in primary and secondary prevention of CV events seems to be mediated by other mechanisms (beyond LDL-C reduction) as well. Statins exert beneficial effects even

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in patients with low, near-baseline LDL-C levels, even <80 mg/dl [4, 5]. Evidence also supports that statin-mediated health benefits are observed well before LDL-C levels decrease [6–9].

Erectile dysfunction (ED) is defined as the persistent inability to attain and/or maintain penile erection sufficient for sexual intercourse. ED is highly prevalent in the general male population and its prevalence increases with age. Traditionally, ED was considered to be either a psychological or an anatomic issue. Thus, the condition was managed by mental health professionals and urologists. However, advances in understanding the pathophysiology of ED in recent years lead the conclusion that origin of ED for the majority of patients is mainly vascular. Specifically, the reduced bioavailability of nitric oxide in the penile tissue in patients with atherosclerosis is the main pathological pathway of erectile dysfunction.

ED is highly prevalent in males with CV risk factors, especially in patients with arterial hypertension, diabetes mellitus, or obesity. The prevalence of ED in patients with dyslipidemia and the effects of statins on erectile function are not completely defined. This review aims to present available data on the relationship between dyslipidemia and ED and critically evaluate existing data about the effects of statins and other hypolipidemic agents on erectile function.

13.2 Epidemiology

In a Canadian Study of primary care physicians, ED was independently associated with cardiovascular disease. However, the study failed to highlight dyslipidemia as an independent risk factor [10]. On the contrary, Smith et al. [11] reported a high prevalence of newly diagnosed hypercholesterolemia and hypertriglyceridemia in men attending an ED clinic. In a large cohort of 272,325 patients with ED, the prevalence of hyperlipidemia was 20.2 %, and the age-specific prevalence ranged from 3.9 to 52.3 % [12]. In addition, ED was significantly more prevalent in individuals with dyslipidemia, coronary artery disease (CAD), and metabolic syndrome. In another study, ED was significantly more prevalent in patients who had both hypercholesterolemia and hypetriglyceridemia [13].

13.3 Pathophysiological Correlation Between ED and Dyslipidemia

Dyslipidemia-induced ED with high LDL-C concentrations as the major culprit has been proposed by Kim [14]. Similar erection response to intracavernous injection of papaverine, a smooth muscle relaxant, of patients with and without hyperlipidemia suggests that the endothelium-dependent relaxation is impaired in ED. This was further supported by in vitro experiments of cavernal tissue, where tissues taken from hyperlipidemic patients demonstrated impaired relaxation response to vasoactive agents, in comparison to tissues from normolipidemic individuals. Oxidized LDL

inhibited this relaxation. The production of superoxide radical and the activity of total superoxide dismutase (SOD) (acts as a scavenger) in the hyperlipidemic group were both increased, suggesting a functional impairment of response to endothelial stimuli. Rao et al. [15] confirmed these findings, and others emphasized oxidized LDL as the major factor of impaired relaxation response, as well as the role of nitric oxide (NO), and its reduced generation or bioavailability in penile and vascular tissue [16]. Three experimental studies on rats and mice further support the aforementioned findings. Erectile responses to nerve electrical stimulation, in hypertriglyceridemic rats, was impaired following an increase in triglyceride levels by administration of 10 % fructose and restored when triglycerides were lowered [17]. High-cholesterol diet also had similar detrimental effects on erectile and endothelial function in rats [18, 19].

13.4 Statins and ED

13.4.1 Mechanism of Action

Statins are the cornerstone treatment against hypercholesterolemia. Statins lower blood cholesterol concentrations by inhibiting HMG-CoA reductase. This enzyme catalyzes the conversion of HMG-CoA into mevalonic acid, a cholesterol precursor, thus reducing the endogenous cholesterol synthesis. Apart from that, statins exhibit pleiotropic effects. They intervene intracellular molecular signaling pathways, antagonize accumulation of macrophages and inflammatory processes, and exert a protective action on endothelial cell function, increasing serum NO levels. Statins also reduce smooth muscle cell (SMC) proliferation, stabilize the atherosclerotic plaque, and inhibit platelet activation and coagulation process, hence reducing the cardiovascular risk. The well-established adverse effects are myopathy and elevation of liver enzymes [20]. Another, lately investigated possible adverse effect of statins is hypoandrogenemia, attributed to the inhibition of steroid hormones derived from cholesterol, including testosterone [21]. Statins might also decrease libido through central mechanisms [22].

13.4.2 Clinical Studies

The majority of interventional studies involve the use of atorvastatin in a relatively small number of patients. In general, these studies support that the use of statins improve penile rigidity and sexual function when compared to placebo [23–25]. There is also evidence to support that the effects of sildenafil on erectile function in hypercholesterolemic patients is enhanced when combined with statin therapy [26]. In addition, patients who do not respond to sildenafil exhibited a modest improvement in erectile function when treated with statins [27].

A prospective single-blind study compared the effect of atorvastatin and tadalafil on ED. Subjects ($n = 120$) were randomized to receive atorvastatin 10 mg/day,

tadalafil 20 mg three times/week, a combination of the two for 3 months, or no medication. Mean improvement of IIEF score was significantly higher in both tadalafil group compared to control group ($p=0.0001$), and atorvastatin group compared to control group ($p=0.001$). The improvement in the tadalafil group was more profound than the atorvastatin group. There was no synergic effect of atorvastatin and tadalafil [28].

Not all studies reported favorable outcomes with statin therapy [29, 30]. In a randomized double-blind longitudinal study, 173 men with untreated ED were treated with 40 mg simvastatin daily ($n=90$) or placebo ($n=83$) for 6 months. Patients with high cardiovascular risk, hypertension, and angina and those already on ED or statin therapy were excluded. No significant difference in erectile function between the simvastatin and placebo groups ($p=0.27$) was noted [31].

A cross-sectional study of patients referred to a lipid clinic for dyslipidemia, and 339 age-matched men found that there were more impotent men in the group of patients treated with hypolipidemic drugs ($p=0.003$). Multivariate analysis showed that erectile dysfunction was dependent on treatment with fibrate derivatives (odds ratio, 1.46; 1.27–1.68) and statins (odds ratio, 1.51; 1.26–1.80) [32].

Cases of ED associated with statins were collected by the Spanish and French pharmacovigilance system. In the Spanish database, 38 cases were recognized, 93 % of which resolved after statin withdrawal. In the French database, 37 cases were reported, 85 % resolved after withdrawal and 5 cases exhibited a positive rechallenge [33].

In a prospective observational study including 80 men attending cardiovascular risk clinics, IIEF scores were measured prior to initiation and after 6 months of statin therapy. Prior to statin therapy, the mean IIEF score was 18.7, and 52 % had significant reduction of erectile function. After statin therapy, IIEF scores were reduced to 10.4 ($p<0.001$), and 22 % experienced new onset ED [34].

In a study of 1,899 men, there was no association between hyperlipidemia drug treatment and ED, except among younger men (<55) who had diabetes and/or CVD, where a strong association was observed (OR = 10.39, 95 % CI: 3.25, 33.20). In a statins-only analysis, the OR for treated hyperlipidemia was still substantial (OR = 8.86, 95 % CI: 2.69, 29.20), but no information was given regarding the type of statins and dosage [35].

Do et al. [36] assessed the same relation between statins and ED using a case/non-case method within the French Pharmacovigilance System Database. Among the total of spontaneous reports selected (110 685), exposure to statins was identified in 4,471 cases, of which 51 reports (1.1 %) concerned ED, whereas 431 (0.4 %) cases of ED were found in the 106 214 reports without exposure to statins ($p<0.0001$). No relationship was found between statin dosage, duration of statin therapy, and ED.

Corona et al. [37] reported that in a cohort of 3,484 men with ED, individuals who were treated with statins had significantly lower levels of total and free testosterone when compared to the rest of the sample ($p<0.0001$ for both). Statin treatment was also associated with reduced testis volume and a higher prevalence of hypogonadism-related symptoms and signs ($p<0.01$). Also, in the statins

group, follicle-stimulating hormone levels were significantly higher compared to the untreated group, suggesting a possible mechanism for statin-related ED. These findings were confirmed by Cohen [38] who also noted an exacerbated free and total testosterone level reduction in individuals with preexisting hypoandrogenic anabolic deficiency state (decreased pregnenolone and DHEA concentrations).

In contrast to the aforementioned studies, a double-blind, randomized, placebo-controlled, clinical trial in patients with ED and endothelial dysfunction reported no significant difference in penile erection between those treated with simvastatin and the placebo group [39].

In another most recent prospective study, ED was assessed in a group treated with rosuvastatin 10–20 mg daily ($n=46$) and atorvastatin arm ($n=44$). The investigators reported no adverse effect on ED in those treated with atorvastatin, whereas the IIEF score was significantly lower after 6 months of rosuvastatin treatment ($p=0.019$). This is the first study to suggest that different types of statins may have a different effect on ED [40] (Table 13.1).

13.4.3 Experimental Data

In an experimental study (Wistar rats), it was found that pretreatment with atorvastatin increased the potency of sildenafil-induced relaxation ($p<0.01$), the plasma NOx concentrations, and sildenafil-induced hypotension and tachycardia [41]. These findings suggest a synergy through NO-mediated mechanisms, in the vascular relaxation. In another study, atorvastatin ameliorated sildenafil-induced penile erections in spontaneously hypertensive rats, by interfering with the Rho-kinase signaling pathway within the penis [42]. Atorvastatin benefits on erectile function were also observed in diabetic rats and diabetic rabbits [43]. Similar beneficial effects on erectile function were also observed with rosuvastatin in obese diabetic rats [44]. Simvastatin showed similar benefits in restoring erectile function when added to insulin, by inhibiting the RhoA-/Rho-kinase pathway [45].

13.5 Other Hypolipidemics and Erectile Dysfunction

Case reports or small series of patients who were treated with gemfibrozil suggest that ED might appear after 1–3 weeks of treatment and subside after withdrawal of the drug [46–49]. A review of clinical trial experience with fenofibrate reported ED as an adverse effect on 1.3 % of the patients [50].

In a single-center prospective randomized placebo-controlled parallel-group trial of 160 male patients with ED and dyslipidemia, niacin was associated with improvement of erectile function compared to placebo for 12 weeks [51]. In another single-blind, one-arm study of 54 men with untreated ED, niacin had beneficial effects on erectile function when given combined with propionyl-L-carnitine and L-arginine for 3 months [52].

Table 13.1 Comparative table of studies on statins and erectile function

Study, year	No. of patients	Study type	Study drugs	ED assessment	Outcome
Saltzman et al., 2004	9	Single-arm open-label	Atorvastatin	IIEF questionnaire, RigiScan	Improvement
Herrmann et al., 2006	12	Randomized, double-blind placebo-controlled	Atorvastatin	IIEF questionnaire	Improvement
Bank et al., 2006	35	Randomized, double-blind placebo-controlled	Atorvastatin, quinapril	IIEF questionnaire, endothelium-independent relaxation, Doppler blood flow	Improvement
Gokkaya et al., 2008	25	Single-arm open- label	Atorvastatin	IIEF questionnaire	Improvement
Dadkhah et al., 2010	131	Randomized, -blind placebo-controlled	Atorvastatin	IIEF questionnaire	Improvement
Gokce et al., 2012	120	Single-center, randomized, single-bind study	Atorvastatin	IIEF questionnaire	Improvement
			Tadalafil	Serum testosterone, nocturnal penile tumescence	
Pedersen et al., 1999 (comment on the Scandinavian Simvastatin Survival Study 1994)	4,444	Randomized, single-bind study	Simvastatin	IIEF questionnaire	No deterioration likely
Trivedi et al., 2013	173	Randomized, double-bind study	Simvastatin	IIEF questionnaire, male ED-specific quality of life, quality adjusted life years	Improvement
Bruckert et al., 1996	678	Crossover study	Simvastatin, pravastatin, fibrates, resins	Medical history	Hypolipidemic drugs as a possible cause of ED
Carvajal et al., 2006	38	Analysis of the cases of impotence of the Spanish and French pharmacovigilance system	Statins	Reports from patients	Possible cause of ED

Solomon et al., 2006	93	Prospective observational study	Statins	IIEF questionnaire	Possible cause
Hall et al., 2009	1,899	Observational crossover study	Hypolipidemics, meta-analysis on statins	IIEF questionnaire	Hypolipidemics, and statins may cause ED
Do et al., 2009	110,685	Case/non-case method on data within the French Pharmacovigilance System Database	Statins	Spontaneous reports	Statins
Corona et al., 2010	3,484	Crossover observational study	Statins	ANDROTEST, measurement of blood-testosterone	Statins may induce hypogonadism
Mastalir et al., 2005	41	Double-blind, randomized, placebo-controlled	Simvastatin	IIEF questionnaire, ED Index of Treatment Satisfaction	No relationship between simvastatin and ED
Nurkalem et al., 2014	90	Single-blind randomized	Atorvastatin, rosuvastatin	IIEF questionnaire	Atorvastatin increased ED
					Rosuvastatin showed no effect

Conclusions

This review sought to summarize available evidence regarding the relationship between ED and dyslipidemia. Most evidence support that dyslipidemia is associated with ED through induction of impaired relaxation response upon cavernal tissue. Hypercholesterolemia decreases the gene expression of endothelium-specific cell-to-cell junction proteins and decreased endothelial content in the corpus cavernosum. High levels of ox-LDL induce lower bioavailability of NO.

Available data regarding the effects of statins on erectile function is conflicting. Experimental data point towards a beneficial effect of statins on erectile function through several mechanisms. Clinical data, however, does not confirm these beneficial effects in all cases. Available clinical studies show positive, neutral, or even negative effects on erectile function. However, existing data is not of the highest quality. Many studies are observational with all inherent limitations of this study type, and available prospective randomized studies have usually small study samples and short follow-up. Moreover, the assessment of erectile function in other studies was not based on validated methods. Finally, information regarding a dose-dependent effect or within-class differences are inconclusive.

Information regarding other hypolipidemic agents, apart from statins, is scant and fragmented. Gemfibrozil appears to have detrimental effects on erectile function, while niacin might beneficially affect erectile function; however, available data needs to be confirmed by appropriately designed and adequately powered clinical trials.

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