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REVIEW ARTICLE

# Reversion of penile fibrosis: Current information and a new horizon

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**KEYWORDS**

Fibrosis;
Corpora cavernosa;
Tunica albuginea

**ABBREVIATIONS**

SM(C), smooth muscle (cells); (i)(e)NO(S), (inducible) (endothelial) nitric oxide (synthase);
ECM, extracellular matrix;
ED, erectile dysfunction;
PGE, prostaglandin E;
CVOD, corporal veno-occlusive dysfunction;
PD, Peyronie's disease;
ROS, reactive oxygen species; HIF-1α, hypoxia-inducible factor-1α;
PDE5-I, phosphodiesterase type 5 inhibitor

**Abstract** Ageing has a detrimental effect on cavernous tissue and the tunica albuginea of the penis. Furthermore, atherosclerosis of the penile vessels that occurs with ageing causes a decrease in penile oxygen tension. A reduction in smooth muscle cells (SMCs) was shown in relation to diminution of oxygen tension. Chronic ischaemia is therefore not only associated with fibrosis but also with nitric oxide-cyclic guanosine monophosphate reduction. The sensitivity of the α-adrenoceptors on the SMCs increases with ageing. The decrease in penile elasticity and compliance are explained by the changes in the ratio of penile collagen that occur with ageing. Contradictory to the view that testosterone is only necessary for sexual desire, numerous recent studies showed that androgen deprivation produces penile tissue atrophy, alterations in dorsal nerve structure, alterations in endothelial morphology, reduction in trabecular SM content, increase in deposition of extracellular matrix and accumulation of fat-containing cells (adipocytes) in the subtunical region of corpus cavernosum. The aim of the current review is to shed some light on the underlying aetiology of corporal fibrosis especially ageing, cavernous nerve damage, androgen deprivation and tunical fibrosis. Ultimately I will address the proposed prevention of erectile dysfunction associated with penile fibrosis.


## Introduction

Erectile dysfunction (ED) is associated with the loss of smooth muscle cells (SMCs), and an increase in fibrosis has been repeatedly reported in corporal tissue of patients with ED

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[1]. TGF-β1 increases collagen synthesis in human corpus cavernous SM cells in culture, and is induced by hypoxia [2]. Furthermore, hypoxia can induce TGF-β1 expression and inhibit prostaglandin E (PGE) synthesis. In a cell culture study, one application of PGE1 was sufficient to significantly suppress TGF-β1-induced collagen synthesis [2].

Cavernous fibrosis is a process that decreases the content or function of the corporal SMCs and can predispose to the development of corporal veno-occlusive dysfunction (CVOD). Cavernous nerve injury after radical prostatectomy (RP) and diabetes are detrimental factors in this process [3].

Peyronie's disease (PD) is a condition where the fibrosis is characterized by an increase in collagen over the intracellular compartment; the fibrosis is associated with the production of profibrotic factors, such as TGF-β1, plasminogen activator inhibitor-1, and reactive oxygen species (ROS) during oxidative stress [4,5]. This is accompanied by the induction of the inducible nitric oxide synthase (iNOS), which acts as an endogenous antifibrotic mechanism in response to the profibrotic processes [6]. The expression of iNOS accompanying fibrosis and oxidative stress has also been seen in rat models of ageing of the arterial vessels, cavernous nerve damage, and types 1 and 2 diabetes, as well as in chronic smoking [7].

The objective of current review is to address the underlying aetiology of corporal fibrosis and eventually highlight the prospect of reversion of penile fibrosis.

## Penile tissue fibrosis: aetiology

*Ageing and corporal fibrosis (Box 1)*

**Box 1** Mechanisms of corporal fibrosis related to ageing

- Loss of SMCs
- Fibrosis in the corpora cavernosa.
- CVOD.
- Excessive deposit of collagen fibers.
- Same changes occur in media of penile arteries due to increased oxidative stress and/or other profibrotic factors (that stimulate SMC apoptosis and collagen deposition).
- Angiopoietin 1 and 2 up-regulation in human-aged penile tissue suggest a vascular endothelial growth factor – independent vascular remodeling mechanism.
- Differential activation of the intracellular signaling mediator mitogen-activated protein p42/44 kinase in cavernosal tissue, which may promote ECM expansion and fibrosis.

SMCs steadily decrease in number with ageing; the corpora show excessive deposits of collagen fibers that result in corporal fibrosis, and these changes also occur in the media of penile arteries [8]. These histological changes in aged corpora are caused by increased oxidative stress and/or other profibrotic factors that stimulate SMC apoptosis and collagen deposition [8].

Changes in elastic fibers or collagen types can provoke mechanical alterations of the penis, which reduce its elasticity and compliance. The collagen in the corpus cavernosum tissue is predominantly types I, III and IV. The endothelial cells are believed to be responsible for the secretion of type IV collagen, which forms the basement membrane of blood vessels. In the penis, there is an equal abundance of types I and IV collagen with concomitant diminution of type III [9]. A recent immunofluorescence study of cellular markers showing Angiopoietin 1 and 2 up-regulation in human-aged penile tissue suggested that there was a vascular endothelial growth factor (VEGF)-independent vascular remodeling mechanism [10].

Postmortem studies show that ageing is associated with increasing degrees of atherosclerotic vascular alteration in the arterial bed of the penis, which is likely to be caused by hypoxia-induced overexpression of TGF-β1 [11].

TGF-β1 is a pleotrophic cytokine that has been shown to increase collagen synthesis in corpus cavernosum SMCs in vitro. Under ischemic conditions, TGF-β1 induces its own mRNA, leading to a further increase in TGF-β1 synthesis that reinforces the development of severe fibrosis [11]. Furthermore, the number of NOS-containing nerve fibers was reduced by half in old rats. These findings emphasize the role of NO in erectile physiology, and a reduction of NOS nerve fibers might be an important neurological factor of age-related changes [12]. A recent interesting study showed that with advancing age there is a differential activation of the intracellular signaling mediator mitogen-activated protein p42/44 kinase in cavernous tissue, which might promote expansion and fibrosis of the extracellular matrix (ECM), and ultimately ED in the elderly [13].

*Diabetes and penile fibrosis (Box 2)*

**Box 2** Mechanisms of corporal fibrosis related to diabetes mellitus

- Excessive deposition of collagen and ECM accompanied by loss of functional cells that characterize tissue fibrosis.
- Appearance and accumulation of myofibroblasts or the switch to a synthetic phenotype producing ECM of the original cell components, such as fibroblasts and/or SMC in the penis.
- Diabetic model developed both abnormal corporal SMC relaxation and a generalized fibrosis of the arterial media. These processes seem to uniformly underlie CVOD.
- Exacerbation of fibrosis by iNOS deletion is seen in the iNOS knockout diabetic mouse.
- Up-regulation of the expression of TGF-β1 and phospho-activation of the Smad pathway.
- Loss of SMCs and increase in apoptosis occurs in the penile dorsal artery and the aorta.
- Alteration of the expression of the gap junction protein Cx43 and of particular P2R subtypes in the rat penile corpora.

The excessive deposition of collagen and ECM that characterize tissue fibrosis is due to the appearance and accumulation of myofibroblasts in the penis. The main factor in eliciting these cellular alterations is an insult to the tissue, associated with different conditions, such as in ageing, diabetes

and heavy smoking [14]. There was a progressive but mild fibrosis peaking at 20 months of age in animal experiments. A similar exacerbation of fibrosis by iNOS deletion was seen in the iNOS knockout diabetic mouse. iNOS is also overexpressed in aged arteries and its blockade leads to an increase in fibrosis. In a model for type 2 diabetes in the rat, an identical loss of SMCs and increase in apoptosis occurs in the penile dorsal artery and the aorta [15]. Ageing and diabetes mellitus were reported to markedly alter the expression of the gap junction protein Cx43 and of particular P2R subtypes in the rat penile corpora. These changes provide the molecular substrate for altered gap junction and purinergic signaling in corpora cavernosa, and thus probably contribute to the early development of ED in ageing and in diabetic rats [16].

Another recent study showed that diabetes also causes impairment of neurogenic relaxation in human corpus cavernosum and penile resistance arteries. The basal and stimulated content of cGMP in human corpus cavernosum was significantly decreased in patients with ED, especially in diabetic patients [17].

The blockade of the SMAD pathway, which is a common downstream signaling mechanism for both TGF-β1 or myostatin, is a potential antifibrotic strategy, as up-regulation of the expression of TGF-β1 and phospho-activation of the SMAD pathway was shown to occur in the penis of the diabetic rat (a model for type 1 diabetes) [18].

*Cavernous nerve damage and corporal fibrosis (Box 3)*

**Box 3** Mechanisms corporal fibrosis related to cavernous nerve damage

- Penile biopsy after ROP showed replacement of corporal SM with collagen.
- CVOD develops in rats with bilateral cavernous nerve resection, as a result of the early loss of corporal SMC by the neuropraxia-induced apoptosis, followed by fibrosis.
- The time course of iNOS induction supports the antifibrotic role of iNOS.

An experimental study showed that removing the cavernous nerve caused no significant morphological or functional changes in the penile erectile tissue of rats. On the other hand, protein expression of collagens I and III was significantly higher in the neurotomy group, which is consistent with an increased expression of TGF-β1 [19]. An interesting study investigated the effects of nerve injury alone; electrical cauterization was used to destroy the cavernous nerves. The results showed that protein expression and immunohistochemical staining of hypoxia-inducible factor-1α (HIF-1α) were significantly higher in the neurotomy group, confirming the theory that hypoxia of rat penis was induced by the loss of nocturnal erections [20].

Cavernous nerve damage after RP was reported to be associated with corporal fibrosis and loss of SMCs [20]. Penile biopsy after RP showed replacement of the corporal SMCs with collagen [21]. Furthermore, neuropraxia-induced apoptosis, followed by fibrosis, was reported to be responsible for CVOD that develops in rats with bilateral cavernous nerve resection, as a result of the early loss of corporal SMCs [22].

ED after RP is significantly more common in men who undergo non-nerve-sparing RP than in men who have a nerve-sparing RP, and a neurogenic cause is recognized to be a main factor for ED in this case. Moreover, maintenance of sexual potency after nerve-sparing RP has been reported to occur in 39–86% of men who have at least unilateral nerve preservation [23]; the recovery rate of erectile function from surgery is time-related, and it can take 6–18 months to occur [24].

*Androgen deprivation and corporal fibrosis (Box 4)*

**Box 4** Mechanisms of corporal fibrosis related to androgen deprivation

- Penile tissue atrophy.
- Alterations in dorsal nerve structure.
- Alterations in endothelial morphology.
- Reduction in trabecular SM content.
- Increase in deposition of ECM.
- Accumulation of fat-containing cells (adipocytes) in subtunical region of corpus cavernosum.

The age-related decline of circulating testosterone in men has received increasing attention recently, not only in relation to sexual functioning but in the wider context of male health. A decline in testicular function with a consequent decline in testosterone level is recognized as a common occurrence in older men [25,26]. Experimental research shows convincing evidence that testosterone has profound effects on tissues of the penis involved in the mechanism of erection, and that testosterone deficiency impairs the anatomical and physiological basis of erectile capacity [27].

Surgical or medical castration results in a significant reduction in trabecular SM content and marked increase in connective tissue deposition. These structural alterations are also associated with loss of erectile function. An ultrastructural study showed that the cavernous SM in castrated animals appeared to be disorganized, with many cytoplasmic vacuoles, whereas in intact animals the SMCs had normal morphology and were arranged in clusters [28].

The potential role of androgens in maintaining the structure and function of many pelvic ganglion neurones was reported. Rogers et al. [28] showed that castration altered the dorsal nerve ultrastructure in the rat, concomitant with loss of erectile function. Furthermore, fat-containing cells have been found in the subtunical region of penile tissue sections from orchidectomized rabbits [29]. This could lead to a venous leakage, which has been reported in a subset of hypogonadal patients with ED, who improved upon testosterone administration [30]. The alterations in cavernous tissue composition and structure were accompanied by a reduced erectile response to pelvic nerve stimulation [29].

There is marked interest in understanding the mechanisms by which androgens regulate growth and differentiation of vascular SMCs. Singh et al. [31] hypothesized that androgens promote the commitment of pluripotent stem cells into a muscle lineage and inhibit their differentiation into an

adipocyte lineage. The total number of circulating vascular progenitor cells might also be dependent on testosterone levels [32]. Regulation of progenitor cell differentiation is a complex process, dependent on numerous hormones, growth factors, and specific activation of a cascade of gene expression

In castrated animals, testosterone or 5α-dihydrotestosterone administration restored the erectile response and NOS expression in the penis [33]. In summary, based on animal experiments, androgen deprivation produces penile tissue atrophy, alterations in dorsal nerve structure, alterations in endothelial morphology, reduction in trabecular SM content, increase in deposition of ECM and accumulation of fat-containing cells (adipocytes) in subtunical region of corpus cavernosum.

**Tunical fibrosis: (Box 5)**

**Box 5** Mechanisms of tunical fibrosis

- Fibrosis is characterized by increase collagen over intracellular compartment.
- Fibrosis is associated with production of profibrotic factors (i.e. TGF-β1 and plasminogen activator inhibitor-1).
- Myostatin or its cDNA construct increased the myofibroblast number and collagen in tunica albuginea cells.
- Fibrin trapping.
- Collagen/elastin changes.
- ROS production.
- NO/NOS imbalance.
- Cellular transformation.
- Collagenase deficiency.
- Genetic predisposition/autoimmune.
- Chromosomal/cytogenetic abnormalities.
- Aberration in cell-cycle regulation.

The multilayered nature of the tunica appears to be distinct and layers are able to slide upon adjacent layers, thus providing flexibility. In plaques of PD, collagen fibers are more densely packed, irregular, premature and result in the noncompliant nature of the tunica in PD. The affected area of the tunica albuginea does not expand upon erection, and therefore causes tethering and curvature of the penis. In PD, fibrosis of the tunica albuginea is characterized by an increase in collagen in the intracellular compartment. Several studies show that fibrosis is associated with the production of profibrotic factors (i.e. TGF-β1 and plasminogen activator inhibitor-1 [4,6,34]). Regulation of collagen synthesis by many endogenous and exogenous factors, especially producers of oxygen-free radicals such as ascorbic acid, and other biologically active peptides such as epidermal growth factor and insulin-like growth factor, have been reported as factors with a role in the pathogenesis of PD. TGF-β has gained considerable attention as a factor implicated in the cause of chronic fibrotic conditions. TGF-β is a cytokine that affects the deposition of ECM and induces fibrosis in the tunica albuginea [4,34]. Further studies using an animal model showed activation of nuclear factor kappa-β, which regulates the expression of several genes and encoded adhesion molecules, after TGF-β injection and injury to the rat penis. NOS isoforms, particularly iNOS, are reported to modulate the onset and progression of fibroblast or wound healing. Inhibition of iNOS resulted in increased deposition of collagen around the TGF-β1-induced lesions, suggesting that iNOS suppresses collagen production in PD. Bivalacqua et al. [35] reported that iNOS was increased in PD probably due to inflammation. iNOS is the key control element for peroxynitrite formation, arginase II expression, and eNOS down-regulation in the induction of a Peyronie's-like condition in the rat.

Shen et al. [36] reported that the structure of the tunica albuginea in rats is also influenced by androgens. Four weeks after castration, the tunica was thinner with fewer elastic fibers, and the collagen appeared more disorganized. Depletion of elastic fibers and replacement fibrosis was also noted in intact rats treated with finasteride, although the thickness of the tunica did not differ from intact controls [36]. PD was reported to be associated with type II diabetes and with more impairment of vascular elements of erection in diabetic patients [37]. The relationship between tunical fibrosis and androgen depletion and medical comorbidities is an interesting area of research that could help to understand the pathogenesis of PD.

**Proposed reversion of penile fibrosis**

The reversion of penile fibrosis is a target for all researchers in this area. Promising recent results and future investigations might achieve this objective. In this section we address some of the important available data.

*Cavernous fibrosis after RP: phosphodiesterase type 5 inhibitors (PDE5-I)*

In animal studies using cavernous nerve injury models, Vignozzi et al. [38] reported protection against cavernous tissue protein and mRNA changes, and preservation of PDE5 expression and tadalafil efficacy after a 3-month treatment course of daily tadalafil (2 mg/kg) after bilateral cavernous neurotomy in the rat. Using a similar rat model, Ferrini et al. [7,8] reported that long-term vardenafil might prevent CVOD after RP by preserving SM content and inhibiting corporal fibrosis. These mechanisms could be due an effect on iNOS and result in functional normalization of the dynamic infusion cavernosometry decrease rate and SM-to-collagen ratio.

Another study by Ferrini et al. [22] showed that CVOD in aged rats is associated with a significant reduction of the SMC:collagen ratio in the penile corpora cavernosa compared with young rats. It was reported that long-term and continuous administration of a PDE5-I, sildenafil, corrected ageing-associated vasculogenic ED, as measured by cavernosometry. Ultimately, in the ageing rat model a PDE5-I corrects CVOD and ameliorates the underlying corporal fibrosis. Based on these results, long-term sildenafil affects SM compliance by a mechanism additional to the elevation of the SMC:collagen ratio, via the counteraction of oxidative stress or TGF-β1 expression [7,8,22].

Another factor that affects corporal SM compliance and that might be influenced by long-term PDE5-Is, as opposed to acute effects on SM relaxation, is the expression of contractile proteins, such as ACTA2, smoothelin, and others, which

are fundamental for the corporal SM relaxation/contraction process that operates in penile tumescence and detumescence. Another important target that could be affected by PDE5-Is is the Rho kinase system, by mechanisms alternative to PTPN11 induction or VAV down-regulation. These mechanisms might be phosphorylation or direct inhibition of Rho kinase, or the availability of cGMP substrate for these processes [39].

The application of molecular technologies such as gene therapy could also have a role in reversing penile fibrosis. Gene therapy might also 'cure' underlying conditions in ED, including fibrosis [5,14]. Furthermore, gene therapy might help to prolong the efficacy of the PDE5-Is by improving penile NO bioactivity. Frequent low-dose use of sildenafil and/or tadalafil combined with testosterone was reported to have a pronounced anti-apoptotic effect on the cavernous tissues of aged diabetic rats [40]. Another recent study showed that long-term administration of a novel PDE5-I (udenafil) ameliorated penile hypoxia and fibrosis induced by cavernous nerve resection. That study also suggested a potential beneficial role of repeated dosing of udenafil in the recovery of erectile function in patients with neuronal ED [41].

Bivalacqua et al. [42] reported that inhibition of RhoA/Rho-kinase by transfection of the streptozotocin-induced diabetic rat penis with an adeno-associated virus encoding the dominant-negative RhoA mutant (AAVTCMV19NRhoA) restored cavernosal eNOS protein. Therefore, erectile function in diabetes can be restored by gene therapy targeting RhoA/Rho-kinase.

### *PDE5-I after RP*

In a clinical study that reported on 40 volunteers who had undergone RP and were treated with sildenafil every other day for 6 months, after the treatment period cavernous biopsies showed preservation of the SM at the 50 mg dose, and decreased levels of fibrosis and substantially increased SM content at 100 mg doses [43].

Padma-Nathan et al. [44] reported, from their multi-institutional randomized controlled trial on 76 men after nerve-sparing RP who used sildenafil 50–100 mg nightly for 36 weeks, a 27% successful intercourse rate in sildenafil-treated men compared with 4% in placebo-treated men. While these preliminary results were encouraging, the possibility of selection bias and the heterogeneity of the treatments used for rehabilitation necessitate further prospective studies to address the role of PDE5-I in penile rehabilitation. A recent study compared early vs late penile rehabilitation in patients with nerve-sparing radical cystoprostatectomy, based on a prospective randomized trial, and concluded that early erectile rehabilitation shortens the natural healing time of potency and maintains erection [45]. Another study reported that long-term therapy with the new PDE5-I mirodenafil might improve erectile function after RP by preserving the SM content and inhibiting fibrosis of the corpus cavernosum [46].

Furthermore, pentoxifylline treatment after cavernous nerve injury in rats improved erectile recovery, enhanced nerve regeneration, and preserved the corpus cavernosum microarchitecture. The clinical availability of this compound merits its application in penile rehabilitation studies after RP in the near future [47].

### *Other agents that could affect penile fibrosis*

The application of vasoactive methods such as intracavernous PGE1, which improves cavernosal blood flow and increases oxygenation to the corpus cavernosal SMCs, might theoretically down-regulate fibrosis. Unfortunately, the precise time and frequency of these preventive treatments remain speculative. Future therapies could focus on noninvasive measures, such as topical PGE1 application, to increase patient compliance. Topical PGE1 is recognized to have a lower response rate for inducing penile rigidity. However, hypoxic prevention measures do not necessarily require a rigid erection to increase oxygenation and benefit the cavernous SMCs under such postoperative circumstances. A recent animal experimental study showed that cavernous tissue cGMP was significantly increased in mesenchymal stem cells of transplanted rats in all investigated groups compared with the controls [48]. The incidence of CVOD is 66–75%, and therefore, regardless of age or aetiology, ED caused by corporal fibrosis and ultimately CVOD itself can be prevented; then the possibility remains that ED could possibly become a preventable condition.

## Peyronie's disease

Long-term overexpression of NOS2A and NO production via intratunical NOS2a cDNA gene transfer, or long-term oral administration of the PDE5-A inhibitors sildenafil and vardenafil, which elevate cGMP, or long-term treatment with the PDE-4 inhibitor pentoxifylline, which increases cAMP, reduces penile fibrosis in a rat models of PD and/or cavernous nerve damage [7,8]. Vardenafil has been shown to slow and reverse the early stages of PD-like plaque in the rat, with amelioration of more advanced plaques. Once-daily vardenafil treatment resulted in reduced collagen/SM and collagen III/I ratios, and myofibroblasts and TGF-β1-positive cells, and selectively increased the apoptotic index in the PD-like plaque [7]. Pentoxifylline a nonspecific cAMP-PDE-I that has been shown to decrease the expression of collagen I and α-SM actin. Similar findings were reported for the application of sildenafil with L-arginine. These findings can be explained by the observation that iNOS is expressed in human PD plaques and inhibition of iNOS leads to a significant exacerbation of tissue fibrosis. Furthermore, an antifibrotic regimen consisting of up-regulators of NO production (pentoxifylline and sildenafil), showed amelioration of the corporal fibrosis associated with recalcitrant priapism [7,8,22]. However, the use of pentoxifylline as a therapeutic agent for the treatment of PD and priapism is still investigational.

In addition, the oxidative stress and TGF-β1 levels were not affected by sildenafil. This is not surprising, as cGMP is not a direct inhibitor of TGF-β1 expression but interferes with TGF-β1 signaling both by blocking pSMAD-2 and -3 nuclear translocation or SMAD-induced gene expression, and by the conversion of latent TGF-β1 to its active form [49]. In addition, in contrast to NO, cGMP is not a key modulator of oxidative stress, although it is possible that a sildenafil effect might be detected by markers of this process other than xanthine dehydrogenase. PDE5-I did not affect the collagen III:I ratio, the alteration of which, either as an increase or a decrease, is associated with tissue fibrosis in the penis [7,8].

Antagonizing TGF-β signaling through the use of neutralizing antibodies, soluble type II receptors and antisense

oligonucleotides inhibited various types of TGF-β-mediated fibrosis [50]. PDE5-I affects oxidative stress and TGF-β1 levels through interfering with TGF-β1 signaling by blocking phospho-SMAD-2 and -3 nuclear translocation or SMAD-induced gene expression and conversion of latent TGF-β1 to its active form [49].

## A prospective view of penile fibrosis reversion

An emerging approach to treat corporal fibrosis is the replacement of the lost SMCs by implanted stem cells [51]. It was shown that stem cells isolated from the skeletal muscle of mice can be implanted into the rat corpora cavernosa of old rats with ED, and generate SMCs. By undergoing this conversion, the muscle-derived stem cells corrected the ED in the aged rats. The blockade of the SMAD pathway, which is a common downstream signaling mechanism for both TGF-β1 or myostatin, is also a potential antifibrotic strategy, as up-regulation of the expression of TGF-β1 and phospho-activation of the SMAD pathway was shown to occur in the penis of the rat with streptozotocin-induced diabetes [18]. However, the pharmacological modulation of endogenous stem cells in the penis to produce SMCs and to block myofibroblast generation could also be a promising approach. These endogenous stem cells might be good candidates for antifibrotic pharmacological modulation, particularly with agents belonging to the NO/cGMP and TGF-β1 pathway. Furthermore, regular exercise was reported to up-regulate eNOS and nNOS expressions in the aged and young rat penis [52].

In addition, an interesting study showed that nanoparticles encapsulating erectogenic agents resulted in increased erectile function when applied to the penis of a rat model of ED. This study suggested that nanoparticles represent a potential novel route for the topical delivery of erectogenic agents, which could improve the safety profile for existing orally administered drugs by avoiding effects of absorption and first-pass metabolism, and would be less hazardous than injection [53]. These recent approaches, as well as regular gene and stem cell therapy, could help to improve penile fibrosis and restore the normal cellular pattern in penile tissue [54].

## Conclusions

Correcting, at least partially, the relative loss of SMCs occurring with ageing, diabetes, or cavernous nerve damage should be the target of therapy to prevent the ED associated with these conditions. Up-regulation of NO-cGMP pathway might have a role in preventing and reversing fibrosis in the tunica albuginea and in the corpora cavernosa. Therefore, long-term and continuous treatment with available PDE5-Is might be pharmacologically effective for partly reversing the underlying alterations in the corpora that lead to ED, thus potentially curing this disorder, as opposed to the current on-demand administration of these compounds for eliciting an erection. This chronic use of PDE5-Is could prevent or reverse endothelial dysfunction and possibly inhibit the atherosclerotic process. Furthermore, therapies aimed at blocking the TGF-β signaling pathway might be effective in ameliorating or preventing tunical fibrosis. This might open the door for the emergence of treatment for PD.

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