The role of statins in erectile dysfunction: a systematic review and meta-analysis

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To evaluate the effect of statins for erectile dysfunction (ED), a systematic review of the literature was conducted in the Cochrane Library, Embase and PubMed from the inception of each database to June 2013. Only randomized controlled trials (RCTs) comparing treatment for ED with statins were identified. Placebo RCTs with the International Index of Erectile Function (IIEF) as the outcome measure were eligible for meta-analysis. A total of seven RCTs including two statins with a total of 586 patients strictly met our criteria for systematic review and five of them qualified for the meta-analysis. A meta-analysis using a random effects model showed that statins were associated with a significant increase in IIEF-5 scores (mean difference (MD): 3.27; 95% confidence interval (CI): 1.51 to 5.02; \(P < 0.01\)) and an overall improvement of lipid profiles including total cholesterol (MD: −1.08; 95% CI: −1.68 to −0.48; \(P < 0.01\)), low-density lipoprotein (LDL) cholesterol (MD: −1.43; 95% CI: −2.07 to −0.79; \(P < 0.01\)), high-density lipoprotein (HDL) cholesterol (MD: 0.24; 95% CI: 0.13 to 0.35; \(P < 0.01\)) and triglycerides (TGs) (MD: −0.55; 95% CI: −0.61 to −0.48; \(P < 0.01\)). In summary, our study revealed positive consequences of these lipid-lowering drugs on erectile function, especially for nonresponders to phosphodiesterase type 5 inhibitors (PDE5Is). However, it has been reported that statin therapy may reduce levels of testosterone and aggravate symptoms of ED. Therefore, larger, well-designed RCTs are needed to investigate the double-edged role of statins in the treatment of ED.

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INTRODUCTION

Erectile dysfunction (ED) is defined as the persistent inability to attain and maintain an erection sufficient to permit satisfactory sexual performance.\(^1\) It is thought that between 3% and 71% of the male population, varying with age, experiences this problem.\(^2,3\) The pathophysiology of ED is multifactorial and may include arterial, neurogenic, hormonal, cavernosal, iatrogenic and psychogenic causes. It is now widely accepted that ED can be a consequence of a generalized vascular disorder caused by endothelial dysfunction.\(^4\) In these patients, the decrease of nitric oxide (NO) production by the vascular endothelium results in decreased formation of cyclic guanosine monophosphate, which is the second messenger that induces arterial and corporal vasodilation in the corpus cavernosum.\(^5\) Phosphodiesterase type 5 inhibitors (PDE5Is), the first-line therapy for ED, prevents PDE5 from degrading cyclic guanosine monophosphate.\(^6\) Therefore, PDE5Is restore smooth muscle relaxation, which increases arterial blood flow, leading to compression of the subtunical venous plexus and penile erection.\(^7\) However, many patients do not respond to PDE5Is. Endothelial dysfunction is considered to be the main factor resulting in PDE5Is treatment failure\(^8\) because PDE5Is are unlikely to reverse endothelial dysfunction with reduced NO bioavailability.\(^9\)

Statins are an inhibitor of the enzyme 3-hydroxy-methylglutaryl-CoA reductase. It suppresses the conversion of 3-hydroxy-methylglutaryl-CoA to mevalonate, which is the rate-limiting step in de novo synthesis of cholesterol.\(^10\) Functionally, statins reverse endothelial dysfunction by decreasing the action of oxidized low-density lipoprotein (LDL) on endothelial cells, resulting in an increase of NO activity.\(^11\) Several studies found that statins could rapidly improve endothelial function, even before changing the lipid profile.\(^12,13\) However, it has been shown that elevated serum cholesterol and reduced high-density lipoprotein (HDL) cholesterol levels are associated with an increased risk of ED.\(^14\) However, it has not been established whether the correction of dyslipidemia can decrease the risk of developing ED. In addition, it was reported that statin therapy was associated with reduced levels of testosterone and even symptoms of hypogonadism.\(^15,16\) Based on the aforementioned data, a debate is open on the effects of lipid-lowering drugs on the quality of erections.

Thus, we integrated all qualified randomized controlled trials (RCTs) available and conducted a systematic review and meta-analysis of these studies to assess the effects of statins on the quality of erections for patients with ED.

MATERIALS AND METHODS

Study search strategy

A comprehensive search of databases, including Cochrane Library, Embase and PubMed, was conducted from the inception of each database to June 2013. The search was restricted to published English articles. Computer searches used combinations of medical subject headings or other keywords (i.e., statin, 3-hydroxy-methylglutaryl-CoA reductase, lovastatin, pravastatin, simvastatin, atorvastatin, fluvastatin, \(...\)
rosvastatin, impotence, erectile dysfunction, penile erection, endothelial dysfunction, male and human). We tried to contact all corresponding authors when data were found to be missing.

Identification of articles and data extractions

After the studies were reviewed, it was noted that none of the previously performed meta-analyses of RCTs reported statins as a treatment for ED. With 629 articles identified, seven studies were retrieved that were RCTs.17–22 (Figure 1). The International Index of Erectile Function (IIEF) is a validated and widely used multidimensional, self-report instrument for the evaluation of male sexual function.24 The full version of the IIEF consists of 15 questions that measure several domains of male sexual function, including erectile function, orgasmic function, sexual desire, intercourse satisfaction and overall satisfaction. Two specific segments of the full IIEF are used to measure erectile function, namely an abridged five-item version (IIEF-5; questions 2, 4, 5, 7 and 15) (Table 1) and the ED domain (questions 1–5 and 15). The inclusion criterion for ED was defined as IIEF-5 ≤ 21 or EF domain score <25. The study inclusion criterion was a RCT design of patients diagnosed ED. Included studies compared treatment with statins against a control (placebo or no treatment). Our primary outcome measures were IIEF-5 scores and secondary outcomes were lipid parameters, including total cholesterol, HDL cholesterol, LDL cholesterol and triglycerides (TGs). Characteristics and outcome variables in individual RCTs are listed using standard forms.

Quality assessment of included studies

The articles were retrieved and assessed for inclusion according to the above criteria by two independent researchers. Dispute between the investigators over inclusion of a study was resolved by a discussion. The articles were retrieved and assessed for inclusion according to the above criteria by two independent researchers. Dispute between the investigators over inclusion of a study was resolved by a discussion.

RESULTS

Study characteristics

Our systematic review included a total of 586 patients, with a dropout rate ranging from 0 to 23.4%. The mean participant age was 55.5–62.7 years. The primary findings of five studies was an improvement of erectile function after statins administration,17–21 whereas, the other two studies had no significant difference between the statins and the control groups.22,23 The methods used to assess erectile function was IIEF-5 in five trials,17–19,22,23 and ED domain score in two trials.20,21 The ED domain score could not be integrated in the meta-analysis because one study did not provide the standard deviation.20 Hence, only the five studies applying IIEF-5 scores to evaluate erectile function were included in the meta-analysis.17–19,22,23 We did not perform a test for funnel plot asymmetry because only five studies were included in the meta-analysis.17–19,22,23 This small number of studies rendered the power of the tests too low to distinguish chance from real asymmetry.

The statin used was atorvastatin in five trials,17–21 and simvastatin in the other two trials.22,23 Among these studies, six were placebo-controlled.17–19,21,23 The 7th study compared atorvastatin with a control group in which no treatment was performed.20 Four trials investigated patients with an inadequate response to sildenafil, which is commonly used as one type of PDE5Is.17–19 Of these four studies including patients with no response to sildenafil, three studies allowed the patients to continue proper usage of sildenafil (100 mg) throughout the trials.17,18,21 However, the other three studies researched eligible patients with untreated ED.20,22,23 As shown in Table 2, the trial duration also differed among all the studies in our meta-analysis. One study included two phases of trials, with an additional intake of vardenafil for 4 weeks after the initial 6 months.

Data synthesis and data analysis

Meta-analyses were performed for the primary and secondary outcomes. Review Manager 5.2 software (The Cochrane Collaboration, Oxford, UK) statistical package was used to generate statistical values. Mean differences (MDs) were calculated for continuous variables and a random effects model was applied because of the limited number of studies. Statistical heterogeneity was expressed as the I² index as described by Higgins and colleagues. P < 0.05 and I² < 50% were considered statistically significant. The confidence intervals were established at 95%.

Table 1: The abridged five-item version of the International Index of Erectile Function

| Question | Description | Response options |
|----------|-------------|------------------|
| 2 | When you had erection with sexual stimulation, how often were your erections hard enough for penetration? | 0=did not attempt intercourse, 1=almost never/never, 2=a few times (much less than half the time), 3=sometimes (about half the time), 4=most times (much more than half the time), 5=almost always/always |
| 4 | During sexual intercourse, how often were you able to maintain your erection after you had penetrated (entered) your partner? |
| 5 | During sexual intercourse, how difficult was it to maintain your erection to the completion of intercourse? |
| 7 | When you attempted sexual intercourse, how often was it satisfactory for you? |
| 15 | How do you rate your confidence that you could get and keep an erection? |

The response options for all questions are as follows:

Table 2: Characteristics of studies included in the meta-analysis

| Study | Statin | Duration | Response to sildenafil | Placebo-controlled | Additional treatment |
|-------|--------|----------|------------------------|-------------------|---------------------|

Figure 1: Process of study selection. ED: erectile dysfunction; RCT: randomized controlled trial.
of daily simvastatin or placebo.21 Hence, the second phase of it was excluded for the withdrawal of simvastatin in the last 4 weeks.

**RCTs with placebo arm and statins efficacy**

We identified five RCTs with a total of 351 patients who assessed the efficacy of statins using IIEF-5 scores (Table 3). Atorvastatin was investigated in three trials,22–24 and simvastatin was investigated in two trials.25,26 The IIEF-5 scores after treatment were 173 for statins and 176 for placebo, and the random-effect model MD was 3.27 (95% confidence interval CI) 1.51, 5.02; P < 0.01) (Figure 2). Therefore, our results indicate that statins were associated with a significant improvement in erectile function.

The lipid profile analyses from the five studies included in the meta-analysis of IIEF-5 scores are listed in Table 4. Four meta-analyses of lipid parameters regarding total cholesterol, HDL cholesterol, LDL cholesterol and TGs were performed. In our quantitative analysis, statins were associated with a significant decrease in total cholesterol (MD: –1.08; 95% CI: –1.68 to –0.48; P < 0.01) (Figure 3), LDL cholesterol (MD: –1.43; 95% CI: –2.07 to –0.79; P < 0.01) (Figure 4), TG (MD: –0.55; 95% CI: –0.61 to –0.48; P < 0.01) (Figure 5), and a significant increase in HDL cholesterol (MD: 0.24; 95% CI: 0.13 to 0.35; P < 0.01) (Figure 6).

Our pooled estimates from these studies had obvious heterogeneity in the IIEF-5 scores and lipid profiles. We tried to explain the heterogeneity by performing subgroup analyses involving trial duration, types of statins, additional PDE5Is regimens and responsiveness to PDE5Is. However, the I² test in these analyses remained to be over 50%, indicating that the heterogeneity could not be explicitly explained by these confounding factors.

**Other trials**

Two studies were not included in the quantitative analysis described above. One was a double-blind, placebo-controlled trial,21 and the other was a single-blind, no treatment controlled trial.20 Herrmann et al. reported an improvement in ED score with atorvastatin compared to placebo (Table 3).

### Table 3: IIEF-5 scores of clinical trials before and after treatment

| Source               | Pretreatment | Posttreatment |
|----------------------|--------------|---------------|
| Statins              | Control      | Statins       | Control      |
| Bank et al. 2006     | 11.1 (1.5)   | 10.2 (1.6)    | 16.7 (2.0)   | 11.3 (2.1)   |
| Dadkhah et al. 2010  | 10.4 (3.3)   | 10.1 (2.9)    | 13.9 (3.7)   | 10.5 (3.3)   |
| El-sisi et al. 2013  | 11.85 (2.36) | 13.15 (2.34)  | 18.15 (1.69) | 13.4 (1.79)  |
| Herrmann et al. 2006 | 12.7 (6.6)   | 10.7 (7.8)    | 15.6 (7.0)   | 15.0 (8.7)   |
| Mastair et al. 2011  | 13.0 (5.1)   | 14.1 (4.49)   | 14.02 (7.14) | 14.39 (6.94) |

### Table 2: Characteristics of the randomized clinical studies included in the systematic review

| Study               | Country | Trial duration | Inclusion criteria | Intervention between groups (number of patients) | Additional PDE5I regimen | Dropout rate | Quality score (failing items) |
|---------------------|---------|----------------|-------------------|-------------------------------------------------|--------------------------|--------------|-------------------------------|
| Bank et al. 2006    | USA     | 3 months       | IIEF-5 score < 21 | Atorvastatin 40 mg (n=12) Quinapril 10 mg (n=10) Placebo (n=13) | Sildenafil 100 mg         | 0            | 5 (A, D, E)                   |
| Dadkhah et al. 2010 | Iran    | 12 weeks       | IIEF-5 score < 21 | Atorvastatin 40 mg (n=59) Placebo (n=59)         | Sildenafil 100 mg         | 9.9%         | 8                             |
| El-sisi et al. 2013 | Egypt   | 6 weeks        | IIEF-5 scores > 21| Atorvastatin 80 mg (n=20) Vitamin E 400 IU (n=20) Placebo (n=20) | NA                       | NA           | 6 (A, E)                      |
| Herrmann et al. 2006| USA     | 12 weeks       | ED domain score < 16 | Atorvastatin 80 mg (n=8) Placebo (n=8) | Sildenafil 100 mg         | 0            | 7 (D)                         |
| Mastair et al. 2011 | Brazil  | 6 months       | IIEF-5 score < 21 | Simvastatin 20 mg (n=20) Placebo (n=21)       | Vardenafil 10 mg in phase 2 trial | 4.7%         | 6 (D, E)                      |
| Gokce et al. 2012   | Turkey  | 3 months       | ED domain score < 16 | Atorvastatin 10 mg (n=41) Tadalafil 20 mg (n=40) No treatment (n=39) | NA                       | NA           | 10.4%                         | 5 (C, D, E) |
| Trivedi et al. 2012 | UK      | 6 months       | IIEF-5 score < 21 | Simvastatin 40 mg (n=64) Placebo (n=64) | NA                       | 24.3%        | 7 (D)                         |

ED: erectile dysfunction; IIEF: international index of erectile function; s.d: standard deviation. All data are reported as mean (s.d.); IIEF-5 scores

**Figure 2:** Pooled estimate of IIEF-5 scores between statins and control groups. CI: confidence interval; IIEF: international index of erectile function; IV: intravenous; s.d.: standard deviation.
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Figure 3: Pooled estimate of total cholesterol levels between statins and control group. CI: confidence interval; IV: intravenous; s.d.: standard deviation.

Figure 4: Pooled estimate of LDL cholesterol levels between statins and control groups. CI: confidence interval; IV: intravenous; LDL: low-density lipoprotein; s.d.: standard deviation.

Figure 5: Pooled estimate of triglycerides levels between statins and control groups. CI: confidence interval; IV: intravenous; s.d.: standard deviation.

Figure 6: Pooled estimate of HDL cholesterol levels between statins and control groups. CI: confidence interval; HDL: high-density lipoprotein; IV: intravenous; s.d.: standard deviation.

with placebo. Statin intake decreased the mean LDL cholesterol by 43% and an obvious improvement of sildenafil efficacy was observed in the domain score increase of 7.8; whereas, no significant change was found in men taking placebo. The other study demonstrated that atorvastatin alone improved erectile function with approximately a seven-point increase in ED domain scores compared with not using any medication. The effect of statin treatment is more obvious in patients with elevated LDL cholesterol levels. Although patients treated with atorvastatin reached normal serum lipid levels at the end of the trial, all patients with elevated LDL cholesterol in the statins group had normal nocturnal penile tumescence test results, while only 34% of ED patients with normal LDL levels treated with atorvastatin had normal nocturnal penile tumescence test results.

DISCUSSION

To our knowledge, this is the first systematic review and meta-analysis of RCTs investigating the effects of statins for the treatment of ED. The seven RCTs in our systematic review, which were published between 2006 and 2013, studied two statins, atorvastatin and simvastatin. In our meta-analysis, we identified five placebo-controlled RCTs that...
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Table 4: Variable outcomes of lipid parameters before and after treatment

| Lipid Profile | Bank et al.27 2006 | Dadkhah et al.28 2010 | El-sisi et al.29 2013 | Mastalir et al.30 2011 | Trivedi et al.31 2012 |
|---------------|-----------------|------------------|------------------|------------------|------------------|
| Total cholesterol | 4.83 (0.18)/5 (0.2) | 4.13 (0.86)/4.08 (0.8) | NA | 5.7 (1.45)/5.02 (1.11) | NA |
| Pretreatment | 3.26 (0.16)/4.8 (0.18) | 3.32 (0.32)/4.15 (0.84) | NA | 4.45 (1.29)/5.15 (1.31) | NA |
| Posttreatment | 1.22 (0.05)/1.03 (0.05) | 1.17 (0.22)/1.22 (0.22) | NA | 1.25 (0.23)/1.19 (0.31) | NA |
| HDL cholesterol | 1.24 (0.08)/1 (0.05) | 1.59 (0.14)/1.25 (0.22) | NA | 1.33 (0.22)/1.27 (0.4) | NA |
| Pretreatment | 3.0 (0.18)/3.28 (0.16) | 3.57 (0.55)/3.45 (0.84) | NA | 3.64 (1.18)/3.03 (0.81) | NA |
| Posttreatment | 1.66 (0.16)/3.1 (0.18) | 1.88 (0.18)/3.5 (0.84) | NA | 2.59 (1.14)/3.06 (0.82) | NA |
| TG | 1.34 (0.19)/1.38 (0.19) | 1.7 (0.37)/1.7 (0.34) | NA | 3.5 (0.73)/3.5 (0.93) | NA |
| Pretreatment | 0.81 (0.07)/1.38 (0.14) | 1.18 (0.19)/1.7 (0.35) | NA | 2.6 (1.03)/3.4 (0.95) | NA |

HDL: high-density lipoprotein; LDL: low-density lipoprotein; NA: not applicable; TG: triglyceride. All data are reported as mean (s.d.) and the unit is millimole per liter.

evaluated these two statins for the treatment of patients with ED. The outcome measure was the IIEF-5 score (normal erectile function, 22–25; mild ED, 17–21; mild to moderate ED, 12–16; moderate ED, 8–11; and severe ED <7). The pooled results across all five trials demonstrated a significant increase in IIEF-5 scores by 3.27 points and an overall improvement of lipid profiles in patients treated with statins compared with placebo controls. The minimal clinically important difference in the erectile function domain is accepted to be a four-point improvement in the IIEF-5 score.27,28 Nevertheless, minimal clinically important difference varies according to the baseline ED severity (mild ED, 2.0; moderate ED, 5.0; and severe ED, 7.0 points improvement in IIEF-5 score).29 Therefore, our meta-analysis result of an improvement of 3.27 points on the IIEF-5 score might not demonstrate clinically important differences for moderate and severe ED. However, the MD of 3.27 in IIEF-5 score improvement is consistent with significant improvement in mild ED, but may indicate less improvement for patients with more advanced ED.

Our meta-analysis has the following limitations: (i) PDE5I regimens varied among studies, which may lead to an overrated assessment of statins on the improvement of ED. Sildenafil was only administered continuously in patients whose IIEF-5 scores were still under 21 after sildenafil therapy.27,28 Nevertheless, it may confound our evaluation because the application of statins may boost PDE5I efficacy through an increase in the bioavailability of NO, which results in functional synergism with PDE5Is. (ii) The IIEF-5 scores integrated in the meta-analysis were subjective self-evaluations, and no physiologic or laboratory indicators of ED were provided. (iii) Other possible limitations could be the heterogeneity of treatment duration (6 weeks to 6 months) and the use of two different statins.

A recent experiment on statins demonstrated that the enhanced RhoA/Rho-kinase signaling pathway played a crucial role in ED and was associated with a declined response to PDE5Is.29 The downregulation of penile Rho-kinase signaling by intake of statins restored erection through the reduction of geranyl pyrophosphate, an essential step in RhoA activation, in rat models of ED.30,31 Hence, the mechanism of statin therapy for ED may be through the normalization of the Rho-kinase signaling pathway.

Another potential mechanism for statin efficacy on erectile function is the modification of endothelial function. A previous study showed that treatment with atorvastatin increased plasma NO concentrations,32 which was consistent with the outcomes in the most recent trial in our review.18 This manifestation could be explained by the upregulation of endothelial NO synthase (eNOS) expression.33 Therefore, statins may rescue PDE5I nonresponders through an increase in the production and concentration of NO. Through the effects of statins, the cyclic guanosine monophosphate levels improved, and smooth muscle relaxation was restored through increased arterial blood flow, leading to improved erectile function. Furthermore, we found that the efficacy of statins for the treatment of ED was associated with modulated lipid levels. Accordingly, larger, well-designed, RCTs should investigate the correlation between dyslipidemia correction and erectile function.

Although statins exert potential beneficial effects on ED through the aforementioned mechanisms, they have also been reported to have a negative influence on erectile function. In a prospective observational study, 93 male patients starting on lipid-lowering therapy were recruited from the cardiology and lipid clinics and 82 completed the IIEF-5 questionnaire. Before statin administration, the median IIEF-5 score was 21 and 57% had erectile function impairment. After statin administration, the median IIEF-5 score decreased significantly to 6.5 and 22% of these patients suffered new onset of ED. Before statin therapy, no correlation was observed between IIEF-5 score and any individual cardiovascular risk factor. After 6 months of statin administration, lower IIEF scores correlated significantly with age, diabetes and weakly with cigarette smoking.34 Another retrospective study examined the association between treated hyperlipidemia and ED in 1899 men, using the IIEF-5 scores to assess erectile function.35 In multivariate models stratified by age and the presence of diabetes and/or cardiovascular disease, no association between lipid-lowering drug treatment and ED was observed, except among younger men (<55 years) who had diabetes and/or cardiovascular disease. However, a recent meta-analysis of RCTs assessed the effects of lifestyle interventions and pharmacotherapy for cardiovascular risk factors, including statins, on the severity of ED. It demonstrated that cardiovascular disease-related interventions and pharmacotherapy were associated with significant improvement in erectile function.29 Therefore, it appears that ED following statin therapy is more likely in patients with severe endothelial dysfunction owing to established cardiovascular risk factors including age, smoking and diabetes. Treatment for these cardiovascular risk factors could improve erectile function in patients with ED.

Previous systematic reviews containing case reports, review articles and information from clinical trials suggested that statins may cause ED.16,37 A recent study by Corona et al.35 evaluated the association between statin therapy and hormonal parameters in a large number of patients with ED. They found that both total and free testosterone levels were significantly lower in patients taking statins compared with those not using lipid-lowering drugs. The use of statins also correlated with a reduced testicular volume and a higher prevalence.
of hypogonadism-related symptoms and signs, as assessed by higher ANDROTEST scores. Based on these outcomes, they concluded that statin therapy might induce an overt primary hypogonadism and may be considered as a risk factor for ED. This negative effect of statins on testosterone levels were attributed to the suppression of presqualenic steroid synthesis within the testis by inhibiting mevalonate formation, thus interfering with testosterone production. Therefore, it is necessary to evaluate the effect of statins on hormone metabolism in more RCTs with high-quality and large sample sizes.

CONCLUSIONS
Theoretically, statins seem to be a double-edged therapy for patients with ED. Although our study revealed positive consequences of these lipid-lowering drugs on erectile function, especially for patients with no response to PDE5Is, the study was limited in the number of RCTs included and high heterogeneity existed in the meta-analysis. Hence, additional large, well-designed RCTs with high-quality are needed to explore the general effects of statins for the treatment of ED.

AUTHOR CONTRIBUTIONS
KJW provided the original ideas and introduced the writing of this article. XC and YT researched and assessed the literature. TW and CXC extracted the data from each article and SYB drew the tables and figures of the review. XC also wrote the manuscript. All authors read and approved the final manuscript.

COMPETING INTERESTS
The authors declare no competing interests.

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