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Review

A review of regenerative therapies as penile rehabilitation in men following primary prostate cancer treatment: Evidence for erectile restoration and cavernous nerve regeneration

Eric Chung [a,b,c,*]

[a] *AndroUrology Centre, Brisbane, QLD, Australia*
[b] *University of Queensland, Princess Alexandra Hospital, Brisbane, QLD, Australia*
[c] *Macquarie University Hospital, Sydney, NSW, Australia*

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Abstract *Objective:* The following article explores our evolving understandings of the role of regenerative technology as an effective penile rehabilitation tool in men with erectile dysfunction (ED) in the setting of prostate cancer (PCa) treatment and PCa survivorship.
Methods: This narrative clinical review paper summarizes what is currently known about various modalities of regenerative therapy in restoring spontaneous erectile function (EF) in men following PCa treatment with an emphasis on penile rehabilitation strategies.
Results: Conventional medical therapy often does not reverse underlying endothelial dysfunction or promote neuro-vasculogenesis to preserve penile health in men with ED. Over the past decade, there has been considerable interest in the role of regenerative therapy to restore endothelial dysfunction and ED without future dependency on medical therapy. Regenerative therapy can be classified into cellular-based (immunomodulators, stem cells, and platelet-rich plasma), biomaterials (nerve graft transfer), and device-related technology (low-intensity shockwave). Although published literature shows early promise in the role of regenerative technology for ED, there is a paucity of high-quality clinical trials in the setting of penile rehabilitation and PCa survivorship to support their use as standard care and be adopted in clinical guidelines.

* AndroUrology Centre, Brisbane, QLD, Australia.
E-mail address: ericchg@hotmail.com.
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Conclusion: While the use of regenerative technology to restore EF is exciting and highly innovative, considerable limitations remain regarding actual clinical translation and the need for longer-term efficacy and safety data as well as governmental regulation on clinical framework and more robust clinical studies before they can be accepted as standard of care to restore EF in men following PCa treatment.

1. Introduction

Significant scientific advances in various treatment modalities of prostate cancer (PCa) have improved the survival rate in men with clinically localized PCa [1]. The concept of PCa survivorship has been coined to reflect the greater desire and need for men to maintain or recover pre-treatment physical functioning including sexual health and function [2]. Contemporary literature has shown the incidence of post-radical prostatectomy erectile dysfunction (ED) is as high as 60% despite medical hype relating to robotic technology [3]. For those who received radiation therapy, ED tends to occur later and is generally more severe in men who received external beam radiation group compared to those who underwent brachytherapy [4]. Men who received androgen deprivation therapy and those who need to undertake salvage therapy are more likely to develop medically refractory ED [2]. Furthermore, each modality of PCa treatment can be associated with different levels of male sexual dysfunction, and the recovery of erectile function (EF) can vary depending on exact definitions, pre-existing medical comorbidities, response to individual therapies, and presence of other confounding factors including urinary or bowel complications, supportive partner, and social network [2,5—7].

The concept of penile rehabilitation was first established in 1997 and since then, it has been accepted as the standard of care in men following radical prostatectomy [8,9]. Existing penile rehabilitation protocols and medical interventions to address ED in the setting of PCa treatment need to take into account other relevant factors such as the extent of cavernosal nerve injury, presence of other concurrent male sexual disorders, and co-existent of urinary dysfunction as well as changes in the psychosocial relationship as a result of PCa treatment [2]. The recovery of EF is often less likely in men who received adjuvant or salvage therapy for locally advanced or metastatic PCa [10]. Conventional medical therapy such as oral phosphodiesterase type 5 inhibitor (PDE5i) has significant limitations including lack of sexual spontaneity, inconsistent treatment outcomes, presence of treatment-related adverse effects, and long-term outcomes especially in the setting of corporal fibrosis from ED [5].

In recent years, various basic science research and clinical studies have shown early promise in the role of regenerative technology. Novel regenerative strategies to treat ED aim to restore the structure and function of diseased erectile tissue and allow for long-term maintenance of EF through downstream regulation of growth factors along with both cavernous nerve and smooth muscle cell regeneration. Regenerative therapy can be classified into cellular-based (immunomodulators, stem cells, and platelet-rich plasma), biomaterials (nerve graft transfer), and device-related technology (low-intensity shockwave). Although there is considerable preliminary research undertaken on the role of regenerative therapeutic options for ED, there is a paucity of good quality human data to support their use as standard therapy in clinical practice. The following article explores the evolving understandings and the role of regenerative technology on ED in the settings of PCa treatment and PCa survivorship.

2. Materials and methods

This article was formulated based on a review of the PubMed database for English language original articles and narrative reviews published up to December 2020. Keywords search included regenerative therapy, low-intensity shockwave therapy, stem cell therapy, platelet-rich plasma, immunomodulators, nerve transfer, ED, and penile rehabilitation.

This narrative clinical review paper is not meant to provide a full systematic review and meta-analysis on this topic, and published studies in animal models have been excluded. The goal of this review is to summarize what is currently known and utilized to restore spontaneous EF in men following PCa treatment with an emphasis on penile rehabilitation (Table 1). Proposed mechanisms of action of each regenerative therapeutic agent have been added including a discussion on the future directions for these technologies.

3. Regenerative technology to restore cavernous nerve and penile erection

3.1. Immunomodulators

Immunomodulators such as neurotrophins and immunoligands are thought to have neuroprotective and nerve regenerative properties and can be useful to improve EF recovery in the setting of cavernous nerve injury following radical prostatectomy [11]. While the exact mechanism(s) of action of these immunomodulators on penile erection remains indeterminate, they are thought to promote lymphocyte activation, interleukins production, and anti-inflammatory as well as activate anti-oxidative/nitrosative and/or antiapoptotic pathways [10—14]. Despite numerous published studies on the positive effect of these

Table 1 Published studies on regenerative technology to restore EF in men following prostate cancer therapy.

Regenerative therapy	Proposed mechanism of action	Published clinical study	Clinical concern and limitation
Immunomodulator	- Neuro-regenerative effects by preventing nerve injury and enhancing functional recovery	- Mulhall et al. [15]; First et al. [16]	- No improvement in EF compared to PDE5i drug
SCT	- Cellular proliferation and multi-differentiation to repair damaged tissues through paracrine, neurogenic, and anti-apoptotic effects; synergistic action with neurotrophic and angiogenic growth factors	- Yiou et al. [25]; Haahr et al. [26]; Haahr et al. [27]; Protogerou et al. [28]	- Short-term data; inconsistent effect on EF to determine the ideal candidate for SCT
Platelet-rich plasma	- Recruitment of stem cells, modulation of inflammatory responses, and stimulation of angiogenesis and neuronal regeneration	- Matz et al. [36]	- Heterogenous study; clinical trial focuses on safety and feasibility rather than EF outcome
Low intensity extracorporeal shockwave therapy	- Induce tissue neovascularization and alteration in tissue apoptosis through release of angiogenic factors	- Frey et al. [42]; Baccaglini et al. [44]	- Small study population; single centre study with short-term data; lack of objective measures with penile color duplex ultrasound
Nerve transfer (neurorrhaphy)	- Somatic-to-autonomic neurorrhaphy to restore neural conduit	- Souza Trindade et al. [51]; Reece et al. [52]	- Retrospective analysis; clinical effect questionable in radiation group and those with ED more than 2 years

SCT, stem cell therapy; EF, erectile function; ED, erectile dysfunction; PDE5i, phosphodiesterase type 5 inhibitor.

immunomodulators on cavernous nerve injury animal model [11–14], there are no convincing clinical studies published in men following PCa treatment.

Tacrolimus (FK 506) has been investigated in a randomized, double-blind, placebo-controlled study in prevention ED following bilateral nerve-sparing radical prostatectomy, and it was shown that oral administration of tacrolimus failed to improve EF as evidenced by the lack of significant difference in patients achieving normal spontaneous erection and deterioration in EF scores compared to placebo group [15]. Similarly, another study using low dose tacrolimus also did not report any significant improvement in sexual outcomes in men following bilateral nerve-sparing radical prostatectomy [16]. As a calcineurin inhibitor, tacrolimus has been associated with significant side effects such as renal toxicity, neurotoxicity, gastrointestinal upset, and hypomagnesemia. While immunomodulators show great promise at least in the animal studies, further clinical research will need to be conducted on the ideal candidate and whether the role of immunophilins resides in pre-treatment phase to prevent PCa treatment-related ED.

3.2. Stem cell therapy (SCT)

SCT has emerged as a promising regenerative strategy due to its ability of cellular proliferation and multi-differentiation into specific cells to repair damaged tissues [17]. SCT encompasses the injection of mesenchymal stem cells (MSCs) or stromal vascular fractions, whose therapeutic effects include cellular differentiation and paracrine actions through release of various cytokines and growth factors responsible for the regenerative effects [17–19]. Currently, MSCs are the most frequently used due to easy access, little tumorigenic potential, and no bioethical constraints [18]. Over the past decade, there has been considerable interest in SCT to treat ED [17,19] and various adjunctive measures such as recombinant DNA (lenti-rBDNF) [20], exosomes [21], nano-particles [22], and low-intensity shockwaves [23]. The safety aspect of SCT in men with localized PCa pre-prostatectomy was shown by Schweizer et al. [24] with no homing of MSCs to prostatic tissue based on standard *ex vivo* expansion protocols.

One of the earliest phase 1 clinical trial in men with post-prostatectomy ED by Yiou et al. [25] reported significant EF improvements in nine out of 12 patients with International Index of Erectile Function (IIEF) domains on intercourse satisfaction (6.8 *vs.* 3.9, $p=0.044$), EF (17.4 *vs.* 7.3, $p=0.006$), and erection hardness score (2.6 *vs.* 1.3, $p=0.008$) in combination with a PDE5i, without serious adverse events. Another research group found that a single dose of autologous adipose-derived stem cells (ADSCs) could improve IIEF scores at six-month duration, where 53% of patients were able to achieve penetrative sexual intercourse without the use of oral medications [26]. This clinical effect was shown to be sustained even after 12 months at subsequent follow-up study [27]. In a different pilot study, Protogerou et al. [28] showed combined ADSC and platelet lysate were more effective in a group of men with mixed etiologies of ED.

Nonetheless, numerous concerns remain on SCT before it is accepted as a standard ED therapy especially in the setting of PCa. Methodological issues such as the optimal passage number after *ex vivo* stem cells expansion and cellular concentration, the timing of delivery, amount and number of treatment cycle as well as the choice between autologous and allogenic injection remain uncertain and need to be standardized. There exists a need to evaluate longer-term clinical efficacy and safety outcomes to meet ethical and regulatory prospective concerns. The use of adjunctive tools like nanoparticles and shockwave technology will need to be evaluated in more details too. Larger and more robust, placebo-controlled, double-blind randomized design multicenter studies will need to be conducted to assess the true efficacy and safety of SCT in men following PCa treatment.

3.3. Platelet-rich plasma (PRP)

Platelets play an important role in both coagulation and wound healing pathways. The clinical application of platelet-rich concentrates to treat ED has been intriguing since the preparation and bioethics concern of PRP are simpler than SCT [29]. The PRP utilizes the patient's own blood to create a concentrated product rich in various growth factors (such as vascular endothelial growth factor, platelet-derived growth factor, and fibroblast growth factor) which are responsible for modulation of tissue inflammation and neuro-vasculogenesis [29—32]. Once administered, these growth factors and cytokines promote neuronal regeneration, enhance endothelial nitric oxide synthase pathway, and decrease cellular apoptotic markers and tissue fibrosis in an animal model of cavernous nerve injury [31,33—35].

To date, there have been limited human PRP clinical trials with relatively promising short-term efficacy and safety data in a small number of participants [35,36]. Epifanova et al. [35] found that administration of PRP increased various growth factors in men with ED, while Matz et al. [36] reported an average improvement in post-treatment IIEF score of four points with no serious adverse outcomes following an intracavernous injection of PRP performed in a total of five patients with ED. Another single center pilot study demonstrated that the addition of platelet lysate plasma to ADSC injection can further enhance improvement in EF [28].

Based on published literature, the clinical utility of PRP appears sound given the presence of growth factors; however, the current data using PRP for ED have low patient numbers, absence of placebo group, and questionable clinical efficacy [29]. At present, the evidence to support PRP as a standard treatment for ED is not robust, and existing trials are not standardized nor designed in the setting of penile rehabilitation protocol. Like SCT, this novel technology shares longer-term efficacy and safety concerns especially in men living with PCa. There is a lack of understanding as to whether PRP can play a true neuroprotective role in the setting of cavernous nerve injury, while the optimal dose, timing, and treatment schedule require further investigation and large-scale prospective randomized clinical trials.

3.4. Low-intensity extracorporeal shockwave therapy (LIESWT)

LIESWT is a form of micro-energy technology that has been shown to improve EF in both animal models and human clinical studies [37]. LIESWT promotes the release of various angiogenic factors (such as vascular endothelial growth factor and endothelial nitric oxide synthase) to promote angiogenesis, and in turn triggers tissue neovascularization through enhanced macrophage activity, alteration in cellular apoptosis, synthesis of cellular proteins, and activation as well as differentiation of stem or progenitor cells [37]. Published literature including systematic reviews and meta-analyses showed statistically significant improvements in sexual outcomes in men with ED [38—40] and various shockwave machines appears to produce a positive effect in EF recovery [41].

In a pilot study, Frey et al. [42] reported that LIESWT did not significantly improve the EF in 16 patients who have ED following bilateral nerve-sparing surgery. On the other hand, Zewin et al. [43] found that men who received LIESWT had higher recovery of EF compared to the placebo group (76.2% *vs.* 60.5%; $p<0.001$), although the improvements in EF was lower in the LIESWT group than those taking PDE5i used for penile rehabilitation. A more recent study by Baccaglini et al. [44] demonstrated that LIESWT did not significantly improve IIEF-5 score in a randomized open-label two parallel arms clinical trial. Other studies that examine the EF recovery with LIESWT in mixed ED etiologies showed men with vasculogenic ED fared better than post-prostatectomy men [45,46].

Clinical data on the use of LIESWT in post-prostatectomy ED men are accruing [47,48] while various sexual medicine organizations have released clinical guidelines to advocate a cautious approach in adopting LIESWT as standard ED treatment outside of research setting [37,49]. Existing clinical trials have significant heterogeneity among shockwave machine parameters, treatment protocols, and non-uniform use of other erectile drugs, thereby making direct comparison and interpretation difficult. The use of adjunctive therapies such as PDE5i or cellular-based technology in men receiving LIESWT will require formal evaluation too. Furthermore, post PCa treatment-related ED often affects sexual function beyond penile erection alone, and the higher expression of pro-fibrotic factors following corporal hypoxia will likely limit the cavernosal neovascularization and neuro-regeneration effects of LIESWT.

3.5. Nerve transfer

There have been several major advances in the field of radical prostatectomy including the identification of the cavernous neurovascular bundles, refinements of the nerve-sparing techniques, and introduction of robotic technology to preserve EF [2,8,9]. Nerve graft or neurorrhaphy is thought to promote nerve regeneration and functional reconstruction with preservation of adjacent nerve function simultaneously to maintain or promote axonal regrowth. While the idea of intraoperative cavernous nerves identification for inter-positional nerve grafts is exciting, the actual translation from basic research to human trials has been

unrewarding. To date, the largest randomized clinical trial [50] reported less than satisfactory outcome in EF recovery following unilateral sural nerve grafting in nerve-sparing radical prostatectomy men. This is likely a reflection of the complexity of trying to restore the neural conduit amidst an intricate prostatic-cavernous plexus, and other factors such as postoperative inflammatory changes, need for further radiation or hormonal therapy, and damage to other structures resulting in anejaculation and urinary incontinence, can also contribute to the sexual dysfunction.

More recently, two clinical studies utilizing a novel penile re-innervation technique with an end-to-side nerve grafting using a somatic-to-autonomic neurorrhaphy to restore EF [51,52] have reinvigorated the concept of neurorrhaphy in cavernous nerve regeneration. In a pilot study, Souza Trindade et al. [51] reported that 60% of patients with mixed PCa treatments were able to achieve full penetration following re-innervation surgery that involved bridging of the femoral nerve to the dorsal nerve of the penis and the inner part of the corpus cavernosum with sural nerve grafts and end-to-side neurorrhaphies. Reece et al. [52] found end-to-side nerve grafting restored EF in 71% of men with post-prostatectomy ED and 94% of men had clinically relevant improvements in sexual quality of life scores. However, these remarkable outcomes have not been replicated by other units. Furthermore, numerous questions arise whether the direct implanting of a somatic nerve end (genitofemoral nerve) into the corporal tissue (instead of directly onto the cavernous nerve) will restore the neural conduit for penile erection, and the possibility that a delayed neurorrhaphy can actually reverse corporal fibrosis with loss in penile size and change in penile shape which typically occurred in men with ED post PCa treatment.

4. Conclusions

While the use of regenerative technology to restore EF is exciting and highly innovative, considerable limitations remain regarding actual clinical translation and the need for longer-term efficacy and safety data. Considering the lack of high-level evidence in these regenerative therapeutic agents, coupled with concerns regarding commercialization and financial gain over patient well-being in this vulnerable demographic, proper governmental regulation on clinical framework and more robust clinical studies are needed to rigorously evaluate these novel regenerative therapies before they can be accepted as standard of care to restore EF in men following PCa treatment.

Conflicts of interest

The author declares no conflict of interest.

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