Review

Penile rehabilitation after radical prostatectomy: what the evidence really says

Mikkel Fode, Dana A. Ohl,* David Ralph† and Jens Sønksen

*Department of Urology, Herlev University Hospital, Herlev, Denmark, *Department of Urology, University of Michigan, Ann Arbor, MI, USA, and †Institute of Urology, London, UK*

The pathophysiology of erectile dysfunction after radical prostatectomy (RP) is believed to include neuropraxia, which leads to temporarily reduced oxygenation and subsequent structural changes in penile tissue. This results in veno-occlusive dysfunction, therefore, penile rehabilitation programmes focus on tissue oxygenation. Animal studies support the use of phosphodiesterase type 5 inhibitors (PDE5Is) after cavernous nerve damage but results from human studies are contradictory. The largest study to date found no long-term effect of either daily or on-demand PDE5I administration after RP compared with placebo. The effects of prostaglandin and vacuum erection devices are questionable and high-quality studies are lacking. Better documentation for current penile rehabilitation and/or better rehabilitation protocols are needed. One must be careful not to repeat the statement that penile rehabilitation improves erectile function after RP so many times that it becomes a truth even without the proper scientific backing.

Keywords

erectile dysfunction, penile rehabilitation, prostate cancer, radical prostatectomy

Introduction

Radical prostatectomy (RP) is a commonly used treatment option for localized prostate cancer. Unfortunately, the procedure carries a risk of post-surgical complications including erectile dysfunction (ED) [1]. The main pathophysiological mechanism behind this is considered to be damage to the cavernous nerves; therefore, nerve-sparing procedures are routinely used [2]. Functional outcomes are not always optimal, however, and, in spite of increased surgical precision, a recent meta-analysis found that new robotic surgical techniques could not be convincingly shown to improve erectile function after RP [3]. This has led to advanced theories about ED after RP and to the development of several penile rehabilitation programmes, designed to improve long-term erectile function after nerve-sparing surgery. The present review examines the theoretical background behind these programmes as well as the current evidence regarding their effect.

Methods

We performed a systematic review of the literature regarding ED and penile rehabilitation published between January 1990 and November 2012. Articles describing the mechanism of ED after RP and articles exploring clinically applicable methods of penile rehabilitation were considered. We restricted our search to English-language studies and included articles regarding both animal studies and studies in humans. We searched Medline and the Cochrane Library for the following terms: 'prostate cancer', 'prostatectomy', 'erectile dysfunction' and 'penile rehabilitation'. Articles were screened based on titles and abstracts, and relevant articles were selected based on a full review. Reference lists for these articles were manually searched. Only full-text articles were included in the final analysis.

Results

Pathophysiology of ED after RP

As findings indicate that the course of the cavernous nerves are more complex than previously thought, incomplete nerve-sparing is an obvious cause of ED [4]; however, even during true nerve-sparing procedures it is likely that nerves are affected by direct trauma, stretching, heating, ischaemia and local inflammation [5,6]. This is believed to cause neuropraxia, defined as a temporary block of nerve transmission despite an anatomical intact nerve fibre, and erectile function has been shown to improve for up to 4 years after RP [7,8]. There is evidence to suggest that temporary nerve dysfunction leads to structural changes in the penile tissue. This is linked to the finding that oxygen tension is 25–43 mmHg in the flaccid penis, while it increases to about 100 mmHg in the erect state [9]. During the period of neuropraxia, the penile tissue is in a constant state of low oxygen supply, which may lead to smooth muscle apoptosis and fibrosis [10]. This disrupts the veno-occlusive mechanism, which is crucial in normal erectile function [11] and structural damage could be the cause of long-term ED after nerve-sparing prostatectomies [12]. To reduce neuropraxia, the most updated surgical guidelines specifically recommend avoiding thermal energy near the nerves and minimizing traction during surgery [13].

Reductions in smooth muscle content and increased fibrosis in penile tissue after damage to the cavernous nerves have been shown in several animal studies. Apoptosis of the smooth muscle is evident in rodents as early as 1 day after denervation and increases over time [14–17]. The changes are most pronounced with bilateral nerve damage [15,18–20]. Many animal studies have also shown that there is reduced intracavernosal pressure after either injection of vasoactive substances or electrical stimulation [18,19,21–24]. The presence of TGF-β1 [19,25,26] and hypoxia-inducible factor-1α [25], and overexpression of endothelin-1 type B receptor [16,27] have confirmed hypoxia as a possible pathophysiological background to ED. Oxidative stress has also been noted as a potential contributor [22], while a recent study has found an increase in several pro-fibrotic genes and a concomitant decrease in expression of genes promoting smooth muscle growth [28].

In humans, fibrosis after RP has only been confirmed in one small study [29]. Corpora cavernosa biopsies were performed in 19 men with normal erectile function before RP, and repeated 2 and 12 months after surgery. Nerve-sparing was not ensured in most of the cases. In all of the 2-month postoperative biopsies, elastic fibres and smooth muscle fibres were decreased and collagen content was increased compared with preoperative biopsies ($P < 0.001$). In the 12-month biopsies the changes were further amplified ($P < 0.001$). None of the patients in that small study had nightly erections or erections sufficient for sexual intercourse during follow-up.

Penile Rehabilitation

The hypoxia theory has raised hope that erectile function can be improved by oxygenating the cavernosal tissue during the period of neuropraxia. In 2008, Müller et al. [24] showed that hyperbaric oxygen therapy after cavernous nerve crush in rats improved erectile function ($P = 0.005$) and provided a trend ($P = 0.06$) toward higher smooth muscle preservation.

A clinically more applicable effect of tissue oxygenation has been sought in ED treatments including: prostaglandin E1 therapy, applied through intracavernosal injection therapy and urethral suppositories, such as those used in the Medicated Urethral System for Erection (MUSE); PDE type 5 inhibitors (PDE5Is) as per oral therapy; and vacuum erection devices (VEDs).

Prostaglandin E1 Therapy: Injection Therapy and MUSE

The first attempt at penile rehabilitation was performed by Montorsi et al. in 1997 [30]. In their innovative study, 30 patients were randomized after nerve-sparing RP and the treatment group ($n = 15$) received intracavernous injections of alprostadil three times per week for 12 weeks. The control group received no treatment. Twelve patients completed the treatment and eight of these reported that they needed injection therapy in <50% of attempts at sexual activity, which was considered a return of spontaneous erections. The group used injection therapy at a mean of every 4.2 attempts at intercourse. In the control group, three patients reported erections sufficient for satisfactory intercourse while 10 reported some recovery of erectile function insufficient for intercourse in most cases. In the treatment group, normal penile haemodynamics were found in 10 patients, and 7 patients had at least one erection per night. In the control group, 5 patients had normal haemodynamics and 3 patients had nocturnal erections. The study was ground-breaking as it introduced the idea of penile rehabilitation; however, limitations included the low number of patients, a lack of preoperative assessment of erectile function, lack of placebo treatment, the reliance of patient history as the main outcome, and the lack of long-term follow-up. Injection therapy in penile rehabilitation has not been tested in a randomized fashion since.

The only randomized study investigating MUSE for penile rehabilitation compared MUSE treatment with nightly sildenafil in 139 patients [31]. There was no statistically

significant difference in erectile function between the two groups 1 year after surgery; however, as there was no placebo or no-treatment group, the study cannot be considered as adequate documentation of either treatment in penile rehabilitation. Raina et al. [32], also studied MUSE therapy in men after bilateral nerve-sparing RP. A total of 56 men were treated with MUSE (125 or 250 μg three times per week for 6 months) while the remaining 35 patients received no ED treatment. This resulted in 74 and 37% of patients regaining erections sufficient for intercourse in the treatment and control groups, respectively, and in mean scores on the five-item International Index of Erectile Function (IIEF-5) questionnaire of 18.9 and 15.8, respectively; however, patients were allocated into the two groups by choice, meaning that the MUSE group consisted of patients opting for early penile rehabilitation while the control group did not. This is likely to have skewed the results in favour of the rehabilitation group. Furthermore, 32% discontinued MUSE treatment, most commonly because of lack of efficacy, reduced sexual interest and adverse effects, and these patients were not included in the final analysis.

Other publications on injection therapy and MUSE have similar methodological drawbacks. These include comparing patients who actively choose to participate in penile rehabilitation programmes with patients who either were not interested or who chose to delay treatment, and excluding patients not complying with treatment regimens [33,34]. This is problematic because of the subjective nature of ED assessment and because a lack of treatment effects has been shown to influence discontinuation of penile rehabilitation heavily [35,36]. Thus, the drop out from the active treatment groups may in reality be elimination of patients with particularly poor erectile function, thereby introducing an artificial treatment effect. Other studies have lacked control groups altogether [37–39].

PDE 5 Inhibitors: Animal Studies

The use of PDE5Is in penile rehabilitation has been studied extensively in rodents. Vignozzi et al. [16], performed bilateral cavernous neurotomy in male rats, which induced penile hypoxia and a reduction in smooth muscle content. Sildenafil was given to some animals 1 h before they were killed, which reduced hypoxia. In another study, the same group found that hypoxia induced by bilateral cavernous neurotomy was completely ameliorated after 3 months of daily tadalafil (2 mg/kg/day) while smooth muscle apoptosis and fibrosis were reduced substantially [27]. Vardenafil has also proven effective in reducing structural changes in penile tissue after cavernous nerve resection by increasing smooth muscle cell replication [23] and tadalafil has reduced apoptosis of endothelial cells in mouse penile tissue [17]. These beneficial effects have been confirmed in several studies [17–21,28].

Treatment with PDE5Is has also improved surrogate measures of erectile function. Using dynamic infusion cavernosometry, Ferrini et al. [23] found that veno-occlusive dysfunction after bilateral cavernous nerve resection was prevented by vardenafil treatment in rats (30 mg/L in the drinking water). A similar result has been found with sildenafil treatment (20 mg/kg/day) [19]. Likewise, Kovanecz et al. [18], found that tadalafil after cavernosal nerve crush in rats increased intracavernosal pressure after papaverine injection compared with no-treatment controls. Two similar studies have found that the intracavernosal pressure in rats exposed to nerve crush was also improved with sildenafil 20 mg/kg/day [21,22]; however, the pressure was still lower than in sham-operated groups in both studies and no improvement was seen with a dose of 10 mg/kg/day sildenafil [21]. A recent study has found that *in vitro* relaxation of smooth muscle from bilateral nerve resected rats in response to high-frequency (32 Hz) electrical stimulation was decreased [20]. This was not changed by sildenafil treatment, indicating that some residual nerve function may be nessesary for a functional sildenafil effect [20].

Many different mechanisms of action have been proposed to explain the protective effect of PDE5Is. Sildenafil has been found to affect several genes involved in smooth muscle preservation and to reduce oxidative stress [22,28]. Tadalafil has been found to increase the activation of survival-associated kinases [17]. Other studies have implicated a nitric oxide (NO) mechanism. Thus, both expression and activation of endothelial NO synthase has been increased with sildenafil treatment compared with a control group [21]. Likewise inducible NO synthase (iNOS) has been found to be increased with vardenafil treatment [23]. Meanwhile, Kovanecz et al. [19] performed cavernosal nerve resection on 344 rats and treated a group with sildenafil (20 mg/kg/day) for 45 days. Two other bilateral nerve-resected groups received an iNOS inhibitor, with or without concurrent sildenafil. The pro-fibrotic factor TGF-β1 as well as iNOS were found to be increased with nerve resection. TGF-β1 was restored to sham values with sildenafil, while iNOS was not affected by this treatment. The iNOS inhibitor increased fibrosis and veno-occlusive dysfunction in the non-sildenafil treated rats but not in the sildenafil treatment group, suggesting that the sildenafil effect was not dependent on iNOS induction [19]. In another study, tadalafil neither influenced TGF-β1 nor iNOS, and it was theorized that the effects on smooth muscle preservation and fibrosis reduction were caused by direct cGMP activation [18]. Finally, an increased amount of myelinized nerve fibres at the area of the previous nerve crush has been identified in a group of rats treated with

sildenafil compared with control animals, suggesting a neuro-protective mechanism [21].

As evident from the above studies, the mechanisms and cellular pathways behind the PDE5I effect on post-nerve resection/crush in rats are not clear. Taken together, the studies point to increased oxygenation, activation of endothelial NO/cGMP and nerve protection, as well as to more complicated cellular mechanisms, including activation of anti-apoptotic and antifibrotic factors.

PDE 5 Inhibitors (PDE5I): Human Studies

Schwartz et al. [40] randomized 40 patients to either sildenafil 50 mg or 100 mg every other night for 6 months after nerve-sparing RP. Biopsies from cavernous tissue were taken before surgery and after 6 months in the 21 patients who completed the protocol. Patients receiving the 50 mg dose showed no difference in the mean amount of smooth muscle content ($P = 0.81$), while patients in the 100 mg group showed an increase from a mean preoperative smooth muscle content of 42.8% to a mean postoperative smooth muscle content of 56.9% ($P < 0.05$). There was no difference in postoperative smooth muscle content when comparing the two groups directly ($P = 0.33$). The study did not include an assessment of postoperative erectile function. Iacono et al. [41] conducted a similar study, in which 21 patients received sildenafil 50 mg, three times a week, for 2 months after RP. Biopsies were performed both before surgery and after the 2 months of treatment. Neither elastic fibres nor connective tissue content changed significantly. In that study unilateral nerve-sparing at least was attempted in all cases and 4 patients reported erections sufficient for penetration at 2 months, while 6 patients reported nightly erections. There was no control group and no long-term follow-up. When compared with the original study by Iacono et al. [29], where no PDE5Is were administered and where smooth muscle content diminished, these two studies point to an effect from PDE5I; however, it is likely that the results were influenced by differences in nerve-sparing and no final conclusions can be drawn, because of the lack of control groups.

Only two randomized and placebo-controlled trails assessing the clinical effects of PDE5I in penile rehabilitation have been conducted. In the first of these, men scheduled for bilateral nerve-sparing RP and with intact preoperative erectile function were randomized to receive 100 mg sildenafil, 50 mg sildenafil or placebo every night for a period of 9 months [42]. Responders were defined as patients with a combined score of ≥8 for questions 3 ('Over the past 4 weeks, when you attempted sexual intercourse, how often were you able to penetrate your partner?') and 4 ('Over the past 4 weeks, during sexual intercourse, how often were you able to maintain your erection after you had penetrated your partner?') of the IIEF, and a positive response to the question 'Were erections good enough for satisfactory sexual activity?'. After the 9-month double-blind treatment period, patients received no treatment for an 8-week period. After this wash-out, 14/51 patients who completed sildenafil treatment were responders (27%) with no significant difference between the 50 mg group and the 100 mg group. Only 1/25 in the placebo group (4%) fulfilled the criteria as a responder. The mean IIEF Erectile Function domain (IIEF-EF) score was also significantly higher in the sildenafil group than in the placebo group (13.1 ± 9.5 vs 8.8 ± 7.0). Unfortunately, enrolment in the study ceased early owing to an interim analysis which showed a lower response rate than expected, and only 76 men completed the study protocol. A subgroup ($n = 54$) underwent evaluation of nocturnal penile tumescence and rigidity and was analysed in a subsequent paper by the same study group [43]. It was found that nightly sildenafil improved nocturnal erections compared with placebo, with the greatest response in the 100-mg group [43]. None of the groups returned to baseline values.

The second randomized, placebo-controlled study was performed by Montorsi et al. [44]. This well-designed study included men with a preoperative IIEF-EF score of at least 26, and an operative report confirming bilateral nerve-sparing ($n = 423$). For 9 months patients received either 10 mg vardenafil nightly plus on-demand placebo, on-demand vardenafil plus nightly placebo, or nightly placebo plus on-demand placebo. Responders were defined as patients with an IIEF-EF score of at least 22. Patients were evaluated after the double-blind treatment and a subsequent 2-month wash-out period, during which all patients received placebo medication. The study did not demonstrate any significant difference regarding erectile function between the three groups (response rates of 28.9% for placebo, 24.1% for nightly vardenafil, and 29.1% for on-demand vardenafil). Another assessment was performed after a subsequent 2-month period, with open-label on-demand vardenafil treatment still showing no statistically significant differences between response rates (47.8% for placebo, 52.6% for nightly vardenafil, and 54.2% for on-demand vardenafil).

During the double-blind period of the study, the vardenafil on-demand group had significantly higher IIEF-EF scores than either of the other groups, while the nightly vardenafil group had higher scores than the placebo group. This is not surprising considering that vardenafil is meant to work as an on-demand drug. The on-demand group had the full treatment effect during the drug phase of the study, while the nightly group had an effect so far as their sexual activity coincided with ingestion of the drug.

In addition to these two placebo-controlled studies, a small randomized study from Turkey investigated the effect of tadalafil in penile rehabilitation [45]. In that study, 65 men with preoperative IIEF-EF scores >25 undergoing bilateral nerve-sparing RP were randomized to receive 20 mg tadalafil three times a week for 6 months or no treatment. Patients were then evaluated for changes in penile length and erectile function. At the 12-month follow-up, there was no difference between changes in stretched penile length in the two groups and there was no statistically significant difference in erectile function, with 72.7% in the no-treatment group and 78.1% in the tadalafil group being reported to have IIEF-EF scores >25. Use of PDE5Is at this time was not reported. It may be prudent to interpret the results of that study with caution because of the low number of patients, the unusually high postoperative IIEF scores, and the fact that the primary outcome of the study was penile size.

A small study ($n = 41$) looked at patients with RigiScan®-confirmed nocturnal erections after unilateral or bilateral nerve-sparing RP [46]. Patients were matched by preoperative parameters and nerve-sparing status to either sildenafil 25 mg every night ($n = 23$) or no treatment ($n = 18$). At 52 weeks the IIEF-5 scores differed between groups (14.1 in the sildenafil group vs 9.3 in the control group, $P < 0.001$). While this is clearly a well thought out study, major concerns include that the duration of the nightly sildenafil treatment was not mentioned and that no wash-out period was described before the IIEF scores were assessed. Other limitations include the lack of placebo medication and the highly selected group of patients with nightly erections after surgery.

Vacuum Erection Device

A VED creates a transient increase in arterial blood flow and oxygen supply [47,48], but when applying a constriction band, oxygen saturation gradually drops [48]; therefore the VED is applied without the constriction band in penile rehabilitation.

After cavernous nerve crush in rats the VED has been shown to improve intracavernosal pressure with nerve stimulation and preserved penile size compared with controls [49,50]. A VED also reduced hypoxia-inducible factor-1α, TGF-β1, while increasing endothelial NO synthase expression and smooth muscle/collagen ratios compared with controls [49,50]. Erectile function and tissue preservation was, however, reduced compared with sham-operated animals.

Two randomized trials have tested VED against observation in humans. Kohler et al. [51] randomized 28 men to early or delayed treatment after unilateral or bilateral nerve-sparing RP. One month after surgery the early treatment group was instructed to use VED daily for two consecutive 5-min periods without a constriction band. After the first month the men were also allowed to use constriction bands for intercourse. After 6 months the delayed treatment group was instructed to use VED for intercourse and both groups were offered PDE5Is. The early treatment group had significantly higher IIEF scores at 3- and 6-month follow-up, but there was no difference between the groups after 12 months ($P = 0.75$). Use of PDE5I did not differ between the groups. Importantly, no spontaneous erections adequate for intercourse were reported at 12 months in either group. As it must be assumed that the increased erectile function at 3 and 6 months in the early treatment group represents an acute effect of active treatment the paper does not support the use of a VED in penile rehabilitation. Stretched penile length was measured in both groups to assess if the VED had an effect on penile shortening. At 12 months, two out of 17 patients in the early VED group and five out of 11 patients in the delayed group had penile shortening of at least 2 cm ($P < 0.044$); however, there was no significant loss in penile length in the delayed treatment group compared with the preoperative measurements, which makes the interpretation of this finding difficult.

Raina et al. [52] randomized 109 patients to daily VED for 9 months after RP (nerve-sparing or non-nerve-sparing) or to no treatment. The VED group was allowed to use a constriction band for intercourse. Patients were excluded from the VED group if they did not engage in intercourse using the device. The overall exclusion rate in the group was 14/74 patients (20%) with reasons for discontinuation reported as discomfort (55%), penile bruising (20%), social inconvenience (17%) and inability to use the device (8%).

At 9-month follow-up the mean IIEF-5 score was higher in the treatment group than in the no-treatment group (16 ± 7.33 vs 11.1 ± 1.76, $P < 0.05$); however, the assessment appears to have been performed while the treatment group still had the VED and the control group received no treatment. Some degree of spontaneous erections was reported in 32% of patients in the VED group and in 37% in the no-treatment group. Ten out of 60 patients (17%) in the VED group reported the return of natural erections sufficient for intercourse, while this number was four out of 35 patients (11%) in the no-treatment group. Neither difference was significant. The study lacked an intention-to-treat analysis even though it is likely that the patients who quit using the VED were also the patients with the lowest effect on erectile function. This is supported both by other research [35] and by the observation that all patients who continued to use the device were able to perform sexual intercourse – an unusually high success rate.

Patients were also asked about their penile size and 23% of the successful VED users, reported a decrease in penile length and circumference as compared with 85% of patients who discontinued VED. In the no-treatment group, 63% reported a decrease in size. While this indicates that VED could have an effect in maintaining penile size, the results must be interpreted with caution as the assessment is based solely on subjective and retrospective responses from the patients.

A recent study from the USA has attempted to investigate a PDE5I/VED combination in penile rehabilitation [53]. Patients having undergone bilateral nerve-sparing RP were randomized to either tadalafil 20 mg three times weekly ($n = 7$), or tadalafil plus a VED ($n = 13$). A higher IIEF-5 score was found in the combination group at 6, 9 and 12 months after surgery. Unfortunately, sexual function was evaluated only with treatment, which means that the study confirms the PDE5I/VED combination as a treatment option but reveals nothing about its role in penile rehabilitation.

Psychosocial Interventions

Although erectile functioning has been shown to play the largest single role, it is clear that psychological factors such as relationship closeness and depression/anxiety are also important in sexuality after RP [54]. In addition, it has been shown that a lack of emotional readiness in both patients and their partners can diminish sexual activity even when erectile capacity is restored after RP [55]. In spite of this crucial influence, little research has been done in the area of psychosocial interventions in penile rehabilitation. In a pilot study from 2005, Canada et al. [56], investigated the effects of four sessions of sexual counselling in men who had undergone curative treatment for prostate cancer and who were unable to achieve satisfactory erections either with or without treatment ($n = 84$). The counselling included education on the sexual impact of prostate cancer treatment, information about ED treatments, communication training and cognitive-behavioural therapy. In addition, the patients were given homework with touching exercises and recording of diaries. Men who completed the sessions increased the use of erectogenic aids and showed short-term improvements in all IIEF subscales except sexual desire. The female partners also showed improvement in sexual function; however, only 61% completed all four sessions and at 6-month follow-up most of the improvements had regressed back to baseline in both patients and partners. Subsequent studies have supported the potential role of psychosocial interventions. Thus a randomized study of men who had undergone either non-nerve-sparing RP or cystectomy ($n = 57$) showed that repeated sessions of sexual counselling increased both compliance and satisfaction with injection therapy with 18 months follow-up while it also had a marginally positive effect on treatment efficacy [57]. Another randomized study of 101 men recovering from RP found that a cognitive-behavioural stress management intervention improved sexual function at 2–3 weeks after the end of the intervention [58]. The intervention consisted of weekly 2-h meetings with four to six participants for a period of 10 weeks. A *post hoc* analysis showed that the greatest effect was seen in men who perceived their sexual dysfunction as a threat to their masculinity. Unfortunately this study lacked long-term follow-up.

Other studies have attempted to assess the role of the partner in post-RP sexual dysfunction. It has been shown that a sexually functional partner is associated with better sexual outcomes after RP and that there is there is a strong correlation between male and female sexual dysfunction in couples where the man has undergone RP [59,60]. Interestingly, a study, which included 35 couples, found that patients had greater positive feelings towards their partners than the partners had toward the patients. Likewise, the patients were more satisfied with the prescribed ED treatments than the partners were [61]. Taken together, these findings indicate that the overall success of sexual rehabilitation after RP may improve if partners are involved but, at this time, no specific recommendations for such involvement can be given.

Alternative Strategies

Based on theoretical considerations and animal studies, a large range of alternative compounds have been suggested as potential new treatments in penile rehabilitation. These include nerve growth factors [62], acidic fibroblast growth factor [63], growth hormone [64], IGF [65], erythropoietin [66], vascular endothelial growth factor [67], brain-derived neurotrophic factor [68], sonic hedgehog protein [69], immunophilin ligands [70], neurturin [71], growth differentiation factor-5 [72], polyadenosine diphosphate-ribose polymerase inhibitor [73], triiodothyronine [74], rho kinase inhibitors [75] and stem cell therapy [76,77]. The experience from human trials is limited so far and future trials are needed to evaluate the true potential of such treatments.

One of the most intriguing and controversial suggestions is post-prostatectomy testosterone treatment. Testosterone may play an important role in both cavernous nerve integrity and NO production and is thought to exert trophic effects on smooth muscle tissue along with a reduction of fat and connective tissue in the corpora cavernosa [78].

Although not documented in humans, animal studies imply that there may be an acute phase with hypogonadism after cavernous nerve damage [79]. A role of testosterone is

further implied in the finding that preoperative serum testosterone levels have been found to be positively correlated to post-prostatectomy erectile function [80].

Interestingly, testosterone has also been shown to regulate PDE5 levels in rodents [78] and as testosterone treatment may improve the response to PDE5I in men with hypogonadism [81], it has been speculated that a combination of testosterone and PDE5I may aid penile rehabilitation further. In a rat study, testosterone supplementation alone after bilateral cavernous nerve resection was not able to prevent hypoxia, however, testosterone in combination with tadalafil, completely restored penile oxygenation and prevented fibrosis [79]. The concept is currently being tested in a human randomized trial (NCT00848497).

The role of testosterone treatment in erectile dysfunction, however, remains controversial and a recent randomized study has challenged the notion that testosterone can increase the effect of PDE5I ($n = 140$). Thus, no benefit on erectile function was found when comparing sildenafil + testosterone with sildenafil + placebo in men with low testosterone levels [82]. Furthermore, a comprehensive review by Buvat et al. [83] has questioned both the association between low testosterone and ED in general and the beneficial effect of testosterone replacement therapy on ED in particular. In this review it was quoted that only young patients with testosterone deficiency seem to experience a consistent benefit from testosterone therapy. Another crucial problem with the widespread use of testosterone in penile rehabilitation is the possibility that hormone therapy may increase the risk of recurrence and progression of the disease. While there is no current evidence that testosterone treatment after RP constitutes a risk of disease recurrence, only small retrospective case series in patients with hypogonadism have been published thus far. As intriguing as the concept of testosterone in penile rehabilitation may be, it is important to realize that clinical proof is needed in patients who have undergone RP and that, at the current time, all available preparations of the testosterone for men with hypogonadism are stated to be contraindicated when known or suspected prostate cancer is present [84].

Benefits for Specific Subgroups

Recent studies have begun to outline new significant concepts in penile rehabilitation, namely, identifying subgroups of patients who are not in need of rehabilitation and identifying those who are the best candidates for rehabilitation programmes [85,86]. This is done based on preoperative patient characteristics and may be important as the participants in the cited randomized trials have all been selected to be relatively young with a good preoperative erectile function and a low rate of comorbidities. In one such study, Gallina et al. [85] suggested that penile rehabilitation may be beneficial in older patients and patients with a diminished preoperative erectile function while young men (<55 years of age) with a good erectile function do not benefit from rehabilitation programmes. Another recent study by Briganti et al. [86] found that the recovery of erectile function was improved with PDE5I overall, and that it was similar with on-demand and daily PDE5I treatment in both patients at high risk (age ≥70 years or IIEF-EF score ≤10 or a Charlson Comorbidity Index [CCI] score ≥2) and low risk (age ≤65 years, IIEF-EF score ≥26, CCI score ≤1) of postoperative ED. Meanwhile, the daily treatment showed significantly better effect in intermediate risk patients (age 66–69 years or IIEF-EF score 11–25, CCI score ≤1). Both studies, however, used retrospective data and compare patients who had actively decided to either participate in penile rehabilitation programmes or to opt out of these. As described previously, it is likely that there are differences between such patient groups and the studies neglected to explore this aspect. Furthermore the studies conducted several statistical tests, thus markedly increasing the risk of type 1 errors. This means that, while intriguing, the conclusions of these studies warrant further investigation in prospective trials.

Discussion

The authors and study groups investigating penile rehabilitation must be commended for their ingenuity and persistence with regard to improving patient outcomes after RP. There is no doubt that this is crucial to many patients' quality of life [87]. The work has both highlighted the area and brought promise of significant improvements. At the same time, it is clear that there is still much work to be done.

As described, the literature on both intracavernous injection therapy and MUSE is scarce and contains major limitations. More knowledge is available regarding PDE5Is, but results are conflicting. In the normal treatment of ED the PDE5I mechanism of action is to inhibit the breakdown of cGMP [88]. As this makes the PDE5I effect dependent on an initial supply of neural NO, the rationale behind using PDE5Is in the presence of neuropraxia has been discussed widely. Animal studies point to several plausible protective mechanisms but one must be careful when interpreting these findings as effects might not translate to humans. Erections in rat studies were non-physiological and the PDE5I doses given are generally higher than recommended in men. Furthermore, the studies use a variety of methods to induce nerve damage, which may be very different from the damage induced during nerve-sparing RPs performed in humans. Even with these

limitations, the number of animal studies may seem like compelling evidence at first glance; however, it is crucial to note that in strict terms the data regarding post-nerve-damage erectile function in rats only constitute one highly reproducible experiment. Animal studies may justify human trials but cannot be regarded as clinical evidence. Accordingly, the clinical trials in humans do not uniformly duplicate the clear benefit shown in rodents [42,44]. Perhaps the most intriguing question in the area of penile rehabilitation is why the Padma-Nathan study [42] and the Montorsi study found such different results [44].

Obvious discrepancies include differences in sample sizes, and inclusion of placebo medication in the wash-out period of the Montorsi study. Another difference is that normal erectile function was defined more strictly in the Padma-Nathan study; however, when looking at the number of patients with IIEF-EF scores ≥26, the Montorsi study still did not find a significant treatment effect. Furthermore, a subsequent study by Briganti et al. [89] found that the IIEF-EF score of ≥22 used in the Montorsi study may in fact be the most appropriate threshold for recovery of postoperative erectile function as sexual satisfaction only declines when the score drops below 22.

It can be speculated that psychological factors play a role in the different outcomes in the two studies because their main assessment of ED was subjective and dependent on sexual intercourse with a partner. We must expect that, during the active treatment/placebo phases of the trials, the treatment groups were most capable of an active sex life – this was specifically shown in the Montorsi study but not addressed by Padma-Nathan et al. The long periods without the ability to engage in sexual intercourse owing to neuropraxia and without access to treatment may have negatively influenced the sexual lives of couples in the placebo groups [55]. It can be speculated that the detrimental psychological effects had largest impact in the Padma-Nathan study, as patients in the Montorsi study made no less than 11 study centre visits in which sexual activity was encouraged. The randomized study investigating tadalafil in penile rehabilitation is less vigorously designed. Nevertheless, this study showed no treatment effects on post-prostatectomy erectile function [45].

As PDE5Is have not been directly compared, another explanation for the discrepancies is that there may be a difference in their effects in spite of the theoretically identical mechanism of action. Initially, this does not seem likely based on animal studies and on the universal efficacy of PDE5Is in treating ED [90]. Moreover, the long half-life of tadalafil would seem to offer a theoretical benefit over the other PDE5Is as the penile tissue is subjected to the drug more consistently [91], but in a human study regarding the effects of the three PDE5Is on pulmonary hypertension, only sildenafil improved arterial oxygenation [92]. Sildenafil was also the only PDE5I that improved the haemodynamic response to intracavernous prostaglandin injection over an 8-week treatment period for men with non-neurogenic erectile dysfunction ($n = 134$) [90]. This implies that a difference in drug effects could play a role. Nevertheless, no clinical proof exists to support the notion and studies comparing the three PDE5Is are required.

As with PDE5Is, the VED has shown effect in rodents [49,50], but these results have not been confirmed in humans. In spite of encouraging short-term results, the data do not show a long-term effect on erectile function [51,52]. The treatment may have a positive effect on penile length, but this matter warrants further study.

Psychosocial interventions have shown some promise but the methods employed thus far have been inadequate to induce long-term improvements except regarding compliance with medical treatments. It is also unclear if individual patients may need specific psychosocial interventions tailored to their personality. Clearly, more research is needed in this area. Likewise, more research is required to assess the influence of the partner. Specifically, it would be beneficial to find ways in which the partners could contribute positively to long-term success with both penile rehabilitation and treatment of ED.

In spite of the limitations in the literature, penile rehabilitation programmes containing injection therapy, PDE5Is, MUSE, VED and combinations of these treatments are gaining popularity [93–95]. This trend may have both positive and negative implications for patients. It must be stressed that, in spite of their questionable role in penile rehabilitation, the listed treatments have all proven effective as traditional post-prostatectomy ED treatments [96–103], therefore, early treatment would probably benefit patients' sexuality in the short term and may also have a positive effect regarding long-term psychological and relationship factors, as discussed above. Meanwhile, such effects can only be expected when erections are actually induced and effective treatments should not be replaced by continuous long-term administration of suboptimum rehabilitation regimens in the anticipation that this may improve spontaneous erectile function. Furthermore, the current evidence does not support the notion that patients who are not interested in sexual activity in the short term should endure the inconvenience and expense of today's long-term penile rehabilitation programmes. Finally, and perhaps most importantly, it is crucial for the area of penile rehabilitation, that new treatment methods are explored – opportunities to do so

will be diminished if we act as if current methods are sufficient for what we wish to achieve. In addition to exploring new treatments, future studies should be designed to investigate the effects of penile rehabilitation programmes in specific subgroups as discussed above. More research is also needed to evaluate the long-term effects of psychosocial interventions and to assess the possible effects of treating sexual dysfunction in partners of men undergoing RP. Because of the uncertainties and multifactorial nature of sexual relationships, it is imperative that future studies are designed as randomized and prospective trials.

Conclusions

Theoretical considerations warrant early implementation of penile rehabilitation to ensure cavernous oxygenation, but there is little clinical evidence to support the use of current protocols. Certainly no specific treatment can be recommended. While animal studies are abundant, only few well designed human trials have been conducted and the results are mainly discouraging. Better documentation and/or better methods of penile rehabilitation are necessary to adhere to the principles of evidence-based medicine. Until this is addressed we should consider moving away from a rehabilitation paradigm toward a goal-oriented treatment paradigm in our daily practice. In accordance with patient wishes, treatments should be prescribed in doses and combinations that actually induce erections and allow sexual intercourse if possible. Such treatments should be offered early after RP to minimize the possible detrimental psychological effects. One must be very careful not to repeat the statement that penile rehabilitation regimens improve erectile function after RP so many times that it becomes a truth, even without the proper scientific backing.

Conflict of Interest

MF is a consultant for Eli Lilly. DO is a consultant for Pfizer and a speaker for Eli Lilly. JS is also a consultant and speaker for Eli Lilly. As well as a speaker for Pfizer.

References

1 **Tal R, Alphs HH, Krebs P, Nelson CJ, Mulhall JP.** Erectile function recovery rate after radical prostatectomy: a meta-analysis. *J Sex Med* 2009; 6: 2538–46

2 **Walsh PC, Donker PJ.** Impotence following radical prostatectomy: insight into etiology and prevention. *J Urol* 1982; 128: 492–7

3 **Ficarra V, Novara G, Ahlering TE et al.** Systematic review and meta-analysis of studies reporting potency rates after robot-assisted radical prostatectomy. *Eur Urol* 2012; 62: 418–30

4 **Walz J, Burnett AL, Costello AJ et al.** A critical analysis of the current knowledge of surgical anatomy related to optimization of cancer control and preservation of continence and erection in candidates for radical prostatectomy. *Eur Urol* 2010; 57: 179–92

5 **Masterson TA, Serio AM, Mulhall JP, Vickers AJ, Eastham JA.** Modified technique for neurovascular bundle preservation during radical prostatectomy: association between technique and recovery of erectile function. *BJU Int* 2008; 101: 1217–22

6 **Burnett AL.** Rationale for cavernous nerve restorative therapy to preserve erectile function after radical prostatectomy. *Urology* 2003; 61: 491–7

7 **Le JD, Cooperberg MR, Sadetsky N et al.** Changes in specific domains of sexual function and sexual bother after radical prostatectomy. *BJU Int* 2010; 106: 1022–9

8 **Glickman L, Godoy G, Lepor H.** Changes in continence and erectile function between 2 and 4 years after radical prostatectomy. *J Urol* 2009; 181: 731–5

9 **Kim N, Vardi Y, Padma-Nathan H, Daley J, Goldstein I, Saenz de Tejada I.** Oxygen tension regulates the nitric oxide pathway. Physiological role in penile erection. *J Clin Invest* 1993; 91: 437–42

10 **Moreland RB.** Is there a role of hypoxemia in penile fibrosis: a viewpoint presented to the Society for the Study of Impotence. *Int J Impot Res* 1998; 10: 113–20

11 **Lue TF, Tanagho EA.** Physiology of erection and pharmacological management of impotence. *J Urol* 1987; 137: 829–36

12 **Mulhall JP, Slovick R, Hotaling J et al.** Erectile dysfunction after radical prostatectomy: hemodynamic profiles and their correlation with the recovery of erectile function. *J Urol* 2002; 167: 1371–5

13 **Montorsi F, Wilson TG, Rosen RC et al.** Best practices in robot-assisted radical prostatectomy: recommendations of the Pasadena Consensus Panel. *Eur Urol* 2012; 62: 368–81

14 **Klein LT, Miller MI, Buttyan R et al.** Apoptosis in the rat penis after penile denervation. *J Urol* 1997; 158: 626–30

15 **User HM, Hairston JH, Zelner DJ, McKenna KE, McVary KT.** Penile weight and cell subtype specific changes in a post-radical prostatectomy model of erectile dysfunction. *J Urol* 2003; 169: 1175–9

16 **Vignozzi L, Morelli A, Filippi S et al.** Effect of sildenafil administration on penile hypoxia induced by cavernous neurotomy in the rat. *Int J Impot Res* 2008; 20: 60–7

17 **Lysiak JJ, Yang SK, Klausner AP, Son H, Tuttle JB, Steers WD.** Tadalafil increases Akt and extracellular

signal-regulated kinase 1/2 activation, and prevents apoptotic cell death in the penis following denervation. *J Urol* 2008; 179: 779–85

18 **Kovanecz I, Rambhatla A, Ferrini MG et al.** Chronic daily tadalafil prevents the corporal fibrosis and veno-occlusive dysfunction that occurs after cavernosal nerve resection. *BJU Int* 2008; 101: 203–10

19 **Kovanecz I, Rambhatla A, Ferrini M et al.** Long-term continuous sildenafil treatment ameliorates corporal veno-occlusive dysfunction (CVOD) induced by cavernosal nerve resection in rats. *Int J Impot Res* 2008; 20: 202–12

20 **Ozden E, Ozturk B, Kosan M et al.** Effect of sildenafil citrate on penile weight and physiology of cavernous smooth muscle in a post-radical prostatectomy model of erectile dysfunction in rats. *Urology* 2011; 77: 761–7

21 **Mülhall JP, Muller A, Donohue JF et al.** The functional and structural consequences of cavernous nerve injury are ameliorated by sildenafil citrate. *J Sex Med* 2008; 5: 1126–36

22 **Lagoda G, Jin L, Lehrfeld TJ, Liu T, Burnett AL.** FK506 and sildenafil promote erectile function recovery after cavernous nerve injury through antioxidative mechanisms. *J Sex Med* 2007; 4 (4 Pt 1): 908–16

23 **Ferrini MG, Davila HH, Kovanecz I, Sanchez SP, Gonzalez-Cadavid NF, Rajfer J.** Vardenafil prevents fibrosis and loss of corporal smooth muscle that occurs after bilateral cavernosal nerve resection in the rat. *Urology* 2006; 68: 429–35

24 **Muller A, Tal R, Donohue JF et al.** The effect of hyperbaric oxygen therapy on erectile function recovery in a rat cavernous nerve injury model. *J Sex Med* 2008; 5: 562–70

25 **Leungwattanakij S, Bivalacqua TJ, Usta MF et al.** Cavernous neurotomy causes hypoxia and fibrosis in rat corpus cavernosum. *J Androl* 2003; 24: 239–45

26 **Hu WL, Hu LQ, Song J et al.** Fibrosis of corpus cavernosum in animals following cavernous nerve ablation. *Asian J Androl* 2004; 6: 111–6

27 **Vignozzi L, Filippi S, Morelli A et al.** Effect of chronic tadalafil administration on penile hypoxia induced by cavernous neurotomy in the rat. *J Sex Med* 2006; 3: 419–31

28 **Sirad F, Hlaing S, Kovanecz I et al.** Sildenafil promotes smooth muscle preservation and ameliorates fibrosis through modulation of extracellular matrix and tissue growth factor gene expression after bilateral cavernosal nerve resection in the rat. *J Sex Med* 2011; 8: 1048–60

29 **Iacono F, Giannella R, Somma P, Manno G, Fusco F, Mirone V.** Histological alterations in cavernous tissue after radical prostatectomy. *J Urol* 2005; 173: 1673–6

30 **Montorsi F, Guazzoni G, Strambi LF et al.** Recovery of spontaneous erectile function after nerve-sparing radical retropubic prostatectomy with and without early intracavernous injections of alprostadil: results of a prospective, randomized trial. *J Urol* 1997; 158: 1408–10

31 **McCullough AR, Hellstrom WG, Wang R, Lepor H, Wagner KR, Engel JD.** Recovery of erectile function after nerve sparing radical prostatectomy and penile rehabilitation with nightly intraurethral alprostadil versus sildenafil citrate. *J Urol* 2010; 183: 2451–6

32 **Raina R, Pahlajani G, Agarwal A, Zippe CD.** The early use of transurethral alprostadil after radical prostatectomy potentially facilitates an earlier return of erectile function and successful sexual activity. *BJU Int* 2007; 100: 1317–21

33 **Mulhall JP, Parker M, Waters BW, Flanigan R.** The timing of penile rehabilitation after bilateral nerve-sparing radical prostatectomy affects the recovery of erectile function. *BJU Int* 2010; 105: 37–41

34 **Mulhall J, Land S, Parker M, Waters WB, Flanigan RC.** The use of an erectogenic pharmacotherapy regimen following radical prostatectomy improves recovery of spontaneous erectile function. *J Sex Med* 2005; 2: 532–40

35 **Salonia A, Gallina A, Zanni G et al.** Acceptance of and discontinuation rate from erectile dysfunction oral treatment in patients following bilateral nerve-sparing radical prostatectomy. *Eur Urol* 2008; 53: 564–70

36 **Polito M, d'Anzeo G, Conti A, Muzzonigro G.** Erectile rehabilitation with intracavernous alprostadil after radical prostatectomy: refusal and dropout rates. *BJU Int* 2012; 110: E954–7

37 **Nandipati K, Raina R, Agarwal A, Zippe CD.** Early combination therapy: intracavernosal injections and sildenafil following radical prostatectomy increases sexual activity and the return of natural erections. *Int J Impot Res* 2006; 18: 446–51

38 **Gontero P, Fontana F, Bagnasacco A et al.** Is there an optimal time for intracavernous prostaglandin E1 rehabilitation following nonnerve sparing radical prostatectomy? Results from a hemodynamic prospective study. *J Urol* 2003; 169: 2166–9

39 **Yiou R, Cunin P, de la Taille A et al.** Sexual rehabilitation and penile pain associated with intracavernous alprostadil after radical prostatectomy. *J Sex Med* 2011; 8: 575–82

40 **Schwartz EJ, Wong P, Graydon RJ.** Sildenafil preserves intracorporeal smooth muscle after radical retropubic prostatectomy. *J Urol* 2004; 171 (2 Pt 1): 771–4

41 **Iacono F, Prezioso D, Somma P, Chierchia S, Galasso R, Micheli P.** Histopathologically proven prevention of post-prostatectomy cavernosal fibrosis with sildenafil. *Urol Int* 2008; 80: 249–52

42 **Padma-Nathan H, McCullough AR, Levine LA et al.** Randomized, double-blind, placebo-controlled study of postoperative nightly sildenafil citrate for the prevention of erectile dysfunction after bilateral nerve-sparing radical prostatectomy. *Int J Impot Res* 2008; 20: 479–86

43 **McCullough AR, Levine LA, Padma-Nathan H.** Return of nocturnal erections and erectile function after bilateral nerve-sparing radical prostatectomy in men treated nightly with sildenafil citrate: subanalysis of a longitudinal randomized double-blind placebo-controlled trial. *J Sex Med* 2008; 5: 476–84

44 **Montorsi F, Brock G, Lee J et al.** Effect of nightly versus on-demand vardenafil on recovery of erectile function in men following bilateral nerve-sparing radical prostatectomy. *Eur Urol* 2008; 54: 924–31

45 **Aydogdu O, Gokce MI, Burgu B, Baltaci S, Yaman O.** Tadalafil rehabilitation therapy preserves penile size after bilateral nerve sparing radical retropubic prostatectomy. *Int Braz J Urol* 2011; 37: 336–44

46 **Bannowsky A, Schulze H, van der Horst C, Hautmann S, Junemann KP.** Recovery of erectile function after nerve-sparing radical prostatectomy: improvement with nightly low-dose sildenafil. *BJU Int* 2008; 101: 1279–83

47 **Broderick GA, McGahan JP, Stone AR, White RD.** The hemodynamics of vacuum constriction erections: assessment by color Doppler ultrasound. *J Urol* 1992; 147: 57–61

48 **Bosshardt RJ, Farwerk R, Sikora R, Sohn M, Jakse G.** Objective measurement of the effectiveness, therapeutic success and dynamic mechanisms of the vacuum device. *Br J Urol* 1995; 75: 786–91

49 **Yuan J, Westney OL, Wang R.** Design and application of a new rat-specific vacuum erectile device for penile rehabilitation research. *J Sex Med* 2009; 6: 3247–53

50 **Yuan J, Lin H, Li P et al.** Molecular mechanisms of vacuum therapy in penile rehabilitation: a novel animal study. *Eur Urol* 2010; 58: 773–80

51 **Kohler TS, Pedro R, Hendlin K et al.** A pilot study on the early use of the vacuum erection device after radical retropubic prostatectomy. *BJU Int* 2007; 100: 858–62

52 **Raina R, Agarwal A, Ausmundson S et al.** Early use of vacuum constriction device following radical prostatectomy facilitates early sexual activity and potentially earlier return of erectile function. *Int J Impot Res* 2006; 18: 77–81

53 **Engel JD.** Effect on sexual function of a vacuum erection device post-prostatectomy. *Can J Urol* 2011; 18: 5721–5

54 **Nelson CJ, Choi JM, Mulhall JP, Roth AJ.** Determinants of sexual satisfaction in men with prostate cancer. *J Sex Med* 2007; 4: 1422–7

55 **Son H, Park K, Kim SW, Paick JS.** Reasons for discontinuation of sildenafil citrate after successful restoration of erectile function. *Asian J Androl* 2004; 6: 117–20

56 **Canada AL, Neese LE, Sui D, Schover LR.** Pilot intervention to enhance sexual rehabilitation for couples after treatment for localized prostate carcinoma. *Cancer* 2005; 104: 2689–700

57 **Titta M, Tavolini IM, Moro FD, Cisternino A, Bassi P.** Sexual counseling improved erectile rehabilitation after non-nerve-sparing radical retropubic prostatectomy or cystectomy–results of a randomized prospective study. *J Sex Med* 2006; 3: 267–73

58 **Molton IR, Siegel SD, Penedo FJ et al.** Promoting recovery of sexual functioning after radical prostatectomy with group-based stress management: the role of interpersonal sensitivity. *J Psychosom Res* 2008; 64: 527–36

59 **Schover LR, Fouladi RT, Warneke CL et al.** Defining sexual outcomes after treatment for localized prostate carcinoma. *Cancer* 2002; 95: 1773–85

60 **Shindel A, Quayle S, Yan Y, Husain A, Naughton C.** Sexual dysfunction in female partners of men who have undergone radical prostatectomy correlates with sexual dysfunction of the male partner. *J Sex Med* 2005; 2: 833–41

61 **Davison BJ, Elliott S, Ekland M, Griffin S, Wiens K.** Development and evaluation of a prostate sexual rehabilitation clinic: a pilot project. *BJU Int* 2005; 96: 1360–4

62 **Burgers JK, Nelson RJ, Quinlan DM, Walsh PC.** Nerve growth factor, nerve grafts and amniotic membrane grafts restore erectile function in rats. *J Urol* 1991; 146: 463–8

63 **Ball RA, Lipton SA, Dreyer EB, Richie JP, Vickers MA.** Entubulization repair of severed cavernous nerves in the rat resulting in return of erectile function. *J Urol* 1992; 148: 211–5

64 **Jung GW, Spencer EM, Lue TF.** Growth hormone enhances regeneration of nitric oxide synthase-containing penile nerves after cavernous nerve neurotomy in rats. *J Urol* 1998; 160: 1899–904

65 **Bochinski D, Hsieh PS, Nunes L et al.** Effect of insulin-like growth factor-1 and insulin-like growth factor binding protein-3 complex in cavernous nerve cryoablation. *Int J Impot Res* 2004; 16: 418–23

66 **Allaf ME, Hoke A, Burnett AL.** Erythropoietin promotes the recovery of erectile function following cavernous nerve injury. *J Urol* 2005; 174: 2060–4

67 **Lee MC, El-Sakka AI, Graziottin TM, Ho HC, Lin CS, Lue TF.** The effect of vascular endothelial growth factor on a rat model of traumatic arteriogenic erectile dysfunction. *J Urol* 2002; 167 (2 Pt 1): 761–7

68 **Bella AJ, Lin G, Garcia MM et al.** Upregulation of penile brain-derived neurotrophic factor (BDNF) and activation of the JAK/STAT signalling pathway in the major pelvic ganglion of the rat after cavernous nerve transection. *Eur Urol* 2007; 52: 574–80

69 **Podlasek CA, Meroz CL, Tang Y, McKenna KE, McVary KT.** Regulation of cavernous nerve injury-induced apoptosis by sonic hedgehog. *Biol Reprod* 2007; 76: 19–28

70 **Sezen SF, Lagoda G, Burnett AL.** Role of immunophilins in recovery of erectile function after cavernous nerve injury. *J Sex Med* 2009; 6 (Suppl. 3): 340–6

71 **Bella AJ, Fandel TM, Tantiwongse K et al.** Neurturin enhances the recovery of erectile function following bilateral cavernous nerve crush injury in the rat. *J Brachial Plex Peripher Nerve Inj* 2007; 2: 5

72 **Fandel TM, Bella AJ, Tantiwongse K et al.** The effect of intracavernosal growth differentiation factor-5 therapy in a rat model of cavernosal nerve injury. *BJU Int* 2006; 98: 632–6

73 **Kendirci M, Zsengeller Z, Bivalacqua TJ et al.** Poly(Adenosine diphosphate-ribose) polymerase inhibition preserves erectile function in rats after cavernous nerve injury. *J Urol* 2005; 174: 2054–9

74 **Bessede T, Alsaid B, Ferretti L et al.** Effect of a local delivery of triiodothyronine (T3) within neuroregenerative guide on recovery of erectile function in a rat-model of cavernous nerve injury. *J Sex Med* 2010; 7: 1798–806

75 **Gratzke C, Strong TD, Gebska MA et al.** Activated RhoA/Rho kinase impairs erectile function after cavernous nerve injury in rats. *J Urol* 2010; 184: 2197–204

76 **Bochinski D, Lin GT, Nunes L et al.** The effect of neural embryonic stem cell therapy in a rat model of cavernosal nerve injury. *BJU Int* 2004; 94: 904–9

77 **Albersen M, Kendirci M, Van der Aa F, Hellstrom WJ, Lue TF, Spees JL.** Multipotent stromal cell therapy for cavernous nerve injury-induced erectile dysfunction. *J Sex Med* 2012; 9: 385–403

78 **Traish AM, Guay AT.** Are androgens critical for penile erections in humans? Examining the clinical and preclinical evidence. *J Sex Med* 2006; 3: 382–404

79 **Vignozzi L, Filippi S, Morelli A et al.** Cavernous neurotomy in the rat is associated with the onset of an overt condition of hypogonadism. *J Sex Med* 2009; 6: 1270–83

80 **Kim SC, Song C, Kim W et al.** Factors determining functional outcomes after radical prostatectomy: robot-assisted versus retropubic. *Eur Urol* 2011; 60: 413–9

81 **Shabsigh R, Kaufman JM, Steidle C, Padma-Nathan H.** Randomized study of testosterone gel as adjunctive therapy to sildenafil in hypogonadal men with erectile dysfunction who do not respond to sildenafil alone. *J Urol* 2008; 179 (5 Suppl.): S97–S102

82 **Spitzer M, Basaria S, Travison TG et al.** Effect of testosterone replacement on response to sildenafil citrate in men with erectile dysfunction: a parallel, randomized trial. *Ann Intern Med* 2012; 157: 681–91

83 **Buvat J, Maggi M, Guay A, Torres LO.** Testosterone deficiency in men: systematic review and standard operating procedures for diagnosis and treatment. *J Sex Med* 2013; 10: 245–84

84 **Bhasin S, Cunningham GR, Hayes FJ et al.** Testosterone therapy in men with androgen deficiency syndromes: an Endocrine Society clinical practice guideline. *J Clin Endocrinol Metab* 2010; 95: 2536–59

85 **Gallina A, Ferrari M, Suardi N et al.** Erectile function outcome after bilateral nerve sparing radical prostatectomy: which patients may be left untreated? *J Sex Med* 2012; 9: 903–8

86 **Briganti A, Di TE, Abdollah F et al.** Choosing the best candidates for penile rehabilitation after bilateral nerve-sparing radical prostatectomy. *J Sex Med* 2012; 9: 608–17

87 **Sanchez-Cruz JJ, Cabrera-Leon A, Martin-Morales A, Fernandez A, Burgos R, Rejas J.** Male erectile dysfunction and health-related quality of life. *Eur Urol* 2003; 44: 245–53

88 **Blount MA, Beasley A, Zoraghi R et al.** Binding of tritiated sildenafil, tadalafil, or vardenafil to the phosphodiesterase-5 catalytic site displays potency, specificity, heterogeneity, and cGMP stimulation. *Mol Pharmacol* 2004; 66: 144–52

89 **Briganti A, Gallina A, Suardi N et al.** What is the definition of a satisfactory erectile function after bilateral nerve sparing radical prostatectomy? *J Sex Med* 2011; 8: 1210–7

90 **Jannini EA, Isidori AM, Gravina GL et al.** The ENDOTRIAL study: a spontaneous, open-label, randomized, multicenter, crossover study on the efficacy of sildenafil, tadalafil, and vardenafil in the treatment of erectile dysfunction. *J Sex Med* 2009; 6: 2547–60

91 **Mehrotra N, Gupta M, Kovar A, Meibohm B.** The role of pharmacokinetics and pharmacodynamics in phosphodiesterase-5 inhibitor therapy. *Int J Impot Res* 2007; 19: 253–64

92 **Ghofrani HA, Voswinckel R, Reichenberger F et al.** Differences in hemodynamic and oxygenation responses to three different phosphodiesterase-5 inhibitors in patients with pulmonary arterial hypertension: a randomized prospective study. *J Am Coll Cardiol* 2004; 44: 1488–96

93 **Tal R, Teloken P, Mulhall JP.** Erectile function rehabilitation after radical prostatectomy: practice patterns among AUA members. *J Sex Med* 2011; 8: 2370–6

94 **Giuliano F, Amar E, Chevallier D, Montaigne O, Joubert JM, Chartier-Kastler E.** How urologists manage erectile dysfunction after radical prostatectomy: a national survey (REPAIR) by the French urological association. *J Sex Med* 2008; 5: 448–57

95 **Teloken P, Mesquita G, Montorsi F, Mulhall J.** Post-radical prostatectomy pharmacological penile rehabilitation: practice patterns among the international society for sexual medicine practitioners. *J Sex Med* 2009; 6: 2032–8

96 **Miles CL, Candy B, Jones L, Williams R, Tookman A, King M.** Interventions for sexual dysfunction following treatments for cancer. *Cochrane Database Syst Rev* 2007; (4): CD005540

97 **Costabile RA, Spevak M, Fishman IJ et al.** Efficacy and safety of transurethral alprostadil in patients with erectile dysfunction following radical prostatectomy. *J Urol* 1998; 160: 1325–8

98 **Raina R, Agarwal A, Allamaneni SS, Lakin MM, Zippe CD.** Sildenafil citrate and vacuum constriction device combination enhances sexual satisfaction in erectile dysfunction after radical prostatectomy. *Urology* 2005; 65: 360–4

99 **Raina R, Agarwal A, Zaramo CE, Ausmundson S, Mansour D, Zippe CD.** Long-term efficacy and compliance of MUSE for erectile dysfunction following radical prostatectomy: SHIM (IIEF-5) analysis. *Int J Impot Res* 2005; 17: 86–90

100 **Mydlo JH, Viterbo R, Crispen P.** Use of combined intracorporal injection and a phosphodiesterase-5 inhibitor therapy for men with a suboptimal response to sildenafil and/or vardenafil monotherapy after radical retropubic prostatectomy. *BJU Int* 2005; 95: 843–6

101 **Baniel J, Israilov S, Segenreich E, Livne PM.** Comparative evaluation of treatments for erectile dysfunction in patients with prostate cancer after radical retropubic prostatectomy. *BJU Int* 2001; 88: 58–62

102 **Montorsi F, Nathan HP, McCullough A et al.** Tadalafil in the treatment of erectile dysfunction following bilateral nerve sparing radical retropubic prostatectomy: a randomized, double-blind, placebo controlled trial. *J Urol* 2004; 172: 1036–41

103 **Montorsi F, McCullough A.** Efficacy of sildenafil citrate in men with erectile dysfunction following radical prostatectomy: a systematic review of clinical data. *J Sex Med* 2005; 2: 658–67

Correspondence: Mikkel Fode, Herlev Hospital, Department of Urology, HA54F1, Herlev Ringvej 75, DK-2730, Herlev, Denmark.

e-mail: mikkelfode@gmail.com

Abbreviations: ED, erectile dysfunction; RP, radical prostatectomy; PDE5, phosphodiesterase type 5; PDE5I, PDE5 inbitor; VED, vacuum erection device; MUSE, Medicated Urethral System for Erection; IIEF-5, five-item International Index of Erectile Function; NO, nitric oxide; iNOS, inducible nitric oxide; CCI, Charlson Comorbidity Index; IIEF-EF, IIEF erectile function domain.

