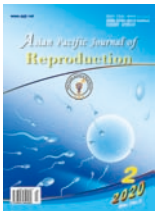

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Erectile dysfunction and statins: The assorted view of preponderance

Hayder M. Al-kuraishy✉, Ali I. Al-Gareeb, Thabat J. Al-Maiahy

Department of Pharmacology, Toxicology and Medicine, College of Medicine, Almustansiriya University, Baghdad, Iraq

ABSTRACT

Objective: To explore the association between statin therapy and the risk of erectile dysfunction by literature review.

Methods: We conducted diversities of search strategies including electronic database searches of MEDLINE, Scopus, Pubmed and Web of Science using MeSH terms, keywords and title words during the search. Reference lists of identified and public articles were reviewed. In addition, only English articles were considered and case reports were not concerned in the review. The key features of recognized applicable search studies were considered and the conclusions were summarized in a narrative review.

Results: Different studies gave a consensus that erectile dysfunction was regarded as an early sign of silent cardiovascular disorder and hidden atherosclerosis. Different studies reported that statins might induce erectile dysfunction through induction of peripheral neuropathy, cognitive deficits, and reduction of circulating testosterone. However, most of recent studies illustrated that statins led to a significant improvement in erectile function and sexual health in men with age over forty years. Atorvastatin advanced endothelial nitric oxide concentrations through activation and upregulation of endothelial nitric oxide synthase and rescued phosphodiesterase-5 inhibitors non-responders since nitric oxide and cyclic guanosine monophosphate increased penile blood flow and improved erectile function.

Conclusions: According to the assorted view of preponderance, statins improved erectile dysfunction is more dominant than statins induced erectile dysfunction. Therefore, statins regardless of its property improve erectile dysfunction through amelioration of penile endothelial dysfunction, and penile neuronal reflexes that are inter-related during sexual excitation and penile erection.

KEYWORDS: Erectile dysfunction; Statins; Testosterone

1. Introduction

Erectile dysfunction is defined as a failure or inability to maintain penile erection for suitable pleasure during sexual intercourse[1]. It affects more than 150 million worldwide, which may be doubled by 2025. Erectile dysfunction is often linked with different cardio-metabolic disorders such as type 2 diabetes mellitus (T2DM), hypertension, ischemic heart disease and hypogonadism. It has been reported that erectile dysfunction is associated with ischemic heart disease since erectile dysfunction proceeds and heralds the onset of ischemic heart disease[2].

The prevalence of erectile dysfunction is surprisingly high, affecting 40% of the population. This prevalence is affected by population characteristics and methods used for the assessment of erectile dysfunction. Since single question may be used for assessment of erectile function while other trials used more sophisticated and validated questionnaires[3]. Although erectile dysfunction affects sexual and mental health, the rates of consultation for erectile dysfunction remain low and not all patients respond to the phosphodiesterase inhibitors[4].

Vasculogenic erectile dysfunction is related to different risk factors including T2DM, hypertension, smoking and dyslipidemia. Moreover, the presence of erectile dysfunction indicates the underling cardiovascular disorders and complications; thus, assessment of erectile function should be part of the evaluation of hypertensive patients mainly those over 50 years[5]. Medical literature and different epidemiological trials illustrated that age is strongly linked to erectile dysfunction. Also, modifiable risk factors such as smoking, sedentary life and dyslipidemia are regarded as second main causes of erectile dysfunction which could be reversed[6].

✉To whom correspondance may be addressed. E-mail: Hayderm36@Yahoo.Com

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Dyslipidemia is strongly associated with erectile dysfunction since every mmol/L increase in serum cholesterol is associated with a 32% increase in erectile dysfunction. Therefore, hyperlipidemia is correlated with erectile dysfunction due to the development of endothelial dysfunction through the impairment of nitric oxide (NO) synthesis and release[7].

Statins that are 3-hydroxy-3-methylglutaryl-coenzyme A (HMG-CoA) reductase inhibitor are the first-line in the treatment of hyperlipidemia and major cardiac events regardless of lipid profile due to pleiotropic properties. Statins improve endothelial function prior to the improvement of total cholesterol[8,9]. 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. However, the relationship between statins and male sexual function is not clear. A number of studies have hypothesized that statins were associated with erectile dysfunction; whereas, some others advocated that statins improve erectile dysfunction[10]. Therefore, the objective of the present study was to elucidate the potential effect of statins therapy on the erectile dysfunction regarding the assorted view of preponderance.

2. Search approach and strategy

A diversity of search strategies was taken on and assumed which included electronic database searches of MEDLINE, Scopus, Pubmed and Web of Science using MeSH terms, keywords and title words during the search. No time limits in this study, so we can know the previous and recent views, regarding the potential effects of statins on the human erectile dysfunction. The terms used for these searches were as follows: [statins or cholesterol-lowering agent] AND [erectile dysfunction or impotence or failure of erection or penile erection or premature ejaculation] AND [HMG-CoA OR HMG-CoA antagonists or HMG-CoA inhibitors] AND [male erectile dysfunction or dyslipidemia induced-impotence or diabetic induced-impotence or autonomic neuropathy or insulin resistance]. Reference lists of identified and public articles were reviewed. In addition, only English articles were considered and case reports were not concerned in the review (Figure 1). The key features of recognized applicable search studies were considered and the conclusions were summarized in a narrative review.

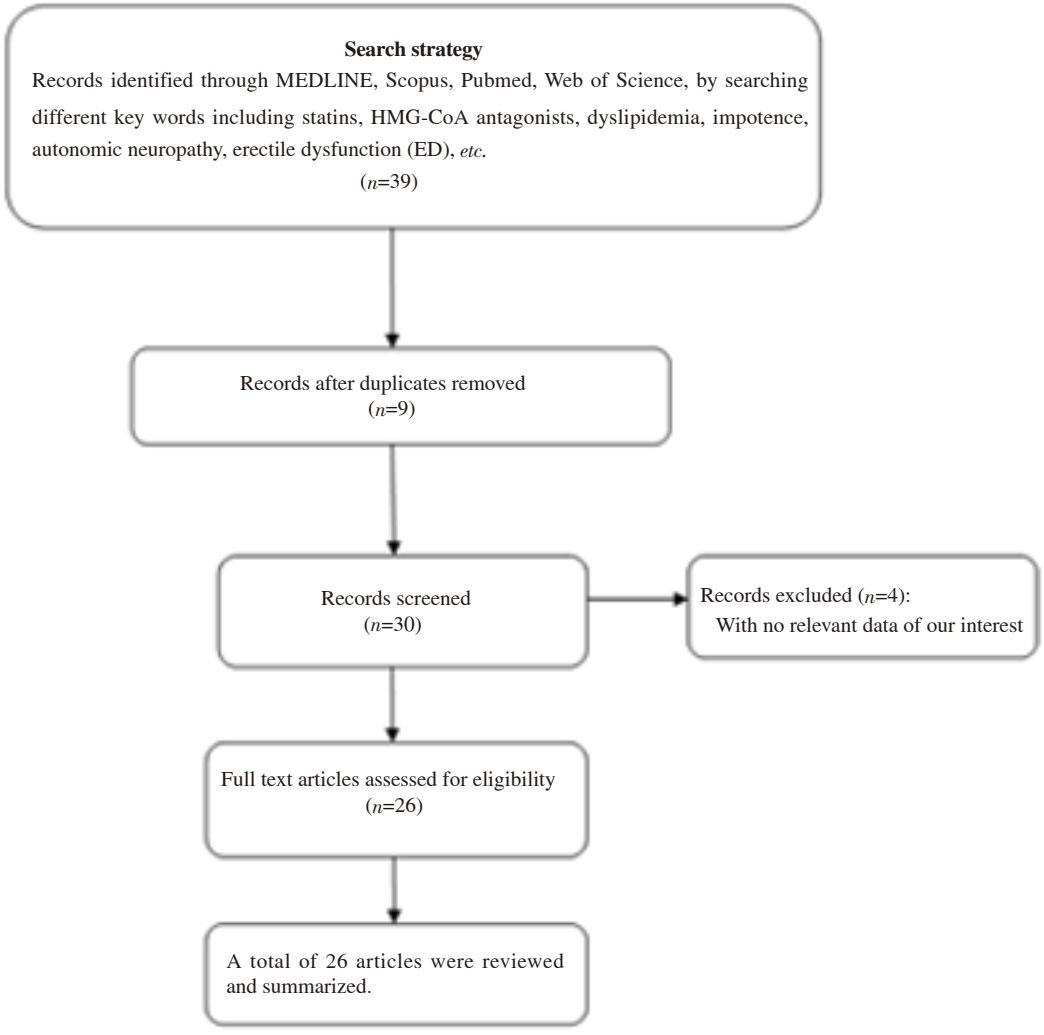

Figure 1. Consort flow-diagram of the present study.

3. Statins induced-erectile dysfunction

Normally, an international index of erectile function (IIEF) is used for the estimation of male erectile function. It is composed of five scores: normal IIEF (22-25), mild erectile dysfunction (17-21), moderate erectile dysfunction (12-16), severe erectile dysfunction (8-11) and very severe (less than 7)[11]. The prevalence of erectile dysfunction depends on the studied population. In some studies, the abridged 5-item version of IIEF-5 addresses the relevant domains of male sexual function (*i.e.*, erectile function, orgasmic function, sexual desire, intercourse satisfaction, and overall satisfaction). The questionnaire is self-administered in clinical settings[12]. Moreover, erectile dysfunction is not screened on a regular basis at cardiology departments in such a high-risk population. In the younger cohort of acute myocardial infarction patients, only 2 out of 25 patients informed their cardiologists about their erectile dysfunction and nobody diagnosed the older patients with erectile dysfunction. As well, erectile dysfunction with reported data is highly prevalent in the group of young acute myocardial infarction survivors. The IIEF-5 questionnaire seems to be a very useful diagnostic tool in the cardiology practice in order to not neglect such an important symptom. There is no direct correlation between erectile dysfunction and type of coronary artery disease. Patients with a single-vessel disease are suffering from erectile dysfunction as well as those with multiple coronary diseases[13].

Different observational studies confirmed that statin therapy leads to significant erectile dysfunction. Solomon *et al* illustrated that statin therapy decreases IIEF from 21.0 to 6.5 and within six months of statin therapy; IIEF was negatively correlated with age and statins duration[14]. Likewise, Hall *et al* demonstrated an association between statin therapy and erectile dysfunction only in male patients with age less than 55 years in a study involved 1 899 patients with cardiovascular complications with or without T2DM[15]. No obvious characteristics could be identified in patients developing erectile dysfunction. Spontaneous reports are often compounded with imperfect clinical formation. The elapsed time of drug exposure to the progress of erectile dysfunction ranged from 1 day to several years, which concurs with other literature. Since the pathways for their actions and the structures of the various types of statins can decrease the cholesterol levels, testosterone synthesis may be affected. This mechanism might make the association between erectile dysfunction and types of statins clear since libido is closely related to serum testosterone levels[16]. Besides, malfunctions of low-density lipoprotein receptor affect *de novo* synthesis of cholesterol, therefore, statins and/or hyperlipidemia are found to be risk factors in the initiation of erectile dysfunction[17].

3.1. Statins induced-hormonal changes

Statins therapy leads to a significant reduction in total and free testosterone that is linked with the development of erectile dysfunction. This reduction is due to notable inhibition of testicular steroidogenesis by statins. As well, long-term statin therapy causes testicular atrophy and hypogonadism which ultimately lead to erectile dysfunction[18]. Previously, Stanworth *et al* promulgated that statins therapy reduced total testosterone but not free or bioavailable one which is the active form and correlated with erectile and gonadal functions[19]. Statins inhibit testosterone production only at higher doses, as well as, atorvastatin but not simvastatin reduced total testosterone due to higher potency and duration of atorvastatin. Also, atorvastatin suppresses the hepatic production of sex hormone-binding globulin causing a significant decline in the circulating total testosterone[20].

Amid different studies concerning the effect of statins on testosterone levels and erectile function, the study of Bolat *et al* disclosed a great link between statins and erectile dysfunction through the reduction of testosterone levels. It has been shown that disruption of cholesterol biosynthesis by statins directly or indirectly affects sexual function and erectile function. Short-term uses of atorvastatin in the management of cardiovascular complications cause a significant reduction in penile intra-cavernosal pressure which is important for a full erection. As well, this short-term effect also leads to a moderate reduction in total testosterone[21]. These effects contribute to erectile dysfunction; thus in consideration of statins therapy, patients with ischemic heart disease should regard the risk of erectile dysfunction. Moreover, long-term statin therapy leads to the accumulation of elastic and collagen fiber in the penile tissue that may affect the intra-cavernosal pressure. It has been reported that elastic fibers undergo degradation and fragmentation with increasing age and severity of the disease accelerating cardiovascular mortality parallel to collagen accumulation[22].

In reality, testosterone plays an essential role in the regulation of endothelial and vascular functions. Testosterone prevents vascular remodeling through inhibition of vascular inflammation and oxidative stress. Physiological testosterone leads to vasodilatation through activation of NO production and by increasing endothelial nitric oxide synthase (eNOS) expression, these effects are partly mediated by the endothelial androgen receptors[23]. Therefore, low testosterone due to different reasons leads to endothelial dysfunction and induction of oxidative stress. So, testosterone replacement therapy inhibits oxidative stress, vascular inflammations and intima-media thickness in men patients with ischemic heart disease[24]. Therefore, testosterone is very important for erectile function since it increases neuronal activations toward

the penis, stimulates the releases of oxytocin and dopamine from the brain medial pre-optic area (which are involved in the sexual arousal), and preservation of penile blood flow through activation of NO synthase[25]. Therefore, theoretically, a reduction of testosterone levels by statin therapy leads to penile endothelial dysfunction and decreases the responsiveness during sexual excitation which eventually causes erectile dysfunction. Although it was statistically non-significant, hypoandrogenemia may be a reasonable cause. Rearrangement of the two different types of fibers in the penis may be associated with a decrease in the intra-cavernosal 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[26].

3.2. Statins induced-neuropathy

Drug induced-peripheral neuropathy is one of the leading causes after diabetes mellitus. This type is of an enormous degree in early diagnosis given that discontinuing the induced drugs leads to significant improvement[27]. Statins cause distal axonal damage, degeneration of myelin sheath and nerve root deterioration. Nevertheless, the potential role of statins in the induction of peripheral neuropathy has not been verified since most statins induced-peripheral neuropathy was reported as a case report[28]. The main mechanism of statins induced-peripheral neuropathy is linked to the decrease of cholesterol which is essential for myelin sheath of peripheral neurons[29]. In addition, statin therapy leads to a significant reduction of coenzyme Q10 which causes impairment of neuronal energy. Coenzyme Q10 is an endogenous antioxidant essential for mitochondrial transport chain found in all cell membranes which participates in the regulation and prevention of lipid and protein peroxidations[30]. Moreover, long-term therapy with statins leads to autonomic neuropathy due to ganglionopathy as statins may cause degeneration of sensory and autonomic ganglions[31]. It is well known that erectile dysfunction is a complication of autonomic and peripheral neuropathies caused by T2DM or induced by drugs. Therefore, statins induced-peripheral neuropathy may be a causative factor for erectile dysfunction which can be attenuated by the administration of coenzyme Q10[32]. It has been shown that one case for every 2 200 statin users developed large fibre neuropathy, which might be due to neuronal mitochondrial dysfunction caused by the inhibition of ubiquinone and/or depletion of neuronal membrane cholesterol[33]. The association between small fibre neuropathy and statin therapy is inadequate. Until that time, Lo *et al* confirmed the association between statins and painful neuropathy[34].

In contrast, the Hernandez-Ojeda's study reported significant ameliorative effects of statins on autonomic neuropathy[35]. Nevertheless, the study of Wallach-Klidemoes *et al* reported a dose-independent effect of statins in the induction neuropathy, so there is no noticeable dose-response pattern between statins and risk of neuropathy which may give evidence for the negative association between statins and risk of neuropathy[36]. Therefore, the risk of statins induced-neuropathy is typically developed after long-term therapy and therefore statins-induced neuropathy is cumulatively dose-dependent[37]. Moreover, *in vitro* previous studies have shown that peripheral and autonomic neurons are less susceptible to the toxic effect of statins compared to the spinal neurons suggesting a different mechanism of neuronal toxicity. Hydrophilic statins, like pravastatin and rosuvastatin, demonstrated less peripheral neuronal damage compared with lipophilic statins, like simvastatin and rosuvastatin, due to the difference in the compartmental pharmacokinetics[38,39]. For that reason, the risk of statins induced-erectile dysfunction through induction of neuropathy is unlikely as it is affected by dose, duration and type of statins which are variable among statins user patients.

3.3. Statins induced-cognitive impairment

Short-term statin therapy is associated with different central adverse effects like cognitive impairment, depression and fatigue[40]. Evans *et al* illustrated a significant association between cognitive deficit and statin therapy[41]. Regardless of cognitive deficit, it causes significant erectile dysfunction due to the overt reduction in cerebral glutaminergic neurotransmission. Therefore, phosphodiesterase-5 (PDE5) inhibitors improve cognitive and erectile functions through inhibition of central PDE5 enzyme and potentiation of cerebral glutaminergic neurotransmission[42].

On the other hand, different studies illustrated that statin therapy improves or not affect cognitive functions[43]. Alternatively, there is evidence of a link between inflammation and depression. Several studies refer to elevated levels of pro-inflammatory cytokines and C-reactive protein in the depression and cognitive deficit[44]. Accordingly, drugs with anti-inflammatory properties, such as statins, could be useful in the treatment of depression and cognitive dysfunctions[45]. Undoubtedly, evidence from observational studies suggests that statins are associated with improvement in depressive mood and in quality of life[46]. Thus, the role of statins induced-cognitive impairment is minimally implicated in the pathogenesis of erectile dysfunction as it is not proofed sufficiently and controversy about it still presents.

4. Statins improved-erectile dysfunction

Different studies gave a consensus that erectile dysfunction is regarded as an early sign of silent cardiovascular disorder and

hidden atherosclerosis. Therefore, amelioration of cardiovascular complications by statins leads to significant improvements of erectile function and sexual health in men with age over forty years[47]. It has been reported that erectile dysfunction is a consequence of endothelial dysfunction since injured endothelium causes a significant reduction of NO which is necessary for corporal vasodilation during sexual excitation and erection. Erectile dysfunction leads to failure in response to PDE5 inhibitors[48]. Statins significantly reverse endothelial dysfunction through inhibition toxic effect of low-density lipoprotein on the vascular endothelium which consequently improves erectile dysfunction. As well, high cholesterol and low high-density lipoprotein is linked with the development of erectile dysfunction[49].

Cavernosal endothelial cells have specific and unique characteristics: they expressed high levels of mRNA for collagen type Ⅳ which was involved in distensibility of sinusoidal spaces and rigid erection. Likewise, cavernosal endothelial cells have specific tight junctions which play a role in maintaining of intra-cavernosal pressure during erection[50]. T2DM and cardiovascular disorders lead to first alterations in the cavernosal endothelial tight junction before any pathological changes in the coronary and other vascular endothelial beds[51]. Therefore, the cavernosal endothelial dysfunction precedes vascular endothelial dysfunction; thus, statins ameliorates erectile dysfunction through prevention of cavernosal endothelial dysfunction before the full prone effect on the lipid profile[52].

Moreover, systemic review and meta-analysis studies confirmed that statins therapy in patients with dyslipidemia and cardiovascular disorders improve erectile function. This therapy increases the IIEF score by 3.27 points compared with the placebo effect; thus, it improves mild-moderate erectile dysfunction only[53]. The potential mechanisms of statins induced-improvement of erectile function are due to the down-regulation of penile RhoA/Rho-kinase pathway. Rho-kinase inhibits the regulatory subunit of myosin phosphatase within smooth muscle cells and maintains the contractile tone under the low-cytosolic calcium concentrations. Upregulated Rho-kinase activity has been reported in erectile dysfunction, so Rho-kinase inhibitors (Y-27632 and SAR 407899) have potent erectile effects and offer another therapeutic target for the treatment of erectile dysfunction. This pathway is associated with a decline in response to PDE5 inhibitors. As well, statins inhibit geranylpyrophosphate which is essential for activation of the RhoA/Rho-kinase pathway[54]. Moreover, atorvastatin inhibits diabetic induced-RhoA/Rho-kinase pathway activation and prevents RhoA membrane translocation in animal model studies[55,56]. Besides, statins significantly improve erectile dysfunction through enhancement of endothelial NO. Atorvastatin advances endothelial NO concentrations through activation and upregulation of eNOS synthase. Therefore, atorvastatin rescues PDE5 inhibitor non-responders since NO and cyclic guanosine monophosphate increase penile blood flow and improve erectile function[57].

As initially mentioned, in spite of the reduction of total testosterone by statins therapy, free testosterone does not affect the main active androgen which is engaged with erectile function. Recently, Hsieh and Huang's study confirmed that rosuvastatin therapy reduces free testosterone and free androgen index, but does not affect erectile function and sexual activity in patients with T2DM[58].

As previously mentioned, different reports and review studies showed that statins may lead to peripheral and autonomic neuropathy which *per se* causes erectile dysfunction. Zangiabadi *et al* illustrated that atorvastatin improves diabetic polyneuropathy within six months of treatment through amelioration of nerve electrophysiological variables[59]. Atorvastatin mainly improves the distal segment of peripheral neurons. The mechanisms of atorvastatin in amelioration of peripheral neuropathy include inhibition of oxidative stress induced-neuropathy, suppression of pro-inflammatory cytokines, restoring the activity of neuroprotective matrix metalloproteinase-7, and blocking neuronal peroxynitrite accumulation[60]. Moreover, statins prevent ischemia induced-neuronal death and preserve neuronal conductive velocity with significant protection of vasa neuronum[61,62]. Therefore, statins improve erectile dysfunction through the preservation of peripheral neurons as the erectile function is solely depending on intact peripheral and autonomic neurons[63].

It has been reported that cognitive deficits, depression and impaired vigilance are associated with erectile dysfunction[64]. Abbasi *et al* illustrated that both simvastatin and atorvastatin have potential antidepressant effects and improve cognitive deficits in patients with acute coronary syndrome[65]. The mechanisms of the antidepressant effect of statins are related to increase of limbic system tryptophan, reduction of brain oxidative stress and neuro-inflammations, improvement of cerebral blood flow, and prevention of neuronal ischemia[66]. Recent studies show that statins, regardless of its type, prevent and ameliorate erectile dysfunction in diabetes mellitus and following prostatic surgery[67,68].

Moreover, different recent studies illustrate that prolonged statins therapy improve erectile dysfunction-related quality of life. As well, statins augment the response to the aphrodiasic agents[69,70]. It has been reported that chronic inflammatory status may cause endothelial dysfunction and subsequent coronary and penile endothelial dysfunctions[71]. Prolonged statins therapy improves endothelial function through anti-inflammatory and anti-oxidant actions. Hereby, statins improve erectile dysfunction *via* amelioration of penile endothelial functions[72,73].

The 26 studies regarding statins improved/induced erectile dysfunction in the present review are summarized in Table 1.

Table 1. Statins and erectile dysfunction.

Author	Year of publication	Experiment content	Main conclusion
Solomon *et al*[14]	2006	Diabetic patients	Erectile dysfunction following statin therapy is more likely in patients with severe endothelial dysfunction
Hall *et al*[15]	2009	Patients with dyslipidemia	Statins therapy may be associated with erectile dysfunction among some men
Akdoğan *et al*[17]	2018	Rats fed a high-cholesterol diet	Statins therapy induces erectile dysfunction through reduction of total testosterone
Corona *et al*[18]	2010	Male with erectile dysfunction with statins therapy	Statin therapy might induce an overt primary hypogonadism through reduction of total and free testosterone
Stanworth *et al*[19]	2009	Diabetic patients with statins therapy	Statin therapy might induce erectile dysfunction through reduction of total but not free testosterone
Ishola *et al*[20]	2017	Diabetic rats	Statin therapy induces erectile dysfunction through attenuation of testosterone action
Bolat *et al*[21]	2019	Normocholesterolemic rats	Statin therapy induces erectile dysfunction through reduction of testosterone and penile intracavernosal pressure
Nisahan *et al*[32]	2019	Diabetic patients with statins therapy	Both statin therapy and T2DM may increase risk of erectile dysfunction
Lo *et al*[34]	2003	Dyslipidemic patients on statins therapy	Statin therapy induces erectile dysfunction through induction of peripheral neuropathy
Evans *et al*[41]	2009	Dyslipidemic patients on statins therapy	Statin therapy induces erectile dysfunction through induction of fatigue and cognitive dysfunction
Katsiki *et al*[49]	2018	Human and animal studies	Statins therapy improves erectile dysfunction through amelioration of endothelial dysfunction
Wessells *et al*[50]	2009	Human with erectile dysfunction on statins therapy	Statins therapy improves erectile dysfunction through amelioration of cavernosal endothelial functions
Rosen *et al*[53]	2011	Dyslipidemic patients on statins therapy	Statins therapy improves erectile dysfunction through amelioration of endothelial dysfunction
Morelli *et al*[54]	2009	Experimental diabetic rats	Statins therapy ameliorates sildenafil-induced penile erections
Cai *et al*[55]	2019	Human with erectile dysfunction on statins therapy	Statins therapy ameliorates sildenafil-induced penile erections
Lasker *et al*[56]	2010	Human with erectile dysfunction on statins therapy	Statins therapy ameliorates sildenafil-induced penile erections
Zemankova *et al*[57]	2015	Human and animal studies	Statins therapy improves erectile dysfunction through amelioration of endothelial functions
Zangiabadi *et al*[59]	2012	Diabetic patients	Statins therapy improves erectile dysfunction through amelioration of diabetic polyneuropathy
Ali *et al*[60]	2011	Diabetic rats	Statins therapy improves diabetic induced-endothelial dysfunction
Camera *et al*[61]	2007	Diabetic patients	Statins therapy improves diabetic induced-endothelial dysfunction
Ding *et al*[67]	2020	Diabetic rats	Statins therapy improves diabetic induced-endothelial dysfunction and neuropathy
Koontz *et al*[68]	2019	Patients with prostatic cancer on radiotherapy	Statins therapy improves erectile dysfunction through amelioration of radiotherapy induced-endothelial dysfunction
Cassidy-Vu *et al*[69]	2018	Human with erectile dysfunction on statins therapy	Statins therapy ameliorates sildenafil-induced penile erections
Marcon *et al*[70]	2020	Human with erectile dysfunction on statins therapy	Statins therapy improves erectile dysfunction through amelioration of penile endothelial functions
Joseph *et al*[72]	2018	Dyslipidemic patients on statins therapy	Statins therapy does not affect male erectile dysfunction
La Vignera *et al*[73]	2018	Human and animal studies	Statins therapy improves erectile dysfunction

5. Conclusion

In this review, there are conflicting findings regarding the potential effect of statins therapy on the erectile dysfunction. Some studies implicate statins as a causative cause of erectile dysfunction, while most of studies report the beneficial effect of statins in prevention of erectile dysfunction. Therefore, this study concludes that statins, regardless of its property, improve erectile dysfunction through amelioration of penile endothelial dysfunction, penile neuronal reflexes and antidepressant effects which are interrelated during sexual excitation and penile erection. For these reasons, the assorted view of preponderance confirms that statins improve erectile dysfunction mainly through the enhancement of erectile endothelial functions.

Conflict of interest statement

The authors declare that there is no conflict of interest.

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Authors' contributions

All authors carried out the conception, wrote, read and approved the final manuscript.

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