UNIVERSIDADE
BEIRA INTERIOR

Penile Rehabilitation Following Radical Prostatectomy

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Dissertação para obtenção do Grau de Mestre em
Medicina
(mestrado integrado)

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abril de 2021

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Resumo

Introdução. A prostatectomia radical é um tratamento de primeira linha para o cancro da próstata localizado. Porém, apesar de aperfeiçoamentos técnicos, tanto a disfunção sexual como a disfunção erétil permanecem importantes complicações pós-cirúrgicas, pelo que a reabilitação peniana visa otimizar a velocidade e extensão de recuperação da função sexual no pós-operatório. Contudo, ainda que hoje considerada parte integrante da gestão do doente e habitualmente utilizada na prática clínica, a reabilitação peniana carece de claras recomendações médicas.

Métodos. Uma pesquisa bibliográfica abrangente foi realizada para identificar publicações relevantes para a reabilitação peniana pós-prostatectomia radical através da PubMed e demais bases de dados. Tanto termos livres como MeSH foram utilizados, tendo a pesquisa sido restrita a artigos em inglês, publicados até fevereiro de 2021. Apenas artigos completos foram incluídos na análise final, juntamente com livros de interesse e publicações encontradas nas listas de referências dos artigos selecionados.

Resultados. Doentes com indicação para prostatectomia radical devem ser informados sobre o risco de disfunção sexual, e não apenas de disfunção erétil. De forma controversa, a reabilitação peniana precoce pode aumentar o potencial de recuperação da função erétil e do tratamento da disfunção, mas alguns doentes podem incorrer em gastos económicos significativos sem obter benefício, daí que não seja possível emitir recomendações para a aplicação de um regime terapêutico específico. Tratamentos de primeira linha incluem inibidores orais da PDE5, alprostadil e dispositivos de vácuo, reservando-se as próteses penianas para situações de fracasso das medidas conservadoras. Li-ESWT e terapias baseadas em células estaminais, plaquetas e genes constituem novas modalidades promissoras em investigação, sugerindo-se ainda aconselhamento psicológico e sexual. Todavia, é necessária investigação de melhor qualidade que transcenda os padrões heteronormativos habituais, incluindo questões sobre líbido e satisfação sexual. Na prática clínica, deve promover-se o envolvimento de ambos os parceiros e a adaptação sexual como meta de reabilitação para além da recuperação da função erétil.

Conclusão. Não há evidência que suporte qualquer protocolo específico de reabilitação. Ainda que inibidores orais da PDE5 permaneçam como escolhas de primeira linha, a seleção do tratamento deve sempre refletir a preferência do doente. No futuro, deve ser

explorado o potencial da medicina regenerativa e adotada a adaptação sexual como objetivo principal da reabilitação.

Palavras-chave

Disfunção erétil; reabilitação peniana; cancro da próstata; prostatectomia radical.

Resumo alargado

Introdução. A prostatectomia radical é um tratamento de primeira linha para o cancro da próstata localizado, de risco intermédio, em homens com esperança média de vida superior a 10 anos. Porém, apesar de aperfeiçoamentos técnicos, tanto a disfunção sexual como a disfunção erétil permanecem importantes complicações pós-cirúrgicas que podem impactar significativamente de forma negativa a qualidade de vida dos doentes. Dado o diagnóstico em idades cada vez mais jovens, a função erétil no pós-operatório ganhou nova relevância nos últimos anos, com a reabilitação peniana a surgir para melhorar ao máximo a velocidade e extensão da sua recuperação. Contudo, ainda que hoje considerada parte integrante da gestão do doente e habitualmente utilizada na prática clínica, a reabilitação peniana carece de claras recomendações médicas.

Métodos. Uma pesquisa bibliográfica abrangente foi realizada para identificar publicações relevantes para a reabilitação peniana após prostatectomia radical através da PubMed e demais bases de dados. Tanto termos livres como MeSH foram utilizados, incluindo “prostate cancer”, “radical prostatectomy”, “erectile dysfunction”, “sexual dysfunction”, “penile erection”, “penile rehabilitation”, “sexual rehabilitation”, “phosphodiesterase type-5 inhibitor”, “alprostadil” e “vacuum device”, tendo a pesquisa sido restrita a artigos em inglês, publicados até fevereiro de 2021. Apenas artigos completos foram incluídos na análise final, a qual abrangeu outros livros de interesse e publicações encontradas nas listas de referências dos artigos selecionados.

Resultados. Doentes com indicação para prostatectomia radical devem ser informados sobre o risco de disfunção sexual, e não apenas de disfunção erétil, gerindo-se expetativas realistas para facilitar tomadas de decisão guiadas pelas práticas sexuais individuais. Historicamente, qualquer reabilitação o mais precocemente possível tem sido considerada preferível a deixar a situação evoluir sem tratamento, já que a recuperação funcional espontânea pode demorar até 4 anos. De forma controversa, a reabilitação peniana precoce pode aumentar o potencial de recuperação da função erétil e do tratamento da disfunção, mas alguns doentes podem incorrer em gastos económicos significativos sem obter benefício, daí que não seja possível emitir recomendações para a aplicação de um regime terapêutico específico. Presentemente, tratamentos de primeira linha incluem: inibidores orais da PDE5, pela comprovada eficácia, segurança, facilidade de uso e impacto positivo na qualidade de vida,

conquanto estejam contraindicados em doentes sob terapêutica com nitratos ou alfa-bloqueantes; alprostadil, embora apresente um perfil mais acentuado de efeitos adversos; e dispositivos por vácuo, nomeadamente em doentes com infrequentes relações sexuais e requerendo opções terapêuticas não invasivas ou medicamentosas. Adicionalmente, o uso diário de inibidores da PDE5 não se mostrou superior à administração no momento da relação sexual, pelo que não deve ser a norma. A colocação de próteses penianas reserva-se a situações de fracasso das medidas conservadoras. Terapêuticas alternativas incluem: abordagem psicológica, sugerida em conjunto com aconselhamento sexual para integrar qualquer plano de reabilitação; masturbação; treino dos músculos do pavimento pélvico; e suplementação de testosterona. Apesar da fraca evidência, ressalva-se que a masturbação, em particular, não acarreta custos nem efeitos adversos e poderá exercer um efeito protetor da função do tecido peniano. Li-ESWT e terapias baseadas em células estaminais, plaquetas e genes constituem novas modalidades promissoras em investigação. Todavia, é necessária investigação de melhor qualidade que transcenda os padrões heteronormativos habituais, incluindo questões sobre líbido e satisfação sexual, para evitar a futilidade terapêutica (*e.g.*, em homens com baixo desejo sexual). Recomendações para populações específicas incluem considerar tratamentos mais invasivos e PrEP em homens que fazem sexo com homens, dada a necessidade de ereções mais firmes para a penetração anal fazer antever menor eficácia das terapêuticas habituais, bem como o menor uso de preservativos e o consequente aumento do risco de transmissão de doenças sexualmente transmissíveis. Na prática clínica, deve ainda promover-se o envolvimento de ambos os parceiros e a adaptação sexual como meta de reabilitação para além da recuperação da função erétil, cabendo aos médicos fornecer um ambiente confortável que permita aos doentes sentirem-se à vontade para revelar livremente os seus problemas sexuais.

Conclusão. Não há evidência que suporte qualquer protocolo específico de reabilitação. Ainda que inibidores orais da PDE5 permaneçam como escolhas de primeira linha, a seleção do tratamento deve sempre refletir a preferência do doente e a frequência da sua prática sexual. No futuro, deve ser explorado o potencial da medicina regenerativa e adotada a adaptação sexual como objetivo principal da reabilitação, uma vez que a satisfação sexual não depende exclusivamente da função erétil e desta forma se garante a preservação da atividade sexual dos doentes mesmo em caso de falha terapêutica. O papel do clínico assume particular relevância por ser modificador de crenças dos doentes relativas à reabilitação peniana e assim poder fomentar a correta utilização do tratamento preferido.

Abstract

Background. Radical prostatectomy is a first-line treatment for localised prostate cancer. Despite refinements in the operative techniques, sexual dysfunction, namely erectile dysfunction, remains an important possible complication. Penile rehabilitation aims to maximally improve the speed and extent of sexual function recovery and is now considered an integral part of patient management after radical prostatectomy with continued use in clinical practice. Yet, clear recommendations remain to be presented.

Methods. A comprehensive literature search was conducted to identify publications relevant to penile rehabilitation following radical prostatectomy using PubMed and other databases. Both free text and MeSH terms were employed in a search restricted to English-language studies published until February of 2021. Only full-text articles were included in the final analysis. Additional relevant sources encompassed books of interest and articles found in reference lists.

Results. Patients undergoing radical prostatectomy should be informed about the risk of sexual dysfunction, and not only erectile dysfunction. Early penile rehabilitation may elevate the potential of both erectile function recovery and dysfunction treatment, yet this trend remains controversial, and some patients may incur in significant financial expenditure without experiencing clear benefits. No recommendation for the use of any specific regimen is possible. First-line treatments include oral PDE5 inhibitors, alprostadil-based therapies, and vacuum devices. Penile prosthesis implantation is reserved for failure of conservative measures. Li-ESWT, and stem cell, gene and PRP-based therapies are promising novel modalities still under investigation. Both psychological and sexual counselling are advisable. Better quality research transcending the usual heteronormative standards is needed, including questions on libido and sexual bother or satisfaction. Clinicians should promote the involvement of both partners and encourage sexual adaptation as a goal of rehabilitation besides erectile recovery.

Conclusion. Current evidence does not explicitly support any penile rehabilitation program. Oral PDE5 inhibitors remain the first-line choice, but treatment selection should ultimately reflect patient preference. Future directions should explore the potential of regenerative medicine and adopt sexual adaptation as the main goal of rehabilitation.

Keywords

Erectile dysfunction; penile rehabilitation; prostate cancer; radical prostatectomy.

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List of abbreviations

APA	accessory pudendal artery
bNSRP	bilateral nerve-sparing radical prostatectomy
cAMP	cyclic adenosine monophosphate
cGMP	cyclic guanosine monophosphate
ED	erectile dysfunction
EF	erectile function
eNOS	endothelial nitric oxide synthase
HIF-1α	hypoxia-inducible factor-1α
HIV	human immunodeficiency virus
ICI	intracavernous injection
IIEF	International Index of Erectile Function
IIEF-EF	erectile function domain of the IIEF
IIEF-5	abridged five-item version of the IIEF
Li-ESWT	low-intensity extracorporeal shock wave therapy
MeSH	Medical Subject Headings
MUSE	Medicated Urethral System for Erection
nNOS	neuronal nitric oxide synthase
NOS	nitric oxide synthase
NSRP	nerve-sparing radical prostatectomy
PDE5	phosphodiesterase type-5
PDE5i	phosphodiesterase type-5 inhibitors
PGE1	prostaglandin E1
PrEP	pre-exposure prophylaxis
PROM	patient-reported outcome measure
PRP	platelet-rich plasma
PSA	prostate-specific antigen
QoL	quality of life
RP	radical prostatectomy
SEP	Sexual Encounter Profile
STI	sexually transmitted infection
TGF-β	transforming growth factor-β
VED	vacuum erection device

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Chapter 1

Introduction

Prostate cancer (PCa) is a major health concern in men (1). In 2020, its 375.304 attributable deaths made it the fifth leading cause of cancer death in men worldwide, while its estimated 1.4 million new cases ranked it as the second most frequent globally and the most frequently diagnosed cancer among men in the majority of world countries (112 of 185, including Portugal), thus accounting for 14.1% of all cancers diagnosed in males (2). In later decades, as the widespread introduction of prostate-specific antigen (PSA) testing allowed the detection of preclinical cancers (2), patients of increasingly younger age undergo radical prostatectomy (RP), a first-line treatment with curative-intent offered to men with intermediate-risk localised PCa and a life expectancy > 10 years (1). It stands to reason that better baseline erectile function (EF) is to be expected more and more, as well as increased awareness concerning the importance of preserving sexual functioning following treatment. Despite refinements in the operative techniques, sexual dysfunction, namely erectile dysfunction (ED), remains an important possible complication of RP with the potential to significantly alter the patients' quality of life (QoL) (3).

To explore this issue, an increasing body of research has focused on the concept of penile rehabilitation, i.e., prevention of cavernous tissue damage during the period of neural recovery (4), which ultimately aims to maximally improve the speed and extent of sexual function recovery before and after any insult to the penile erectile physiological axis (5,6). Given the advent of interventions such as vacuum devices, phosphodiesterase type-5 inhibitors (PDE5i), and transurethral and intracavernous agents, penile rehabilitation is now considered an integral part of patient management after RP (5), with a trend existing for measures to be undertaken as soon as possible following surgery (6). Nonetheless, this body of evidence presents major methodological limitations, e.g., lack of blinding and overall inconsistency owing to the studies' design heterogeneity (6). This, in addition to discordant results and a shortage of meaningfully designed clinical trials, explains how no clear recommendation is possible at this time, despite continued use in clinical practice (1,6).

Therefore, this work aims to summarise the topic's evolution and provide evidence-based advice for better clinical decision-making, while highlighting novel advances and establishing expectations for future clinical and investigational settings' practices.

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Chapter 2

Methods

A comprehensive literature search was conducted to identify publications relevant to penile rehabilitation following RP using PubMed, Medscape, ScienceDirect, Wiley Online Library, *The Journal of Urology*, *The Journal of Sexual Medicine* (JSM), *International Journal of Impotence Research*, and *Nature Reviews Urology* databases. Both free text and MeSH terms were employed to retrieve articles, including the following chosen keywords: “prostate cancer”, “radical prostatectomy”, “erectile dysfunction”, “sexual dysfunction”, “penile erection”, “penile rehabilitation”, “sexual rehabilitation”, “phosphodiesterase type-5 inhibitor”, “alprostadil”, “vacuum device”. Search was restricted to English-language studies, and while no limits were applied concerning the year of publication at the time of initial discovery in October 2020, relevance and later date were criteria used in the selection process. Research was subsequently repeated in February 2021 to ensure accuracy. Resulting articles were screened based on titles and abstracts and selected after a full review. Reference lists were then manually examined to find other relevant articles not reached by initial research. Only full-text articles were included in the final analysis. Additionally, books considered of interest to the topic were also consulted and duly referenced in the final reference list.

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Chapter 3

General approach to radical prostatectomy and sexual dysfunction

3.1 Radical prostatectomy

Radical prostatectomy (RP) has vastly evolved since its first description in 1904 by Hugh Hampton Young. Now performed by an either open, laparoscopic, or robot-assisted approach, this surgical procedure involves removing the entire prostate with its capsule intact and seminal vesicles, followed by undertaking urethrovesical anastomosis (1). Considered a highly effective treatment for localised PCa, it is commonly associated with risk of erectile dysfunction (ED) as a postoperative issue, despite the development of nerve-sparing techniques that preserve the autonomic nerves' anatomical integrity (7). Evidence remains inconclusive as to whether the newer robotic techniques have better long-term functional outcomes compared to pure open or laparoscopic RP (1,8,9).

3.2 Erectile dysfunction

Erectile dysfunction (ED), also known as impotence, is the consistent or recurrent inability to attain and/or maintain penile erection sufficient for satisfactory sexual performance (10). The introduction and continuous optimisation of different surgical techniques has resulted in a wide variation in the overall prevalence of ED after RP, estimated to range from 6% to 68% (9). Patients with comorbid medical conditions or prior users of erectile aids for ED are at greater risk (11). Chances of recovery are strongly influenced by age, vascular risk factors, preservation of the neurovascular bundles during surgery, and pre-existing EF (8,12).

3.2.1 Pathophysiology

The pathophysiology of post-prostatectomy ED has been extensively investigated. Current consensus points towards a multifactorial aetiology (13) in close association with altered neurovascular mechanisms responsible for corporal smooth muscle change (4).

Nitric oxide (NO), the principal mediator in erectile physiology, is generated by cleavage of its precursor L-arginine by the enzyme nitric oxide synthase (NOS) (14). Upon sexual stimulation, the neuronal isoform of NOS (nNOS) found in cavernous nerves terminals leads to activation of the cyclic guanosine monophosphate (cGMP) pathway, inducing a momentary reduction in intracellular calcium concentration (14,15). Consequently, corpora cavernosa vascular smooth muscle relaxation allows the transient increase of oxygenated blood flow into the penis and

provides the vascular endothelial cells with the free oxygen needed to further produce NO from L-arginine, just as the sheer forces on the endothelium resulting from enlargement of the vasculature and sinusoidal spaces within the penis ensure a sustained endothelial NOS (eNOS) release (16,17). Neuronal-derived NO is thus thought to initiate erection, while endothelial-derived NO is thought to help maintain it (14). Such a mechanism for production of bioavailable NO is crucial for occurrence of intercourse-related erections as well as long-term maintenance of corporal tissue health (16,17). The phenomenon of erection occurs once lacunar space radial expansion compresses the subtunical venules against the tunica albuginea (corporal veno-occlusive mechanism), thereby effectively entrapping blood within the penis and blocking venous outflow (15,16).

Since cavernous nerves are essential structures in providing normal EF, neurogenic injury is an important cause of EF impairment. Anatomically of small size and hence harder to visualise during surgery, cavernous nerves are inadvertently more prone to intraoperative trauma and damage (18). However, even during true nerve-sparing procedures, nerves are likely to be affected by direct trauma, mechanical stretching during prostate retraction, thermal damage from electrocauterization, ischaemia secondary to vascular injury, and local inflammation (13,17,19). All of these are considered aetiological hypotheses for neuropraxia, a temporary failure in nerve conduction despite anatomical maintenance of the nerve fibre integrity (19). The proximity of the neurovascular bundle to the prostate makes neuropraxia essentially unavoidable following RP (16), and its immediate effect is the loss of daily and nocturnal erections (4) that may last up to 4 years (20).

During this period, the penile tissue is in a constant state of reduced oxygenation, which may lead to smooth muscle apoptosis and fibrosis of faster onset than pure organic ED, given the sudden cut-off of highly oxygenated blood as opposed to a gradual decrease (16). This state is probably amplified by the absence of erections since some form of exercise is required by all musculature to maintain its integrity and health (5). Significantly higher expression of mammalian transcription factor HIF-1α in neurotomised rats further confirmed that loss of nocturnal erections prompted a low-oxygen environment in rat penises (21). Hypoxia disrupts the NO/cGMP pathway by significantly reducing the synthesis and release of nNOS and NO, thereby compromising the endothelium-dependent and neurogenic relaxation of corpora cavernosa smooth muscle (18). Animal models have linked these processes to inhibition and consequent decrease of antifibrotic mediators' levels, namely prostaglandin E1 (PGE1) and cAMP (4,16,17). No resultant inhibition of proapoptotic and profibrotic substances' accumulation results in increased synthesis of cytokines (namely TGF-β1), reactive oxygen species and endothelin-1 (a potent constrictor of penile smooth muscle), the latter amplified by both TGF-β1 and prolonged hypoxia (4,5,13,17). The cavernous tissue then counteracts these processes through endogenous production of the inducible isoform of NOS (iNOS) and its secondary messenger, cGMP (4,17).

This explains how prolonged exposure to hypoxia results in the promotion of connective tissue synthesis (through upregulation of collagen types I and III) in replacement of elastic trabecular smooth muscle, hence shifting the smooth muscle-collagen ratio in favour of collagen (13,16). Development of fibrosis within the corpora cavernosa compromises smooth muscle radial expansion, eventually leading to insufficient compression of the subtunical venules and venous leak (4,16). Cavernous veno-occlusive dysfunction increases over time and possibly derives from both loss of smooth muscle due to cellular apoptosis (not of the endothelium, and particularly in the subtunical area) (17) and increased collagen deposition, thereby converting a temporary neural injury into permanent ED (22).

Independently from the effect of neuropraxia on cavernous oxygenation, vascular injury has been suggested to promote penile hypoxia following inadvertent intraoperative ligation of accessory pudendal arteries (APAs). APAs are super-diaphragmatic arteries, arising from the femoral, obturator or vesical arteries, that may be present in the male population (8). Rogers et al. (23) found the effect of artery preservation to more than double the likelihood of potency compared with excision, although no significant difference was found when compared with controls, as well as an association with a shorter median time to regain potency (6 vs. 12 months). Conversely, Williams et al. (24) found transection of APAs had no impact on recovery of potency. Hence, while optimal, the actual benefit of APA surgical preservation on EF recovery remains unclear (8).

As it is, both mechanisms may exacerbate relative hypoxia, especially in combination (13). It is worth remembering that nerve injury and hypoxia concurrently lead to a loss of smooth muscle and an increase in collagen with fibrosis within the corpora cavernosa (22).

3.2.2 Patient-reported outcome measures (PROMs)

Several structured, validated tools have been developed to quantify ED severity and its consequences in sexually active men. These include the Erection Hardness Score (EHS), the Sexual Health Inventory for Men (SHIM), the Male Sexual Health Questionnaire (MSHQ), and the International Index of Erectile Function (IIEF), the latter a more detailed instrument consisting of 15 questions that quantify 5 domains (including erectile function [IIEF-EF]) (9,10). The IIEF score is thus a cross-culturally and psychometrically validated measure of EF (3), with IIEF-EF domain scores of 26-30 being consistent with normal EF (10).

Overall, there remains great inconsistency in the definition of what is considered normal baseline and postoperative EF (9). While assessment of patient satisfaction in preoperatively fully potent patients has suggested an IIEF-EF ≥ 22 after bNSRP as an appropriate cut-off in this population (3), not all patients are fully potent prior to surgery nor are their expectations the same regarding postoperative sexual performance. Later, an IIEF-EF ≥ 24 was suggested as an in-between optimal cut-off (25). Return-to-baseline EF has also been proposed (26), but this outcome is unrealistic for most patients and meaningless in men with poor baseline EF (27).

Note that the IIEF questionnaire is not validated in PCa patients (27). Hence, tools assessing cancer-specific QoL and sexual function include the Expanded Prostate Cancer Index Composite (EPIC), the UCLA Prostate Cancer Index (UCLA PCI), and the Prostate Cancer Quality of Life Instrument (PCQoL) (1). Such heterogeneity in questionnaires and arbitrary thresholds in PROMs generates discrepancies in reported outcomes that difficult comparisons between different treatment modalities (26,27). Thereby, the definition of recovery of EF after RP is still highly controversial (28) and possibly unique for the ED literature, as most studies usually include PDE5i responders as those with adequate EF (9).

Nonetheless, sexuality plays a complex part in one's well-being and any tool may disappoint in its proper assessment. Evaluation of sexual function should include a more complete view on the interaction of age, sexuality, self-esteem, and other psychosocial variables. To add insult to injury, questionnaires are almost exclusively dependent on patient recollection of sexual function that can be untruthful and biased (28).

3.3 Orgasmic dysfunctions

The experience of orgasm, as a distinct cortical event from erections, is experienced phenomenologically together with the perception of striated muscle contractions. It results in semen expelled during ejaculation, as mediated through sensory neurons in the pelvic region. Considering that the ejaculatory apparatus (prostate, seminal vesicles, and ejaculatory ducts) is removed with RP, alterations in the orgasmic experience are expected in this population (29,30).

Orgasmic complications encompass climacturia (orgasm-associated urinary incontinence, around 30%), dysorgasmia (painful orgasm, 3.2-18%), anorgasmia (5-39.7%), and altered sensation (up to 78%) (29). The prevalence of such phenomena is highly variable across available literature of questionable quality, since no internationally validated questionnaires may be used. A quick look into the orgasmic function component of the IIEF confirms its inadequacy for the post-RP population, since 1 of those 2 questions addresses ejaculation and is therefore irrelevant. Existing studies have resorted to the application of non-validated questionnaires, meaning all findings must be interpreted accordingly (29,31).

Older age, high mean body mass index, and poor EF have been associated with poor orgasmic ability. At the other end of the spectrum, factors such as nerve-sparing, prostate weight < 59 g, younger age, ED treatment, and higher levels of education have been found to be protective of orgasmic function. Nevertheless, the ability to achieve an orgasm has been noted to be more commonly retained than the ability to attain an erection, which opposes many patients' perception that men who cannot manage an erection cannot reach an orgasm. Oddly enough, researchers have also found that > 60% of patients are unaware of being unable to expel semen after RP (29).

Summarily, orgasmic dysfunctions may have a non-negligible effect on post-RP patients' sexual health. It is the clinician's responsibility to inform patients that, regardless of the lack of ejaculate and perhaps erection, they should still be able to achieve orgasm after RP (29).

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Chapter 4

Penile rehabilitation

The concept of penile rehabilitation following RP, first introduced in the late 1990s (32), is defined by attempting to prevent long-term ED while simultaneously minimising the impairment's extent and the latency of EF recovery (10), ideally with EF returning to its pre-treatment state (back-to-baseline) (11,32). The focus is on inducing penile vascular blood flow and improving cavernous oxygenation to preserve endothelial function and prevent structural changes, such as smooth muscle atrophy and collagenization, until the cavernous nerves recover from neuropraxia (8,10,13,33,34). As it is strongly perceived that a preventative scheme (i.e., before penile fibrosis develops) is maximally protective of erectile mechanisms, rehabilitation should be initiated before or soon after surgery and be continued thereafter as per the protocol's prerogative (10,32). Hence, early postoperative rehabilitation is considered of major importance for enhancement of functional status and recovery of erectile tissue (10). Furthermore, secondarily to the return of spontaneous unassisted EF, another goal of penile rehabilitation is to improve the patients' ability to become drug responders, namely to oral agents (33). Still, a clinical challenge remains in the selection of the best treatment option for each individual patient (32).

4.1 PDE5 inhibitors

Oral phosphodiesterase type-5 inhibitors (PDE5i) act by blocking the degradation of cGMP. Maintenance of high levels of cGMP leads to dilation of the corpora cavernosa smooth muscle and the accompanying penile erection following sexual stimulation (35). Hence, it is worth emphasising that PDE5i effectiveness is dependent on neuronal NO release (36). Data suggest men subjected to RP have more severe ED at baseline and a less robust response to PDE5i (10). Comorbidities such as diabetes can also be responsible for treatment failure (36). Furthermore, PDE5i coadministration with nitrates is contraindicated due to risk of potentially serious hypotension caused by excessive build-up of cGMP and pronounced vasodilatation (17). Caution is also warranted with concurrent use of alpha-blockers and potent CYP3A inhibitors such as antiretroviral protease inhibitors, macrolide antibiotics, azole antifungals, and anti-depressants (36). Dose titration and/or temporal separation of medication intake may be required (35).

Common drugs, each with its own biochemical and pharmacological properties, include sildenafil, vardenafil, tadalafil, and avanafil (35). Sildenafil and vardenafil have similar features, with an onset of action of 30-60 min and a duration of action of up to 10-12 h. Since their efficacies are decreased by high-fat meals, both drugs must be taken on an empty stomach (i.e., 1 hour before or 2 hours after eating) to maximise absorption. Avanafil can act for up to 6 h while simultaneously having the lowest time to peak concentration of 15-30 min. Tadalafil has the

longest onset and duration of action, of 60-120 min and of up to 36 h, respectively. Neither avanafil nor tadalafil are affected by intake of lipids in food (10,36). Given no significant differences in efficacy between the agents have been identified, despite limited data for avanafil (10), pharmacokinetic variances present themselves as key to individualised treatment. For instance, the longer half-life of tadalafil allows for daily usage and more spontaneous sexual activity. Conversely, a shorter half-life may lessen side events and facilitate treatment optimisation. As such, sildenafil, vardenafil and avanafil may be best suited for men who engage in sexual encounters at a more predictable time (35). Suggested starting doses include 100-mg for sildenafil and avanafil, and 20-mg for vardenafil and tadalafil (35), as dosage can be chosen at a higher level when initiating treatment for severe ED after RP. It should, however, be closely monitored and titrated to provide optimal efficacy while minimising adverse effects (36). These may include dyspepsia, headache, heartburn, facial flushing, back pain, nasal congestion, myalgia, visual disturbance, and dizziness, but are few and transient, mild-to-moderate and comparable between drugs (35–37).

Promising results have been elicited by PDE5i trials throughout the years. After 2 months drug-free, a significant return of spontaneous erections was observed in 14 patients treated nightly with sildenafil for 9 months compared with only 1 man receiving placebo (27% vs. 4%) (18), as supported by IIEF-EF scores and nocturnal penile plethysmography. Recovery of EF was associated with restoration of nocturnal erections (38). Response rate was similar between 50- and 100-mg doses of sildenafil (18). Analogous results were obtained when 40 patients were randomised to a 2-month flexible-dose nightly sildenafil group or to a non-treated group. Follow-up at 2-years after bNSRP (i.e., 14-weeks washout period) showed a significant difference in IIEF mean scores (25 ± 6 vs. 17 ± 9) and in the ability to achieve and maintain an erection (87% vs. 56%) between the sildenafil group and the control group, respectively (39). A phase 3 study focused on a more difficult-to-treat population by starting on-demand 100- or 200-mg avanafil in patients with untreated ≥ 6-months-long ED post-bNSRP. After 3 months of treatment, both avanafil groups had significantly greater increases in SEP-3 and change in mean IIEF-EF scores vs. placebo. Particularly, IIEF-EF scores in avanafil treated groups improved 3.6 and 5.2 points for 100- and 200-mg, respectively, compared with an increase of 0.1 points for placebo. The effects of treatment remained regardless of age or baseline ED severity. Since a higher percentage of patients who discontinued the study was in the placebo group and, of those, 58% chose to withdraw consent, self-selection for perceived lack of efficacy cannot be discounted (40).

Uncertainty regarding the better suited frequency of treatment has led to comparisons between nightly and on-demand PDE5i use. The rationale for a bedtime-use regimen is an expected resulting increase in blood supply associated with nocturnal erectile tumescence, thus facilitating nocturnal erections and their believed natural protective role on the corpora cavernosa baseline function (39). In the REINVENT trial, bNSRP patients were randomised to nightly vardenafil, on-demand vardenafil or placebo. Titration of dosing was controlled by

participants. After 9 months, the IIEF-EF scores (namely, IIEF-EF ≥ 22) and SEP-3 success rates were significantly higher for the vardenafil on-demand group compared with the nightly group (48.2% vs. 32.0%, and 45.9% vs. 34.5%, respectively) and the placebo group. These data indicated a greater benefit in the use of on-demand vardenafil over a daily dosing regimen. Dropout rates were high, ranging between 31-35% in the study arms (7). On the contrary, the REACTT trial found early treatment with tadalafil once daily was the most effective regimen for drug-assisted EF, also contributing to protect against penile length loss and structural cavernous changes after NSRP, notwithstanding possible preoperative mild ED. After 9 months of tadalafil 5-mg once daily, tadalafil 20-mg on-demand, or placebo, the proportion of patients reaching an IIEF-EF ≥ 22 was only significantly higher for the tadalafil once daily group compared to the placebo group (25.2% vs. 14.2%) (41). A later post-hoc analysis found that 22.3% of patients on tadalafil once daily had achieved a back-to-baseline IIEF-EF score category, compared with 11.3% on tadalafil on-demand and 7.8% on placebo. Take note that only 1 of these 58 patients back-to-baseline had started from a baseline IIEF-EF < 26 (42). The treatment effect versus placebo was also statistically significant only for tadalafil once daily regarding SEP-3 (33.9% vs. 19.0%) (41) and retainment of stretched penile length. Penile length change was significantly associated with IIEF-EF scores (43). To further confuse the issue, a yearlong double-blind study comparing nightly to on-demand 50-mg sildenafil citrate found mean IIEF-EF scores did not differ significantly between treatment groups at any time point during treatment or after 1-month washout. However, this study lacked a pure placebo arm and had a dropout rate of 26% (44). More evidence understating possible gain with daily PDE5i therapy was a yearlong treatment protocol post-NSRP with nightly 50-mg sildenafil citrate or placebo, plus optional on-demand 100-mg sildenafil citrate. Both objective and self-reported measures were used, yet no statistically significant differences were seen in return to normal EF between treatment arm and placebo at any time point, including after a 1-month drug washout. The authors concluded nightly sildenafil citrate did not provide a therapeutic benefit for recovery of EF post-prostatectomy when compared to on-demand dosing alone. Akin to the previous study, limitations included the absence of a pure placebo group and a 24% dropout rate (45).

Furthermore, other results have implied PDE5i treatment holds no rehabilitative advantage on unassisted EF recovery when compared with the slope of natural recovery (7,42), thus failing to accomplish the main objective of penile rehabilitation. In the REINVENT trial, after a 2-month washout period, no statistically significant differences were observed between groups (7). Likewise, in the REACTT trial, after a 6-week drug-free washout, IIEF-EF and SEP-3 decreased in all groups and the treatment-group difference at the end of treatment was not maintained (41,43). Additionally, rates of EF recovery after bNSRP were not significantly altered by PDE5i therapy in patients < 55 years old with preoperative IIEF-EF ≥ 22 (46), suggesting penile rehabilitation may be more beneficial in older patients and men with a diminished preoperative EF (19,46,47).

Several considerations could be made concerning current literature's methodologies and limitations. Factors such as exclusion criteria including older age and preoperative ED, small sample sizes, high dropout rates, delays in treatment start after surgery, relatively short periods of active drug administration, patient-regulated dosages, unaccounted use of on-demand ED therapy, lack of pure placebo groups, short follow-up periods, heterogeneity in operative technique and surgical outcomes, and inadequacy in drug selection (e.g., short-acting vs. long-acting PDE5i), inter alia, may perhaps be responsible for underscoring or overemphasizing rehabilitative effects (35,44). Also noteworthy, there seems to be a considerable involvement of the pharmaceutical industry in ED-related research (7,18,40–43,45,48).

4.2 Prostaglandin E1 therapy

Alprostadil is a synthetic form of PGE1. Its mechanism of action consists of directly binding to G proteins coupled to smooth muscle cell surface PGE1 receptors, thereby activating the cAMP pathway and leading to a reduction in the cytoplasmic calcium available for smooth muscle contraction. Ultimately, penile vascular smooth muscle relaxes and blood flows through cavernous sinusoids to fill the penile corpora, producing the phenomena of erection. As such, alprostadil's action as a direct agonist obliterates the need for an external stimulus, unlike PDE5i (15,49,50).

Currently, alprostadil is available as topical cream, intraurethral suppository and intracavernous injection (ICI) for the treatment of ED. Pharmacokinetic studies suggest a high bioavailability of alprostadil, with 80% being absorbed within 10 min after intraurethral suppository. ICI alprostadil has a favourable clinical onset of action of 10-15 min, with the subsequent erection lasting between 30 min and 12 h. Its excretion may be impaired in chronic liver, kidney, and pulmonary disorders. There are no known drug interactions (15).

4.2.1 Topical cream

Topical creams are a non-invasive, on-demand treatment option directly applied to the meatus of the glans penis. Newer formulations combine alprostadil with an enhancer, made of novel fatty acid and fatty alcohol esters, to improve the active drug's local skin absorption by temporarily loosening the tight junctions present in skin epithelial cells (49), and thus allowing a fast onset of action unrelated to food or alcohol consumption. Topical alprostadil has a favourable pharmacodynamic profile, with full rigidity achieved within 10-12 min and lasting for longer than 1 h. As for its pharmacokinetic profile, its poor systemic circulation absorption and rapid metabolization predicts a reduced risk of systemic toxicity. Phase II and III studies using a 300-µg dose demonstrated a global efficacy of up to 83% in patients with severe ED, including clinically significant improvements in patients with comorbid cardiac disease or hypertension, and in patients failing sildenafil therapy (51). The available clinical data on long-term use also suggests that such a formulation is safe and generally well tolerated, since systemic adverse events (i.e., dizziness, hyperesthesia, and rash) were reported in only 3% of the treated population, and most treatment-related side effects were mild-to-moderate, transient and

localised at the application site (i.e., genital pain, tenderness, and erythema) (51). Topical alprostadil's favourable toxicity profile and lack of interactions with other drugs allow it to be safely administered in men already undergoing therapy for comorbidities with alpha-blockers, antihypertensive agents, and/or nitrates (49). As such, it may have an important role as an alternative treatment for individuals who cannot tolerate oral PDE5i therapy (49,51).

4.2.2 Intraurethral suppository

Poor patient compliance using penile injections led researchers to devise an intraurethral suppository of alprostadil, commercialised as the "Medicated Urethral System for Erection" (MUSE), which was reported to improve EF in 59-78% of men with ED (15). Raina et al. (52) studied MUSE therapy, applied 3 times weekly for 9 months, in men who underwent NSRP. As follows, 74% versus 37% of men reported adequate EF for successful vaginal intercourse in the treatment and control groups, respectively. The duration of erections after using MUSE was 5-12 min. Noticeably, all patients treated with MUSE reported mild penile aching or urethral burning, and 32% discontinued treatment mentioning lack of efficacy, reduced sexual interest or side effects. As these dropout patients may have had particularly poor EF, an artificial treatment effect may have been introduced by their dismissal in the final analysis (19). Thereby, ICI alprostadil remains being much more widely used due to its arguably higher effectiveness. Additional contraindications when comparing MUSE with ICI include patients with urethral problems (e.g., urethritis, stricture) and the need for a condom barrier for sexual intercourse with pregnant women (15).

4.2.3 Intracavernous injection

In 1997, Montorsi et al. (53) made the first attempt at penile rehabilitation with a protocol of 3 times weekly ICI use of alprostadil for 12 weeks, starting 1 month after NSRP. 8 patients, out of 12 who completed treatment, reported recovery of spontaneous erections sufficient for satisfactory sexual intercourse, a significantly higher rate than in nontreated controls (67% vs. 20%). Limitations of this groundbreaking study included small sample size, reliance on patient history as the main outcome, and lack of a placebo group, preoperative assessment of EF and long-term follow-up (19). Nevertheless, the path had been paved for early administration of erectile drugs to promote erection recovery following RP. Since then, this practice has become increasingly common (54), while published data have been sparse on comparative randomised controlled trials and mimicked some of its limitations (e.g., low number of patients) (50).

In a recent systematic review (50), ICI demonstrated clinical efficacy in 54-100% of patients, early discontinuation rates of ≤ 38% (typically greatest within 3-6 months after treatment start), and adverse events in ≤ 26% (50,54). The commonest side effects were related to the injection site, including penile pain and burning, persistent erections, and penile fibrosis with long-term use (15,50,55). A large population-based study (55) reported a 50% incidence of penile pain or burning. Although usually mild and only occurring after 11% of injections, pain led to the withdrawal of 6% of men. Penile fibrosis and priapism occurred in 2% and 1% of men,

respectively. Thus, penile pain after ICI seems to be a worrisome factor for patients, with a non-neglectable impact on therapeutic compliance and sexual function, as pain may cause loss of motivation or induce a reluctance to increase the treatment's dosage despite an incomplete response. Interestingly, in patients using ICI alprostadil for 12 months, the adverse impact of pain on sexual rehabilitation was significant during the first 6 months and diminished over time (56). Needle-free injection devices are under investigation and may eliminate some of these concerns (50). Combination therapy with PDE5i may also be effective in minimising penile discomfort by ensuring efficacy with a lower ICI dose (15,57). Contraindications of ICI alprostadil include known hypersensitivity to alprostadil, bleeding disorders and conditions predisposing to priapism (e.g., sickle cell anaemia, multiple myeloma), while ICI therapy is also generally contraindicated in patients receiving warfarin or other anticoagulants to avoid increased risk of bleeding and ecchymosis (15).

Other than alprostadil, other molecules under study for injection therapy include papaverine, a non-selective PDE5i, phentolamine, a non-selective alpha-adrenergic antagonist with an inhibitory effect on smooth muscle contraction, and aviptadil, a synthetic vasoactive intestinal polypeptide (VIP) that increases the activity of adenosine cyclase. Papaverine and phentolamine are no longer used as monotherapy, given the first's increased rates of adverse effects, notably priapism and penile fibrosis, and the second's weak efficacy as a single agent. Hence, combination therapies present themselves as an attractive alternative, allowing for better side effect profiles and higher efficacy rates when monotherapy injections have failed. Data supporting an aviptadil/phentolamine combination therapy, clinically approved in some European markets, demonstrated a clinical efficacy of 74% (vs. 13% with a placebo control) and of 67-73% in patients unresponsive to other single monotherapy injections. Notwithstanding the value combination therapies represent to patients with an adverse response to alprostadil alone, formulations should be standardised before achieving widespread acceptance (50).

4.3 Vacuum erection device

A vacuum erection device (VED) can be applied to augment penis volume through a transient increase in largely arterial inflow and venous backflow (58,59) not dependent upon nerve preservation or a fully intact vascular supply (60). Owing to the development of ischaemia when applying a constriction band, these are not recommended for use in penile rehabilitation (59). Animal studies suggested VED acts through antihypoxic, antiapoptotic, and antifibrotic mechanisms (61), with an optimal pressure of -200 mmHg (62). In bilateral cavernous nerve crush (BCNC) rat models, VED therapy promoted the expression of molecular indicators such as eNOS and alpha-smooth muscle actin (α-SMA), while the levels of HIF-1α and TGF-β, promoters of apoptosis and fibrosis, were attenuated (62). Findings of increased cavernous blood oxygen saturation (58) were replicated when significant increases in human corporal oxygenation were seen up to 1 hour after a single, brief application of the VED, despite some decay following an initial increase of 55% (63). VED daily use for 9 months after non-nerve-sparing- and NSRP resulted in 80% (60/74) of patients successfully having intercourse. Of

these, 17% (10/60) reported return of natural erections sufficient to maintain vaginal intercourse, compared with 11% (4/35) of controls not receiving any erectogenic treatment (64). Initiating an early daily VED protocol at 1-month after RP also improved short-term sexual function compared to a later intervention as-needed starting at 6-months postoperatively. After that time, however, no significant difference was found between groups, and at 1-year follow-up no spontaneous erections adequate for intercourse were reported in either group (12).

As such, while not suitable before catheter removal about 1-2 weeks post-RP, early VED use should still be discussed with patients as an additional treatment option with proven efficacy and few adverse events. It stands to attention that its use in combination with PDE5i seems to increase patient compliance and satisfaction, as well as enhance the benefits of penile rehabilitation (60).

4.4 Alternative strategies

4.4.1 Psychosocial interventions

An ICI-oriented sexual counselling protocol significantly increased treatment efficacy (with lower PGE1 doses) and compliance, rate of on-demand PDE5i responders, partners' involvement, and couples' satisfaction, and decreased the dropout rate, over a follow-up of 18 months (65). Similarly, weekly psychotherapy group sessions combined with PDE5i therapy for 1-year post-RP led to less deterioration of EF, and significantly improved the patient's intimacy with a partner and satisfaction with their sex life, compared to either therapy alone or no treatment at all (66).

4.4.2 Masturbation

Masturbation (i.e., stimulation of one's own genitals for sexual pleasure) may have a protective effect on penile tissue by similar molecular mechanisms to VED use, namely by increasing arterial blood flow and leading to higher penile oxygen saturation (34). At 2-years postoperatively, men who masturbated within the last month had a numerically higher rate of moderate to good EF (47.5% vs. 37.5%) and had morning erections significantly more often (54.6% vs. 34.9%) compared to those who did not engage in masturbation (34). It is worth remembering that masturbation neither causes any costs nor adverse effects. As such, this 10% difference in recovery of EF between the two groups, while not statistically significant, may be clinically relevant. It remains unclear, however, whether masturbation is the reason for better EF or if better EF leads to more masturbation, which should not detract physicians from encouraging their patients to masturbate after RP (34).

4.4.3 Pelvic floor muscle training

Since many men choose to defer sexual activity until restoration of continence (e.g., urinary incontinence led to ICI treatment refusal by 26.7% of men) (54), high intensity pelvic floor

muscle (PFM) training regimens may allow a quicker return to continence and thus enable earlier commencement of penile rehabilitation while reducing post-RP ED impact on QoL (67).

4.4.4 Testosterone supplementation

As 3-35% of older men may present with hypogonadism due to age-related decline of testosterone, injection of intramuscular long-acting testosterone undecanoate combined with PDE5i therapy may enhance PDE5i response in difficult-to-treat ED populations by normalising testosterone's levels in 6-12 weeks. Additional data is still needed, e.g., regarding efficacy and safety profiles, and the topic remains controversial (68), namely given that the relationship between testosterone administration and prostate cancer remains poorly understood (69), and hormone therapy may increase the risk of prostate cancer recurrence and progression (19). At the current time, testosterone supplementation is contraindicated in all men with a history of prostate cancer (69).

Chapter 5

Future directions

It is expected that emerging treatments can meet the needs of patients unresponsive to or unsatisfied by current available therapies (37). But rather than prioritise symptomatic relief (10), future directions should focus on nerve injury and nerve regeneration, as the first steps in the pathophysiological cascade of ED post-RP (8).

5.1 Low-intensity extracorporeal shock wave therapy (Li-ESWT)

Low-intensity extracorporeal shock wave therapy (Li-ESWT) on penile tissue is a novel and promising non-invasive modality in the treatment of ED that aims to enable spontaneous erections (70). In rodent models of pelvic neurovascular injury (PNVI)-induced ED, Li-ESWT intervention ameliorated impaired penile haemodynamics, suggesting Li-ESWT contributes to vascular and neuronal tissue restoration by triggering angiogenesis, regeneration of nNOS-positive nerves, and activation of Schwann cells (71,72). However, no clinical evidence of such structural changes' reversal is currently available (73).

In a pilot study, the significant median change in IIEF-5 scores was +3.5 and +1 at 1-month and 1-year, respectively, after the final Li-ESWT treatment in patients with ED after bNSRP, with no severe side effects being reported. Notwithstanding the improvements, most patients still required erectogenic aids to engage in intercourse (73). Another study found potency recovery rates similar in men treated with Li-ESWT or PDE5i, and slightly increased when compared to the untreated control group (76.2% vs. 79.1% vs. 60.5%, respectively) at 9-months post-cystoprostatectomy, although the difference between all groups lacked statistical significance. As both treatments were deemed safe, the authors argued Li-ESWT could be an alternative to oral therapy, especially in the presence of contraindications to PDE5i (70).

With the current level of evidence, Li-ESWT should be considered investigational and performed only for research purposes (10,73). Further trials and standardisation of the procedure are required for its clinical approval and acceptance (74). Practical concerns include patients possibly requiring another ED therapy after completing the Li-ESWT protocol (10).

5.2 Stem cell therapy

Stem cell therapy is a nascent and promising regenerative option for ED. Mesenchymal stem cells, an adult stem cell population, can not only proliferate and multi-differentiate into specific cells to repair damaged tissues, but also be obtained from the tissues they form (74,75). Most studies have employed adipose-derived stem cells (ADSCs) alone or combined with other

cells/growth factors (74), although other stem cell populations obtained from skeletal muscle or adult bone marrow have also been used and applied either to the major pelvic ganglion or injected directly into the penis (76).

In a rat model of cavernous nerve injury, ICI with adipose tissue-derived stem cells (ADSCs) infected with a lentiviral vector encoding rat brain-derived neurotrophic factor (lenti-rBDNF) positively affected cavernous nerve regeneration and functional recovery, as results showed a significantly higher nNOS expression and ratio of smooth muscle/collagen in the treated group (77). As for human studies, Yiou et al. (78) conducted a dose-escalation clinical trial of intracavernous autologous bone marrow-mononuclear cells (BM-MNCs) injection in 12 men after RP and failure of other ED therapies. At 6-months follow-up, significant improvements were reported in the IIEF-EF (17.4 vs. 7.3 at baseline) and intercourse satisfaction domains (6.8 vs. 3.9 at baseline). Increased dosages were associated with greater incidence of spontaneous erections. Overall, no serious side effects occurred, and 9 (of 12) men successfully engaged in intercourse while using medication. Data collected by the same authors after recruitment of 6 additional patients and a longer-term follow-up (mean of 62.1 months) showed a decline in EF improvements over time, suggesting a need for repeated injections (79).

While these represent promising results, there remain ethical and safety concerns regarding the risk of malignant proliferation and potential immunogenicity, as well as uncertainties surrounding long-term efficacy, and optimal source and dosing of stem cells (36,75). Since currently there is no indication that benefits reliably outweigh risks/burdens (e.g., cost, need for tissue harvest), stem cell therapy needs more rigorous study before widespread use as a trusty ED therapy and should only be used in investigational settings (10).

5.3 Platelet-derived therapies

Platelet-derived therapies constitute a potential regenerative approach for ED (74) by targeting inflammation and promoting tissue regeneration (80). Platelet-rich plasma (PRP) is an autologous blood product with a platelet concentration exceeding physiological values by 3-7-fold (80). Its therapeutic effect in improving the tissue's healing process derives from various growth factors and is hypothesised to be produced at the site of administration, hence its application in the form of ICI (81). Meanwhile, platelet rich fibrin matrix (PRFM) emerged to surpass concerns with PRP's early washout and has already been used in organic ED patients with positive results (80). While animal and human studies attest to these therapies' safety and efficacy in the recovery of EF (81), given the multitude of other proven treatment options and the unavailability of reliable evidence, platelet-derived therapies require further investigation and are currently only experimental for ED treatment (10). Remarkably, there is evidence suggesting synergistic PRP and stem cell therapies may possess better regenerative potential when compared to either individual therapy (74).

5.4 Gene therapy

Gene therapy has also shown promise as a potential future ED treatment by restoring erectile activity on rat models (17,76). Its functionality centres on the enhancement of NO production or NO-medicated signalling pathways, of growth factor-mediated nerve regeneration (e.g., through increased levels of neurotrophin-3), and of potassium ion channel activity and conductance in the cavernous smooth muscle (17). However, safety concerns remain due to its high risk of endogenous viral recombination, cancer development, and immunological reaction. Its clinical translation to patients also requires further research (17).

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Chapter 6

Barriers and enablers of rehabilitation

A systematic review regarding ED treatments' use identified treatment ineffectiveness, side effects, the quality of one's intimate relationships and treatment costs as the most prevalent barriers. Notably, men who reported side effects to healthcare professionals were significantly less likely to discontinue treatment, which suggests clinicians play a potentially important role in modifying men's beliefs and improving treatment application (82). In like manner, adopting a pre-habilitative approach to sexual recovery, by offering patients a chance to test an ED treatment prior to undergoing surgery, may improve long-term compliance. For instance, if a man were to attempt using an ICI therapy and witnessed its effectiveness before RP, his willingness to use it postoperatively would potentially increase (83). A trend in the relationship between primary surgeon and rehabilitation success has also been identified, implying surgical technique and methods of follow-up of an individual surgeon could lead patients toward successful outcomes of rehabilitation (84).

Furthermore, setting realistic expectations regarding ED and the probability of sexual recovery can improve resilience and satisfaction with treatments. The sexual recovery process can be long-lasting and even finding the right ED treatment might require some persistence. Early comprehensive education on the matter can help patients deal with feelings of anger and frustration that may arise in the absence of short-term positive results (85). Using a couple-based approach for counselling from the outset of ED treatment's prescription is also likely to improve long-term compliance and help in maximising EF outcomes, warranting assessment of sexual dysfunction in partners of post-RP patients as well. While men have refused ICI treatment due to their partners lack of sexual interest (30.2%) (54), higher preoperative partner Female Sexual Function Index (FSFI) scores have been associated with significantly greater ICI therapy compliance at 6-month follow-up (86). Partners can also be actively involved in treatment administration and help associate this act with sexual pleasure. The concept of eroticising erectile aids is helpful in promoting its effective use, as the treatment itself starts to provoke erotic feelings and give way to positive expectations, becoming a sexual "turn-on" (85).

In a penile rehabilitation protocol consisting of PDE5i with or without VED/ICI therapy, adherence declined overtime, with the most common barriers being cost, inconvenience, and perceived ineffectiveness, while other factors included side effects, time constraints, traveling with therapy, comorbid health problems, frustration with delayed recovery, surgical complications, partner issues and life stressors. High attrition rates were noted with only 45.5% of men completing 2 years of the rehabilitation program (11). In a similar regimen, a participation rate of 53.2% was associated with higher preoperative sexual function, whereas higher preoperative PSA concentrations and the presence of positive surgical margins were

predictors for avoidance of rehabilitation (84). Incidentally, most men claimed disappointment with treatment efficacy (64.7%), injection pain (45%), and difficulties with or fear of performing the injection (35.2%) as dropout reasons for an ICI regimen (54). In line with these findings, age, preoperative EF and sexual desire, the Charlson comorbidity index (CCI), no history of diabetes mellitus, neurovascular bundle preservation, sexual confidence, and intercourse satisfaction have all been identified as key factors predicting postoperative EF recovery (46,47,87).

Chapter 7

Sexual satisfaction

Both physical and psychosocial variables were found to be important determinants of sexual satisfaction in men with PCa. Although EF produced the largest effect, relationship closeness was also positively associated with sexual satisfaction, while depression and anxiety were negatively related (88). Furthermore, though ED may not cause bother per se, significant decreases in sexual satisfaction may persist even after EF is restored to functional levels, confirming EF and sexual satisfaction do not necessarily go hand in hand. That is, effective sexual functioning does not ensure the attainment of sexual satisfaction, since other physical, psychological, and relationship factors may be implicated (89). As sexual desire moderates the relationship between EF and sexual bother, special attention to quaternary prevention is warranted in men with low libido, as sexual counselling might rather aim to avoid overtreatment. Since these patients may not be bothered by poor erections, treatment to improve sexual desire may be preferable (90). In this manner, standard assessment after RP should also include questions related to sexual bother, depressive and anxiety symptomatology, and sexual satisfaction (89).

A brief counselling intervention with PCa survivors addressed ED management, sexual communication, and expression of feelings, and while its short-term positive changes in sexual function and satisfaction in both partners diminished with time, use of ED treatments increased significantly (49% after 6 months vs. 31% at baseline). The authors suggested female partners appreciated the freedom to communicate more openly about sex and express feelings and affection, thus leading to gains in their sexual function and satisfaction. As the men's EF improved with treatment use, women became disappointed by the return of lovemaking patterns focused mainly on vaginal penetration. The consequent decrease in their sexual desire may have in turn affected the men's sexual satisfaction, straining long-term maintenance of gains (91).

Indeed, as each patient's sex life is changed throughout the process, both patient and partner are important in the renegotiation of sexual activity. Physicians should pave the way for open discussions with and between couples, providing advice while assessing the couple's joint willingness to explore novel strategies that might not have been part of their previous sexual practices. The use of personal lubricants may become relevant to alleviate pain and prevent abrasion. For patients experiencing urinary leakage, namely climacturia, some suggestions include urinating prior to sexual activity, using a constriction ring or preparing the scenario by laying a towel on the bed or moving to the shower. Sexual adaptation may also compel couples to broaden their sexual repertoire and explore sexual practices non-dependent on penile erection, such as sensual massage, genital caressing, mutual masturbation, deep kissing, oral

sex, use of sex toys, or an external penile prosthesis. Ultimately, such alternatives would allow the maintenance of sexual intimacy should ED treatments disappoint, while strengthening the couple's bond and triggering physiological and psychological benefits associated with sexual activity. In this regard, clinicians' encouragement of masturbation and partnered sexual activities concurrent with erectile medical assistance can lay the foundation for patients' sexual recovery success and its sustainment. Counselling can thus prepare patients to better manage failures, persist when faced with challenges and preserve sexual activity despite low-quality erections. From a psychosocial perspective, promoting flexibility in sexual practices and including partners as much as possible are key aspects in the management of ED after RP (85).

7.1 Men who have sex with men

Gay and bisexual men may have different sexual concerns from their heterosexual counterparts, resulting in some specific challenges (92). However, few studies have gauged the experiences of men who have sex with men (92). To further complicate matters, application of currently available standardised scales on this population can only reveal part of the picture, as questions tailored for gay sex are needed to better understand how their sexual functioning is affected (93). Hence the importance of asking about sexual orientation and refraining from making assumptions regarding sexuality or relationships (92).

Anal intercourse has been reported to require 33% greater penile rigidity (vs. vaginal) (6). The need for firmer erections for anal penetration forecasts limitations in the effectiveness of first-line ED therapies that work in heterosexual men (92), thus compelling clinicians to consider more invasive treatments sooner in this population (94). In a study with gay and bisexual men treated for PCa, merely 22.4% reported erections sufficient for insertive anal sex (93). A less than ideal solution for treatment failure may be to change one's sexual role (i.e., from insertive to receptive anal intercourse partner) (92), possibly at the expense of losing one's role-in-sex identity (93). Yet, it has been reported that only about 40% of exclusively insertive partners remained in that role after PCa treatment, with less than 20% reporting always being the insertive partner (94). Furthermore, erectile difficulties were cited by 61.3% of participants engaging in insertive anal sex as the underlying reason for not using condoms (93). Increased risk of HIV/STI transmission through role-in-sex change or non-condom use should alert clinicians to ponder PrEP for HIV-negative patients and confirm treatment adherence for HIV-positive ones (93). Prostatectomy may also be responsible for diminishing enjoyment in receptive anal intercourse, as stimulation of the prostate during anal penetration is an important source of pleasure (92). In addition, as the eroticisation of ejaculate and semen is of cultural importance among gay men (94), its shortage after surgery dictates subsequent adjustment (92). Considering these findings, further research is required to better tailor sexual rehabilitation programs to men who have sex with men.

Chapter 8

Conclusions

At a time when PSA testing has made headway on detection of PCa at earlier stages in increasingly younger patients, RP embodies an attractive curative treatment modality with a favourable cancer-free life expectancy. Still, sexual dysfunction and mainly ED remain important complications of RP, regardless of the surgical technique used, eliciting increased awareness in the medical community regarding the impact of the patients' postoperative sexual functioning on their QoL.

Historically, rehabilitation and treatment have been considered undoubtedly superior options to leaving the erectile tissue unattended (30), as recovery of EF can occur up to 4 years after RP (20). As follows, any form of pro-erectile rehabilitation should start at the earliest opportunity to elevate the potential of both EF recovery and ED treatment (30,95). Yet, over the last decade, no evidence has been documented that penile rehabilitation itself increases the chances of spontaneous EF recovery, despite the refinement of surgical care and the growing attention to postoperative rehabilitation protocols (95,96). Even if a trend exists for this practice, penile rehabilitation remains controversial (1), and some patients may incur in significant financial expenditure without experiencing clear benefits.

To this day, guidelines recommend oral PDE5i use as the first-line therapeutic option, mainly due to their demonstrated efficacy, safety, ease of use, and positive impact on QoL (95). Note that the post-RP population tends to respond poorly to PDE5i (95). ICI alprostadil is suggested as an alternative first- or a second-line treatment when oral PDE5i are contraindicated or not adequately effective, although presenting with a less favourable side effect profile. Alternatively, weak evidence proposes the use of topical or intraurethral alprostadil in patients who cannot tolerate oral vasoactive therapy or prefer a less-invasive approach to ICI, and the use of VED in those with infrequent sexual intercourse and requiring non-invasive, drug-free variants (95). After failure of less-invasive treatments, patients may benefit from penile prosthesis implantation (10,30).

As data is inadequate to support the use of any specific regimen (95), treatment selection should reflect patient preference. Until further evidence, daily PDE5i use should not be the norm since there are no definitive conclusions on whether chronic use with rehabilitative intent is superior to on-demand administration (30). Drug choice should depend on the frequency of intercourse and the patient's personal experience (95). Furthermore, both psychological and sexual counselling are of major importance to improve any rehabilitation program, being certainly advisable in combination with the treatment modalities previously mentioned (30).

In clinical practice, management of realistic expectations about functional outcomes facilitates informed decision-making and empowers patients to willingly make a trade-off between their PCa cure and its postoperative risks (27). Patients undergoing RP should be informed about the risk of sexual dysfunction, including ED, libido reduction, altered orgasm-experience, anejaculation, and penile size changes (95), that depending on individual sexual practices may be detrimental for sexual satisfaction (27). To cover the issue of discordant findings in literature, patients should be given individualised outcomes reflecting both patient and surgeon factors (9). Involvement of both partners and prompt evaluation of concomitant sexual dysfunction are crucial to optimise therapy for the couple and improve treatment compliance (86,97). It is up to clinicians to provide a comfortable ambiance for patients to feel comfortable in expressing the full extent of their sexual issues (29). Furthermore, encouraging sexual flexibility helps remove the exclusive emphasis of ED management on EF recovery, and establishes sexual adaptation as a goal of rehabilitation too, providing patients with other options if ED treatments fail (98). These improvements in postoperative ED management, as small as they may seem, will likely contribute to better life satisfaction and superior overall health outcomes (10).

Nevertheless, there is a need for better quality research focused on patient-important outcomes (6) that transcend the usual heteronormative standards (27), including questions on libido and sexual bother or satisfaction (90). Large discrepancies in literature relate to differences in data collection and reporting, with obvious consequences when discussing management and progress of ED post-RP with patients (17). The lack of an objective, reliable, and universal definition of pre- and postoperative EF is a common issue (17). Furthermore, as PDE5i became a mainstay of ED management, the ability to conduct pure placebo-controlled studies has been made difficult by ethical concerns regarding on-demand PDE5i use restriction in that study arm. The same could be said of the implications of banning masturbation, as it would not be ethically justifiable to potentially inflict a significant negative impact on the patients' chances of EF recovery for investigational purposes. Hence, psychological factors cannot be discounted when interpreting findings from studies with control groups made of men who refused rehabilitation, just as outcomes resulting from studies with undisclosed use of erectile aids should be analysed in line with that fact.

Future directions should focus on investigating strategies to intervene in the pathophysiological cascade of ED post-RP (8), and thus explore the potential of regenerative medicine (74) rather than simply try to mitigate symptoms (10). Li-ESWT, and stem cell, gene and PRP-based therapies are promising novel modalities still under investigation (10).

References

1. Mottet N, Bastian P, Bellmunt J, van den Bergh R, Bolla M, van Casteren N, et al. EAU - EANM - ESTRO - ESUR - SIOG Guidelines on Prostate Cancer. In: EAU Guidelines. Arnhem, The Netherlands: EAU Guidelines Office; 2020.
2. Sung H, Ferlay J, Siegel RL, Laversanne M, Soerjomataram I, Jemal A, et al. Global cancer statistics 2020: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA Cancer J Clin. 2021;0:1–41.
3. Briganti A, Gallina A, Suardi N, Capitanio U, Tutolo M, Bianchi M, et al. What Is the Definition of a Satisfactory Erectile Function After Bilateral Nerve Sparing Radical Prostatectomy? J Sex Med. 2011 Apr 1;8(4):1210–7.
4. Magheli A, Burnett AL. Erectile dysfunction following prostatectomy: prevention and treatment. Nat Rev Urol. 2009 Aug;6(8):415–27.
5. Mulhall JP. Penile Rehabilitation Following Radical Prostatectomy [Internet]. Medscape Urology. 2008 [cited 2020 Jan 31]. Available from: https://www.medscape.org/viewarticle/576471
6. Philippou YA, Jung JH, Steggall MJ, O'Driscoll ST, Bakker CJ, Bodie JA, et al. Penile rehabilitation for postprostatectomy erectile dysfunction. Cochrane Database Syst Rev. 2018 Oct 23;(10).
7. Montorsi F, Brock G, Lee J, Shapiro J, Van Poppel H, Graefen M, 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 Oct;54(4):924–31.
8. Weyne E, Castiglione F, Van der Aa F, Bivalacqua TJ, Albersen M. Landmarks in erectile function recovery after radical prostatectomy. Nat Rev Urol. 2015 May 14;12(5):289–97.
9. Salonia A, Adaikan G, Buvat J, Carrier S, El-Meliegy A, Hatzimouratidis K, et al. Sexual Rehabilitation After Treatment for Prostate Cancer—Part 1: Recommendations From the Fourth International Consultation for Sexual Medicine (ICSM 2015). J Sex Med. 2017 Mar 1;14(3):285–96.
10. Burnett AL, Nehra A, Breau RH, Culkin DJ, Faraday MM, Hakim LS, et al. Erectile Dysfunction: AUA Guideline. J Urol. 2018 Sep;200(3):633–41.
11. Albaugh J, Adamic B, Chang C, Kirwen N, Aizen J. Adherence and barriers to penile rehabilitation over 2 years following radical prostatectomy. BMC Urol. 2019 Dec 7;19(1):89.
12. Köhler TS, Pedro R, Hendlin K, Utz W, Ugarte R, Reddy P, et al. A pilot study on the early use of the vacuum erection device after radical retropubic prostatectomy. BJU Int. 2007 Oct;100(4):858–62.

13. Clavell-Hernandez J, Ermeç B, Kadioğlu A, Wang R. Perplexity of penile rehabilitation following radical prostatectomy. Turkish J Urol. 2019 Mar 1;45(2):77–82.

14. Von Thesling Sweet G, Shindel AW. Physiology of Erection. In: Mulhall JP, Hsiao W, editors. Men's Sexual Health and Fertility: A Clinician's Guide. New York, NY: Springer New York; 2014. p. 1–12.

15. Hanchanale V, Eardley I. Alprostadil for the treatment of impotence. Expert Opin Pharmacother. 2014 Feb 26;15(3):421–8.

16. Park DL, Aron M, Rewcastle JC, Boyd SD, Gill IS. A model for managing erectile dysfunction following prostate cancer treatment. Curr Opin Urol. 2013 Mar;23(2):129–34.

17. Saleh A, Abboudi H, Ghazal-Aswad MB, Mayer EK, Vale JA. Management of erectile dysfunction post-radical prostatectomy. Res Reports Urol. 2015 Feb 23;7:19–33.

18. Padma-Nathan H, McCullough AR, Levine LA, Lipshultz LI, Siegel R, Montorsi F, 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 Sep;20(5):479–86.

19. Fode M, Ohl DA, Ralph D, Sønksen J. Penile rehabilitation after radical prostatectomy: what the evidence really says. BJU Int. 2013 Nov;112(7):998–1008.

20. Glickman L, Godoy G, Lepor H. Changes in Continence and Erectile Function Between 2 and 4 Years After Radical Prostatectomy. J Urol. 2009 Feb 1;181(2):731–5.

21. Leungwattanakij S, Bivalacqua TJ, Usta MF, Yang D-Y, Hyun J-S, Champion HC, et al. Cavernous Neurotomy Causes Hypoxia and Fibrosis in Rat Corpus Cavernosum. J Androl. 2003 Mar 4;24(2):239–45.

22. Hanchanale V, Eardley I. Rehabilitation of Erectile Function After Radical Prostatectomy. Eur Urol Suppl. 2013 Jun;12(2):18–24.

23. Rogers CG, Trock BP, Walsh PC. Preservation of accessory pudendal arteries during radical retropubic prostatectomy: surgical technique and results. Urology. 2004 Jul 1;64(1):148–51.

24. Williams SB, Morales BE, Huynh LM, Osann K, Skarecky DW, Ahlering TE. Analysis of Accessory Pudendal Artery Transection on Erections During Robot-Assisted Radical Prostatectomy. J Endourol. 2017 Nov 1;31(11):1170–5.

25. Terrier JE, Mulhall JP, Nelson CJ. Exploring the Optimal Erectile Function Domain Score Cutoff That Defines Sexual Satisfaction After Radical Prostatectomy. J Sex Med. 2017 Jun 1;14(6):804–9.

26. Lovegrove CE, Ficarra V, Montorsi F, N'Dow J, Salonia A, Minhas S. Sexual function outcomes following interventions for prostate cancer: are contemporary reports on functional outcomes misleading? Int J Impot Res. 2020 Sep 13;32(5):495–502.

27. Fode M, Jensen CFS, Østergren PB. Standardized reporting for sexual function following prostate cancer treatment. Int J Impot Res. 2020 Sep 19;32(5):549–50.

28. Di Mauro M, Morgia G, Russo GI. Problems in defining sexual dysfunction in prostate cancer patients. Int J Impot Res. 2020 Aug 28. doi: 10.1038/s41443-020-00350-2. [Epub ahead of print]

29. Clavell-Hernández J, Martin C, Wang R. Orgasmic Dysfunction Following Radical Prostatectomy: Review of Current Literature. Sex Med Rev. 2018 Jan 1;6(1):124–34.

30. Salonia A, Burnett AL, Graefen M, Hatzimouratidis K, Montorsi F, Mulhall JP, et al. Prevention and Management of Postprostatectomy Sexual Dysfunctions Part 2: Recovery and Preservation of Erectile Function, Sexual Desire, and Orgasmic Function. Eur Urol. 2012 Aug;62(2):273–86.

31. Frey AU, Sønksen J, Fode M. Neglected Side Effects After Radical Prostatectomy: A Systematic Review. J Sex Med. 2014 Feb 1;11(2):374–85.

32. Chung E, Gillman M. Prostate cancer survivorship: a review of erectile dysfunction and penile rehabilitation after prostate cancer therapy. Med J Aust. 2014 Jun 2;200(10):582–5.

33. 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 Jul 1;2(4):532–40.

34. Meissner VH, Dumler S, Kron M, Schiele S, Goethe VE, Bannowsky A, et al. Association between masturbation and functional outcome in the postoperative course after nerve-sparing radical prostatectomy. Transl Androl Urol. 2020 Jun 1;9(3):1286–95.

35. Sami S, Stern N, Di Pierdomenico A, Katz B, Brock G. Erectile Dysfunction: A Primer for in Office Management. Med Sci. 2019 Aug 29;7(9):90.

36. Karakus S, Burnett AL. The medical and surgical treatment of erectile dysfunction: a review and update. Can J Urol. 2020 Aug;27(S3):28–35.

37. Kim S, Cho MC, Cho SY, Chung H, Rajasekaran MR. Novel Emerging Therapies for Erectile Dysfunction. World J Mens Health. 2021 Jan;39(1):48–64.

38. 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 Feb 1;5(2):476–84.

39. Pace G, Rosso A Del, Vicentini C. Penile rehabilitation therapy following radical prostatectomy. Disabil Rehabil. 2010 Jan 15;32(14):1204–8.

40. Mulhall JP, Burnett AL, Wang R, McVary KT, Moul JW, Bowden CH, et al. A Phase 3, Placebo Controlled Study of the Safety and Efficacy of Avanafil for the Treatment of Erectile Dysfunction After Nerve Sparing Radical Prostatectomy. J Urol. 2013 Jun 1;189(6):2229–36.

41. Montorsi F, Brock G, Stolzenburg J-U, Mulhall J, Moncada I, Patel HRH, et al. Effects of Tadalafil Treatment on Erectile Function Recovery Following Bilateral Nerve-sparing Radical Prostatectomy: A Randomised Placebo-controlled Study (REACTT). Eur Urol. 2014 Mar;65(3):587–96.

42. Mulhall JP, Brock G, Oelke M, Fode M, Probst KA, Henneges C, et al. Effects of Tadalafil Once-Daily or On-Demand vs Placebo on Return to Baseline Erectile Function After Bilateral Nerve-Sparing Radical Prostatectomy – Results from a Randomized Controlled Trial (REACTT). J Sex Med. 2016 Apr 1;13(4):679–83.

43. Brock G, Montorsi F, Costa P, Shah N, Martinez-Jabaloyas JM, Hammerer P, et al. Effect of Tadalafil Once Daily on Penile Length Loss and Morning Erections in Patients After Bilateral Nerve-sparing Radical Prostatectomy: Results From a Randomized Controlled Trial. Urology. 2015 May 1;85(5):1090–6.

44. Pavlovich CP, Levinson AW, Su LM, Mettee LZ, Feng Z, Bivalacqua TJ, et al. Nightly vs on-demand sildenafil for penile rehabilitation after minimally invasive nerve-sparing radical prostatectomy: Results of a randomized double-blind trial with placebo. BJU Int. 2013 Oct;112(6):844–51.

45. Kim DJ, Hawksworth DJ, Hurwitz LM, Cullen J, Rosner IL, Lue TF, et al. A prospective, randomized, placebo-controlled trial of on-Demand vs. nightly sildenafil citrate as assessed by Rigiscan and the international index of erectile function. Andrology. 2016 Jan 1;4(1):27–32.

46. Gallina A, Ferrari M, Suardi N, Capitanio U, Abdollah F, Tutolo M, et al. Erectile Function Outcome after Bilateral Nerve Sparing Radical Prostatectomy: Which Patients May Be Left Untreated? J Sex Med. 2012 Mar 1;9(3):903–8.

47. Marien T, Sankin A, Lepor H. Factors Predicting Preservation of Erectile Function in Men Undergoing Open Radical Retropubic Prostatectomy. J Urol. 2009 Apr 1;181(4):1817–22.

48. 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 Jun 1;183(6):2451–6.

49. Anaissie J, Hellstrom W. Clinical use of alprostadil topical cream in patients with erectile dysfunction: a review. Res Reports Urol. 2016 Aug 3;8:123–31.

50. Duncan C, Omran GJ, Teh J, Davis NF, Bolton DM, Lawrentschuk N. Erectile dysfunction: a global review of intracavernosal injectables. World J Urol. 2019 Jun 20;37(6):1007–14.

51. Moncada I, Cuzin B. Clinical Efficacy and Safety of Vitaros © /Virirec © (Alprostadil Cream) for the Treatment of Erectile Dysfunction. Urol J. 2015 Apr 3;82(2):84–92.

52. 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 Dec;100(6):1317–21.

53. Montorsi F, Guazzoni G, Strambi LF, Da Pozzo LF, Nava L, Barbieri L, 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 Oct 1;158(4):1408–10.

54. Polito M, D'Anzeo G, Conti A, Muzzonigro G. Erectile rehabilitation with intracavernous alprostadil after radical prostatectomy: refusal and dropout rates. BJU Int. 2012 Dec;110(11c):E954–7.

55. Linet OI, Ogrinc FG. Efficacy and Safety of Intracavernosal Alprostadil in Men with Erectile Dysfunction. N Engl J Med. 1996 Apr 4;334(14):873–7.

56. Yiou R, Cunin P, de la Taille A, Salomon L, Binhas M, Lingombet O, et al. Sexual Rehabilitation and Penile Pain Associated with Intracavernous Alprostadil after Radical Prostatectomy. J Sex Med. 2011 Feb 1;8(2):575–82.

57. 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 Sep 16;18(5):446–51.

58. Lin H-C, Yang W-L, Zhang J-L, Dai Y-T, Wang R. Penile rehabilitation with a vacuum erectile device in an animal model is related to an antihypoxic mechanism: blood gas evidence. Asian J Androl. 2013 May 8;15(3):387–90.

59. 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 Jun;75(6):786–91.

60. Qin F, Wang S, Li J, Wu C, Yuan J. The Early Use of Vacuum Therapy for Penile Rehabilitation After Radical Prostatectomy: Systematic Review and Meta-Analysis. Am J Mens Health. 2018 Nov 5;12(6):2136–43.

61. Yuan J, Lin H, Li P, Zhang R, Luo A, Berardinelli F, et al. Molecular Mechanisms of Vacuum Therapy in Penile Rehabilitation: A Novel Animal Study. Eur Urol. 2010 Nov;58(5):773–80.

62. Yang X-L, Yang Y, Fu F-D, Wu C-J, Qin F, Yuan J-H. Optimal pressure in penile rehabilitation with a vacuum erection device: evidence based on a rat model. Asian J Androl. 2019 Sep 1;21(5):516–21.

63. Welliver RC, Mechlin C, Goodwin B, Alukal JP, McCullough AR. A Pilot Study to Determine Penile Oxygen Saturation Before and After Vacuum Therapy in Patients with Erectile Dysfunction After Radical Prostatectomy. J Sex Med. 2014 Apr 1;11(4):1071–7.

64. Raina R, Agarwal A, Ausmundson S, Lakin M, Nandipati KC, Montague DK, 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 Jan 18;18(1):77–81.

65. 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 Mar 1;3(2):267–73.

66. Naccarato AMEP, Reis LO, Ferreira U, Denardi F. Psychotherapy and phosphodiesterase-5 inhibitor in early rehabilitation after radical prostatectomy: a prospective randomised controlled trial. Andrologia. 2016 Dec 1;48(10):1183–7.

67. Milios JE, Ackland TR, Green DJ. Pelvic Floor Muscle Training and Erectile Dysfunction in Radical Prostatectomy: A Randomized Controlled Trial Investigating a Non-Invasive Addition to Penile Rehabilitation. Sex Med. 2020 Sep 1;8(3):414–21.

68. Aversa A, Francomano D, Lenzi A. Does testosterone supplementation increase PDE5-inhibitor responses in difficult-to-treat erectile dysfunction patients? Expert Opin Pharmacother. 2015 Mar 24;16(5):625–8.

69. Bhasin S, Brito JP, Cunningham GR, Hayes FJ, Hodis HN, Matsumoto AM, et al. Testosterone Therapy in Men With Hypogonadism: An Endocrine Society* Clinical Practice Guideline. J Clin Endocrinol Metab. 2018 May 1;103(5):1715–44.

70. Zewin TS, El-Assmy A, Harraz AM, Bazeed M, Shokeir AA, Sheir K, et al. Efficacy and safety of low-intensity shock wave therapy in penile rehabilitation post nerve-sparing radical cystoprostatectomy: a randomized controlled trial. Int Urol Nephrol. 2018 Nov 19;50(11):2007–14.

71. Wang HS, Ruan Y, Banie L, Cui K, Kang N, Peng D, et al. Delayed Low-Intensity Extracorporeal Shock Wave Therapy Ameliorates Impaired Penile Hemodynamics in Rats Subjected to Pelvic Neurovascular Injury. J Sex Med. 2019 Jan 1;16(1):17–26.

72. Li H, Matheu MP, Sun F, Wang L, Sanford MT, Ning H, et al. Low-energy Shock Wave Therapy Ameliorates Erectile Dysfunction in a Pelvic Neurovascular Injuries Rat Model. J Sex Med. 2016 Jan 1;13(1):22–32.

73. Frey A, Sønksen J, Fode M. Low-intensity extracorporeal shockwave therapy in the treatment of postprostatectomy erectile dysfunction: a pilot study. Scand J Urol. 2016 Mar 3;50(2):123–7.

74. Liu M-C, Chang M-L, Wang Y-C, Chen W-H, Wu C-C, Yeh S-D. Revisiting the Regenerative Therapeutic Advances Towards Erectile Dysfunction. Cells. 2020 May 19;9(5):1250.

75. Matz EL, Terlecki R, Zhang Y, Jackson J, Atala A. Stem Cell Therapy for Erectile Dysfunction. Sex Med Rev. 2019 Apr 1;7(2):321–8.

76. Sopko NA, Burnett AL. Erection rehabilitation following prostatectomy — current strategies and future directions. Nat Rev Urol. 2016 Apr 15;13(4):216–25.

77. Yang M, Sun J-Y, Ying C-C, Wang Y, Guo Y-L. Adipose-derived stem cells modified by BDNF gene rescue erectile dysfunction after cavernous nerve injury. Neural Regen Res. 2020;15(1):120–7.

78. Yiou R, Hamidou L, Birebent B, Bitari D, Lecorvoisier P, Contremoulins I, et al. Safety of Intracavernous Bone Marrow-Mononuclear Cells for Postradical Prostatectomy Erectile Dysfunction: An Open Dose-Escalation Pilot Study. Eur Urol. 2016 Jun;69(6):988–91.

79. Yiou R, Hamidou L, Birebent B, Bitari D, Le Corvoisier P, Contremoulins I, et al. Intracavernous Injections of Bone Marrow Mononucleated Cells for Postradical Prostatectomy Erectile Dysfunction: Final Results of the INSTIN Clinical Trial. Eur Urol Focus. 2017 Dec 1;3(6):643–5.

80. Matz EL, Pearlman AM, Terlecki RP. Safety and feasibility of platelet rich fibrin matrix injections for treatment of common urologic conditions. Investig Clin Urol. 2018 Jan;59(1):61–5.

81. Epifanova M V., Gvasalia BR, Durashov MA, Artemenko SA. Platelet-Rich Plasma Therapy for Male Sexual Dysfunction: Myth or Reality? Sex Med Rev. 2020 Jan 1;8(1):106–13.

82. Williams P, McBain H, Amirova A, Newman S, Mulligan K. Men's beliefs about treatment for erectile dysfunction—what influences treatment use? A systematic review. Int J Impot Res. 2021 Jan 31;33(1):16–42.

83. Wassersug R, Wibowo E. Non-pharmacological and non-surgical strategies to promote sexual recovery for men with erectile dysfunction. Transl Androl Urol. 2017 Nov 1;6(S5):S776–94.

84. Kimura M, Caso JR, Bañez LL, Koontz BF, Gerber L, Senocak C, et al. Predicting participation in and successful outcome of a penile rehabilitation programme using a phosphodiesterase type 5 inhibitor with a vacuum erection device after radical prostatectomy. BJU Int. 2012 Dec;110(11c):E931–8.

85. Walker LM, Wassersug RJ, Robinson JW. Psychosocial perspectives on sexual recovery after prostate cancer treatment. Nat Rev Urol. 2015 Mar 10;12(3):167–76.

86. Moskovic DJ, Mohamed O, Sathyamoorthy K, Miles BJ, Link RE, Lipshultz LI, et al. The Female Factor: Predicting Compliance with a Post-Prostatectomy Erectile Preservation Program. J Sex Med. 2010 Nov 1;7(11):3659–65.

87. Montorsi F, Oelke M, Henneges C, Brock G, Salonia A, D'Anzeo G, et al. Exploratory Decision-Tree Modeling of Data from the Randomized REACTT Trial of Tadalafil Versus Placebo to Predict Recovery of Erectile Function After Bilateral Nerve-Sparing Radical Prostatectomy. Eur Urol. 2016 Sep 1;70(3):529–37.

88. Nelson CJ, Choi JM, Mulhall JP, Roth AJ. Determinants of Sexual Satisfaction in Men with Prostate Cancer. J Sex Med. 2007 Sep 1;4(5):1422–7.

89. Terrier JE, Masterson M, Mulhall JP, Nelson CJ. Decrease in Intercourse Satisfaction in Men Who Recover Erections After Radical Prostatectomy. J Sex Med. 2018 Aug 1;15(8):1133–9.

90. Bravi CA, Tin A, Montorsi F, Mulhall JP, Eastham JA, Vickers AJ. Erectile Function and Sexual Satisfaction: The Importance of Asking About Sexual Desire. J Sex Med. 2020 Feb 1;17(2):349–52.

91. Canada AL, Neese LE, Sui D, Schover LR. Pilot intervention to enhance sexual rehabilitation for couples after treatment for localized prostate carcinoma. Cancer. 2005 Dec 15;104(12):2689–700.

92. McInnis MK, Pukall CF. Sex After Prostate Cancer in Gay and Bisexual Men: A Review of the Literature. Sex Med Rev. 2020 Jul 1;8(3):466–72.

93. Rosser BRS, Kohli N, Polter EJ, Lesher L, Capistrant BD, Konety BR, et al. The Sexual Functioning of Gay and Bisexual Men Following Prostate Cancer Treatment: Results from the Restore Study. Arch Sex Behav. 2020 Jul 23;49(5):1589–600.

94. Hart TL, Coon DW, Kowalkowski MA, Zhang K, Hersom JI, Goltz HH, et al. Changes in Sexual Roles and Quality of Life for Gay Men after Prostate Cancer: Challenges for Sexual Health Providers. J Sex Med. 2014 Sep 1;11(9):2308–17.

95. Salonia A, Bettocchi C, Carvalho J, Corona G, Jones T, Kadioglu A, et al. EAU Guidelines on Sexual and Reproductive Health. In: EAU Guidelines. Arnhem, The Netherlands: EAU Guidelines Office; 2020.

96. Capogrosso P, Vertosick EA, Benfante NE, Eastham JA, Scardino PJ, Vickers AJ, et al. Are We Improving Erectile Function Recovery After Radical Prostatectomy? Analysis of Patients Treated over the Last Decade. Eur Urol. 2019 Feb;75(2):221–8.

97. 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 Nov 1;2(6):833–41.

98. Walker LM. Psychosocial contributors to patients' and partners' postprostate cancer sexual recovery: 10 evidence-based and practical considerations. Int J Impot Res. 2020 Nov 17. doi: 10.1038/s41443-020-00369-5. [Epub ahead of print]