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2013-2014 Updates in Peyronie's Disease Management

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Abstract The number of patients presenting with Peyronie's disease (PD) appears to be on the rise. This review provides an analysis of pertinent recent updates in the management of PD, focusing on data published within the past year. Objective benefit from injectable agents has been reported for years in mostly noncontrolled trials. The safety and efficacy of injectable collagenase clostridium histolyticum is now supported by data from a large-scale phase III randomized controlled trial. Other important advances have also been made in the surgical management of Peyronie's disease, including new modifications to proven surgical techniques and a variety of approaches that can help enhance and restore penile length.

Keywords Peyronie's disease · Penile curvature · Penile straightening · Penile plaque · Tunica albuginea plication · Collagenase clostridium histolyticum · Plaque excision and grafting · Intralesional injection · Penile traction therapy · Penile prosthesis · Manual modeling

Abbreviations

PD	Peyronie's disease
IIEF	International Index of Erectile Function
VAS	Visual Analogue Scale
PDE-5	Phosphodiesterase Type 5
ILI	Intralesional Injection
CCH	Collagenase Clostridium Histolyticum
RCT	Randomized Controlled Trial
TEA	Transdermal Electromotive Agent
PDQ	Peyronie's Disease Questionnaire
ADSCs	Adipose Derived Stem Cells
TGF-beta	Transforming Growth Factor Beta
ESWT	Extracorporeal Shock Wave Therapy
PTT	Penile Traction Therapy
TAP	Tunica Albuginea Plication
ED	Erectile Dysfunction
PIG	Plaque Incision and Grafting
PEG	Plaque Excision and Grafting
IPP	Inflatable Penile Prosthesis

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Introduction

Peyronie's disease (PD) is a fibrotic penile wound-healing disorder of the tunica albuginea that can result in penile curvature/deformity, narrowing, shortening, hinging, and sexual dysfunction [1•]. PD often results in a significant psychological disturbance and can be difficult to manage by the practicing urologist, especially with a lack of strong evidence in support of a myriad of treatment options. PD has a documented incidence of 3-10 % in the general population [2–4]. Prevalence may actually be higher and urologists may see more patients presenting with PD in the near future as awareness of the disease and marketing for injectable agents will likely increase.

Recent comprehensive reviews of the etiology, workup, and historical management of PD can found elsewhere [1•, 3, 5–8]. The purpose of this review is to provide recent pertinent updates in the management of PD; all data critically evaluated in this review has been published within the past fifteen months.

Medical Management

Medical therapies for PD may be appropriate for men with unstable deformity and/or pain in the acute phase or in men in the chronic phase who are not surgical candidates. A wide variety of nonsurgical treatment options for PD have been suggested, including oral medications, topical agents, intralesional injections, extracorporeal shock wave treatment, radiation therapy, and mechanical stretching with vacuum or traction therapy. Unfortunately, in spite of the plethora of nonsurgical treatment options, few are backed by sufficient evidence to offer reliable outcomes.

Oral Therapies

A large variety of oral therapies have been used to manage PD including Vitamin E, potassium aminobenzoate (Potaba), Tamoxifen, colchicine, carnitine, NSAIDs, corticosteroids, antioxidants, and PDE-5 inhibitors. To date, no oral agent has demonstrated clear efficacy and small trials have variable results when used as monotherapy or in combination with other treatment modalities [1•, 6, 9]. The most recent report by the International Consultation on Sexual Medicine does not support routine clinical use of oral agents for PD [1•].

Nonetheless, oral agents continue to be actively evaluated and are frequently offered to patients without evidence-based studies. Recent studies include that of Ozturk and colleagues, who treated 39 PD patients with 50 mg Sildenafil daily or 400 IU Vitamin E daily for 12 weeks. Mild improvements in plaque size and penile curvature favored Sildenafil, but differences were not statistically significant. Sildenafil did result in an expected improvement in International Index of Erectile Function (IIEF) scores (10.10 to 13.90) as well as visual analogue scale (VAS) pain scores (3.24 to 1.95) compared to Vitamin E (IIEF 9.78 to 10.67, and VAS score 3.39 to 2.61). It is hypothesized that phosphodiesterase type 5 (PDE5) inhibitors may inhibit plaque development and progression by decreasing cyclic guanosine monophosphate, promoting apoptosis, and reducing collagen synthesis [10•]. Other investigators have suggested that PDE5 inhibitors enhance tissue oxygenation and reduce local free radical levels, which can prevent fibrosis and improve wound healing [11, 12].

Although oral agents have not been shown to be highly effective as monotherapy, they may prove to be of benefit when used as a component of multimodal therapy. Paulis et al., recently reported treatment of unstable PD patients with intralesional verapamil, oral antioxidants, and topical diclofenac gel with or without oral Vitamin E. The Vitamin E group had better reduction in plaque volume (50.2 % vs 35.8 %) and more improvement in curvature (12.25° vs 6.73°), which may not be clinically meaningful [13]. This study is limited in sample size and the synergistic effects of various modalities will not be clearly defined without larger studies. In addition, it should be recognized that a reduction in plaque size, which is difficult to accurately measure, has not been associated with a reduction in deformity.

Transdermal therapy and Intralesional Injections

Intralesional injection (ILI) therapy for PD was first attempted with intralesional corticosteroids [14, 15]. However, local side effects and inconsistent improvement in curvature or pain in well-run trials have obviated their use [16]. More recent approaches using verapamil, interferon, or purified collagenase clostridium histolyticum (CCH) (Xiaflex™) have shown efficacy in observational studies and preliminary results from larger randomized controlled trials (RCTs) are promising.

Verapamil

Verapamil is thought to inhibit Peyronie's scar formation by preventing exocytosis of collagen, fibronectin, and glycosaminoglycans [17, 18]. ILI verapamil has been used in a variety of multimodal therapy regimens. Although no adequately powered RCTs have been completed, at a minimum ILI verapamil seems to be of benefit in select patients as a disease-stabilizing agent [3, 19, 20]. Most recently, Favilla and colleagues performed a prospective randomized controlled study comparing ILI verapamil alone with ILI verapamil+oral antioxidants. Both groups had similar improvement in plaque volume (-0.26 cm^3, -0.38 cm^3) and penile curvature (-10.86°, -11.97°), respectively. However, patients receiving oral antioxidants were found to have less pain and significant improvement in erectile function, potentially due to the anti-inflammatory effects of antioxidant therapy [21•].

Verapamil is most frequently administered as an injectable agent, but small controlled trials have also shown some objective benefit when applied as a transdermal electromotive agent (TEA). TEA utilizes external electric force to induce passage of ions to the Peyronie's plaque to enhance penetration of verapamil, which is unlikely to reach the tunica albuginea without this assistance [22–24]. Mehrsai et al. recently provided further data in support of TEA Verapamil for PD in a prospective trial with 60 PD patients randomized to six weeks of treatment with either TEA verapamil with dexamethasone or ILI verapamil with dexamethasone. Both groups had similar mild improvements in curvature and International Index of Erectile Function (IIEF) scores. However, the TEA group had a greater decrease in plaque volume (TEA Verapamil: 220.3 mm^3 to 57.9 mm^3, ILI verapamil: 169.8 mm^3 to 105.5 mm^3). The TEA group (VAS score 5.1 to 1.0) was also found to have a significant improvement in pain compared to intralesional verapamil (VAS score 5.4 to 3.6) [25•]. There is evidence of some benefit with TEA, however we would only recommend this approach in men with acute phase disease and pain who do not have severe deformity.

Intralesional Collagenase Clostridium Histolyticum

Perhaps the most important advances in PD management in the past year are related to promising data from two large, multi-institutional, RCTs. The Investigation for Maximal Peyronie's Efficacy and Safety Studies (IMPRESS) I (417 patients, US) and II (415 patients, Australia) trials included a six-week cycle of two office-based intralesional injections followed by penile plaque modeling 24-72 hours later. Patients received up to four cycles (eight total injections) and were compared to a group receiving injections of saline. Patients included had chronic phase PD with a mean penile curvature of 50.5°. Dorsal curvature was present in 51.8 % of patients, with the remainder having some degree of dorsolateral or purely lateral curvature. Patients with ventral curvature and extensive plaque calcification were excluded. In addition to assessing responses in penile curvature, analysis of these patients also included: penile length, plaque size, associated pain, IIEF scores, and Peyronie's Disease Questionnaire (PDQ) values [26••].

Results of IMPRESS I and II are promising. At a 52-week follow-up, mean curvature decreased from 50.1° to 33.1° (34 % decrease) in the CCH group, compared to a decrease of 49.3° to 40.0° (18 % decrease) in the control group. Mean PDQ scores showed more significant improvement (10.8 to 7.9) in the CCH group compared to the placebo group (10.6 to 9.3). Mean improvement in IIEF scores were similar between the two groups (CCH: 5.6 to 6.6, placebo: 5.6 to 6.6). Of note, adverse events occurred in 84.2 % of the CCH group and only 36.3 % of the placebo group. Most adverse events were minor (ecchymoses, swelling, pain), and 79 % of the adverse events resolved without intervention. Serious adverse events occurred in six patients, including three corporeal ruptures and three significant penile hematomas [27••]. CCH was approved by the Food and Drug Administration in the USA in December 2013 for the treatment of palpable plaque with dorsal or dorsolateral curvature >30°. This approach makes clinical sense in that it uses a chemical knife to lyse collagen, which is the primary plaque component.

Other Injectable Agents

Currently, other injectable agents are in the early phases of evaluation in the laboratory setting. Specifically, Adipose-derived stem cells (ADSCs) have been proposed as a novel autologous agent to help prevent Peyronie's scar propagation. In separate studies, both Lin et al., and Castiglione et al., have developed a rat model of Peyronie's penile plaque formation by injecting transforming growth factor beta (TGF-beta) to induce fibrosis. Rats treated with TGF-beta have been shown to develop PD-like plaque formation with extensive tunica and corporal fibrosis and irregular orientation of collagen and elastin. Subsequent injection of ADSCs (24 hours later) seems to prevent the development of penile plaque formation [28•]. Rats injected with ADSCs also have improved erectile function compared to placebo, which correlates with improvement in intracavernous pressure/mean arterial pressure ratios [29•]. This model seems to represent the early acute phase of PD, a stage at which few human subjects present for treatment. At this time, it remains unclear if these agents would provide any benefit in well-formed (chronic phase) plaque or in human subjects.

Extracorporeal Shock Wave Therapy (ESWT) and Radiation Therapy

Shock wave therapy and radiation therapy were initially used as a PD treatment to initiate plaque degeneration. A number of small, retrospective studies have been published with variable results. Controlled investigations have not demonstrated significant improvements in curvature, and neither ESWT nor radiation therapy are currently recommended for treatment of PD [1•, 30–33]. Hatzichristodoulou and colleagues recently reported a placebo-controlled, prospective, randomized, single-blind study evaluating the efficacy of ESWT. They randomized 102 PD patients to six weekly treatments of ESWT (2,000 shock waves per session) vs placebo (interposition plastic membrane prevented shock wave transmission). Although there was a nonsignificant improvement in pain in the ESWT group, penile curvature did not improve after ESWT or placebo and actually worsened in 40 % of ESWT patients [34•].

Penile Traction Therapy

Penile traction therapy (PTT) has been used in PD patients as a means of remodeling the extracellular matrix of PD plaque via a process known as mechanotransduction. Responses to traction therapy are variable, but improvement in curvature by 10-45° has been demonstrated. With diligent use, traction therapy also results in objective gains in penile length up to 2 cm [35, 36, 37•]. Further support for PTT use for PD was published this year. Martinez-Salamanca and colleagues treated 55 acute phase PD patients with PTT for six months and compared them to 44 PD patients with no treatment. The PTT group had a 20 degree decrease in curvature (33° to 13°) compared to a 19° worsening of curvature in the control group. The traction group also demonstrated a 39 % reduction in plaque volume, while the plaque in the control group enlarged. After the study period, 80 % of the patients who received PTT were able to have penetrative intercourse (versus only 15 % in the group without treatment) [38•]. Although larger trials are needed, it seems that a PTT regimen in the acute phase of PD may help prevent disease progression and can potentially reduce the need for surgery in motivated patients. Traction therapy is an underutilized treatment option that can be instituted as

monotherapy or in combination with other medical and surgical treatment modalities. The key to successful traction therapy is time. It appears that a minimum of three hours per day is needed to see changes in length, girth, and curvature. It also appears that there is a dose-response with traction; the longer one wears the device, the greater the potential improvement in length gain and decreased curvature [37•].

Surgical Management

Surgery remains the gold standard treatment option for patients with severe PD and/or those who have an incomplete response to conservative management. Appropriate candidates for surgery have stable PD (at least one year from onset and at least six months of stable deformity), compromised sexual function, extensive plaque calcification, and/or desire the most rapid and reliable correction of deformity [1•].

Plication Procedures

Tunica albuginea plication (TAP) is the preferred method of straightening for men with adequate rigidity and less severe disease (curvature <70°) without narrowing or hinging. Tunical shortening procedures include a variety of corporoplasty or tunica albuginea plication (TAP) procedures including the Nesbit, modified Nesbit, Yachia, Giammusso, Lemberger, Essed-Schroeder, Duckett-Baskin-Levine, and 16-dot or 24-dot plication techniques. Regardless of plication approach, full straightening is expected in 85-100 % of reported patient satisfaction ranging between 70-100 % [5, 6, 8]. The most recent studies on plication have verified the durability of this technique by reporting successful outcomes with long-term follow-up. Cantoro and coworkers recently reported that, among 89 PD patients treated with Nesbit plication since 1990, 91 % had complete correction of curvature and 89 % had adequate erectile function with IIEF-5>21 [39•]. Similarly, Lopes et al., recently reported 18-year plication outcomes in 106 PD patients treated with the Yachia technique. Although nearly all patients experienced subjective shortening, a majority had complete straightening and 95 % had straightening that allowed for successful intercourse [40]. Tunica plication is the least likely surgical technique to result in erectile dysfunction (ED), but remains the most likely to result in reduced shaft length unless traction therapy is used postoperatively [1•, 41•].

Grafting Procedures

Patients with more severe deformity (curvature >60-70°, hinging, severe plaque calcification) with strong erections are considered candidates for plaque incision and grafting (PIG) or partial plaque excision and grafting (PEG). Plaque incision or partial plaque excision is preferred over total plaque excision because the latter may cause irreversible dysfunction of the veno occlusive mechanism of the penis, resulting in high rates of postoperative ED [1•, 5, 6].

Adequate straightening after these procedures is typically achieved in most studies (80-100 %) with patient satisfaction typically ranging from 70-100 %. A wide variety of graft materials have been described including dermis, saphenous vein, buccal mucosa, proximal crura, tunica vaginalis, dura mater, temporalis fascia, fascia lata, pericardium, small intestinal submucosa, and synthetic materials. Currently, the two most common grafts used in North America are Tutoplast (Coloplast US, Minneapolis, MN, USA) processed human and bovine pericardium, and small intestinal submucosa (SIS) grafts (Surgisis ES, Cook Urological, Spencer, IN, USA) [1•, 5–8].

No major changes from previously established PIG or PEG techniques have developed in the past few years, although Miranda et al., recently developed a tridimensional penile model simulating an 85 degree Peyronie's curvature. They used common PIG techniques (double-Y, H-shape, Egydio) and found that all techniques resulted in notable mechanical or geometric distortion because of imprecise wound edges that do not match up well with rectangular grafts. They concluded that these approaches may give suboptimal mechanical, geometric, and cosmetic results. However, it is unclear how accurately this penile model simulates an actual human erection; human PD deformity is often multidimensional and asymmetrical in nature. They advocate for the use of geometric principles to excise triangular portions along the incision to give a larger, more uniform rectangular graft site [42•].

Others have recently reported successful length and girth restoration using geometric principles with circular and longitudinal grafting [43, 44]. Although more aggressive excision and grafting techniques can help restore or enhance penile length, these approaches may be unnecessarily complex and higher rates of postoperative ED have been reported [43, 45, 46]. These techniques should now be reserved for men who have unacceptable shortening and agree to have a penile prosthesis implanted to ensure adequate postoperative rigidity (see below).

Our approach utilizes pericardial grafts because they are not bulky, durable, do not contract, and have minimal risk of infection or rejection. If plaque incision is performed, a modified H or double Y incision at the area of maximum curvature is typically utilized. If partial plaque excision is performed to remove the area of maximum deformity and indentation, the corners of the defect are darted in a radial fashion to enhance correction of narrowing in that area and obviate the need for

excessive plaque excision based on geometric principles. The lateral aspects of the defect should be equivalent to optimize correction with a single graft [47]. PTT is recommended after grafting procedures much like physical rehabilitation after a joint replacement, to ensure straight healing and effectively prevent shaft length loss [41•].

Surgical Management of PD patients with ED

One third of patients with PD have ED refractory to medical therapy and, therefore, may benefit from inflatable penile prosthesis (IPP) placement with manual modeling, as popularized by Wilson [48]. In most men with PD and ED, curvature will not be corrected by IPP alone. Among PD patients undergoing placement of IPP at our institution, 4 % were adequately straightened with prosthesis alone, 79 % required manual modeling, 4 % required tunica albuginea incision, and 12 % required incision and grafting [49]. Typically, incision is indicated if residual curvature is in excess of 30 degrees after modeling attempts and grafting should be performed if the resulting post-incisional defect is >2 cm in any dimension.

In PD patients, three-piece inflatable penile prosthesis placement is recommended because it offers more support during modeling than a malleable prosthesis. Chung et al., recently compared the AMS 700 CX with the Coloplast Titan IPP in a single-center retrospective study in 138 patients with PD and ED who underwent IPP placement with manual modeling. Mean preoperative curvature was 49 degrees and all men had curvature less than 90°. Both devices resulted in high patient satisfaction (~80 %); and there was no significant difference between devices with regard to penile straightening or device survival [50•].

The durability of these devices was also highlighted in a recent review of penile prostheses. Of the currently available three-piece prostheses, 65-85 % are likely to have at least 10-year survival and 91-100 % of implanted patients experience satisfactory sexual activity. The most common complaint is length loss, which is of particular concern in the PD population as the majority of men already have length loss prior to surgery. At least 30 % of PD pts with IPP report reduced length [51].

To prevent length loss, operative techniques including combined IPP with circumferential incision and grafting or combined dorsal/ventral graft placement have been described. Egydio and Sansalone have reported a length gain of over 3 cm by performing circumferential incision and grafting with IPP placement [43]. In PD patients who are unwilling to tolerate any further length loss after IPP placement, another option is preoperative traction therapy. A small pilot study using penile traction for 3-4 months prior to IPP placement resulted in no further length loss after IPP placement, with the majority of patients (70 %) having some length gain (0.5-2 cm) compared to their pretraction stretched length [52].

While IPP placement remains the gold standard for patients with severe PD and associated ED, Kayagil et al., recently reported successful treatment of nine patients with PD (curvature>40 degrees) and ED with penile revascularization and straightening. Patients were confirmed to have vasculogenic ED by color Doppler ultrasound, corporal electromyography, and cavernosometry. ED was treated by anastomosis of the inferior epigastric artery to the proximal deep dorsal penile vein. Straightening was performed using Essed Schroder plication or plaque excision with venous grafting. At mean follow-up of 18 months, they reported complete straightening in all patients and an improvement in mean IIEF-5 scores from 9.8 (preoperatively) to 22.03 [53•]. Although this paper is the first of its kind to report results of penile revascularization as a combination with straightening in PD patients with ED, the technique may be of limited overall utility due to very strict patient selection and complex surgical technique.

Conclusions

A myriad of treatment options exist for PD, many of which lack strong support of efficacy in well-run trials. This past year revealed promising data from a large-scale phase III RCT in support of intralesional therapy with CCH for the nonsurgical management of PD. Verapamil, as both a ILI and TEA agent, also gained further support in smaller trials. Surgery remains the gold standard treatment for severe PD. Modifications of PIG and PEG may help to prevent penile length loss. Although larger studies are necessary, penile traction therapy has good objective outcomes in small trials and can be used in the early phases of PD in motivated patients to prevent length loss and improve curvature. Traction therapy can also be used as a component of multimodality nonsurgical therapy, after grafting procedures, or prior to IPP placement.

Compliance with Ethics Guidelines

Conflict of Interest Dr. Benjamin A Sherer and Dr. Krishnan Warrior each declare no potential conflicts of interest.

Dr. Laurence A. Levine is a speaker and consultant for AMS, Auxilium, and Coloplast. Dr. Levine is on the board for Auxilium, Coloplast, and Absorption Pharmaceuticals.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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