Peyronie's disease: what do we know and how do we treat it?

Paul H. Chung, MD, Timothy M. Han, BA, Ben Rudnik, MD, Akhil K. Das, MD
Department of Urology, Sidney Kimmel Medical College, Thomas Jefferson University, Philadelphia, Pennsylvania, USA

CHUNG PH, HAN TM, RUDNIK B, DAS AK. Peyronie's disease: what do we know and how do we treat it? *Can J Urol* 2020;27(Suppl 3):11-19.

Introduction: *Peyronie's disease is a common, benign condition characterized by an acquired penile abnormality due to fibrosis of the tunica albuginea. This may lead to penile curvature, deformity, discomfort, pain, and erectile dysfunction, resulting in emotional and psychosocial effects on patients. Therefore, it is important for urologists to thoroughly evaluate the extent of the patient's bother and discuss treatment goals, therapeutic options, and expectations.*

Materials and methods: *We provide a review of the current landscape for the diagnosis, management, and treatment of Peyronie's disease, including oral, topical, intralesional, external energy, and surgical therapies.*

Results: *The hallmark of managing Peyronie's disease is attentive patient counseling. Patients may be hesitant to discuss their symptoms unless inquired directly and may not be aware that treatments exist. It is not uncommon for Peyronie's disease to be diagnosed incidentally during a routine or unrelated healthcare visit, with reported rates of incidental diagnosis as high as 16%. Treatment options are stratified by disease phase which is defined by whether symptoms (e.g. penile deformity and discomfort) are actively changing or have stabilized. Conservative therapy is the most common recommendation during the active phase with more invasive treatments reserved for the passive phase. Conservative therapy may include oral or topical medication, intralesional injection, and external energy therapy. These treatments may also have a role in improving symptoms during the passive phase prior to undergoing more definitive surgical treatment. Surgical interventions include tunical plication, plaque incision or excision with or without grafting, and penile prosthesis implantation. Despite the variety of treatment options available to patients, each has a distinct efficacy and adverse effect profile, warranting thorough discussion to meet patients' goals and manage expectations.*

Conclusion: *Peyronie's disease is a common condition that is underdiagnosed and undertreated. Patients with Peyronie's disease will benefit from a comprehensive evaluation and in-depth counseling so that they may become familiar with the natural disease course and have appropriate expectations of each treatment option.*

Key Words: Peyronie's disease, penile deformity, penile curvature, collagenase histolyticum, penile plication, plaque excision

Introduction

Peyronie's disease (PD) is a benign condition characterized by an acquired penile abnormality due to fibrosis of the tunica albuginea. It is a common condition with an estimated prevalence reported to range from 0.5% to 20.3% within specific populations.[1,2] However, given that many patients may be reluctant or embarrassed to seek professional help from their doctors, PD is likely underdiagnosed and consequently undertreated. Often, PD is diagnosed incidentally during healthcare visits for other primary concerns, such as prostate cancer screening (reported 8.9% prevalence) or erectile dysfunction (reported 16% prevalence).[3,4] The most common inciting event is thought to be sexual activity, during which patients may experience penile buckling in the erect or semi-erect state resulting in microvascular trauma to the penile shaft.[5,6] This repetitive minor penile trauma initiates a collagen deposition cascade which results in plaque formation within the penile tunica albuginea. The plaques may be palpable or non-palpable and many patients do not recall a specific incident that preceded symptom onset.

The plaque may restrict tunica lengthening on the affected side during erection leading to curvature with possible deformity, discomfort, pain, and/or erectile dysfunction (ED). These changes in penile appearance and function often take an emotional and psychosocial toll on patients resulting in bother, depression, and relationship difficulties. Therefore, it is important for urologists to thoroughly discuss the extent of bother,

Address correspondence to Dr. Paul H. Chung, Thomas Jefferson University, Department of Urology, 1025 Walnut Street, Suite 1110, Philadelphia, PA 19107 USA

treatment goals, therapeutic options, and expectations with the patient. In this review, we discuss the current landscape for the diagnosis, management, and treatment of PD, including medical (oral, topical, intralesional, external energy) and surgical (penile plication, plaque incision or excision, penile implant) treatments.

Diagnosis

The diagnosis of PD starts with a thorough history evaluating the presentation, duration and evolution of penile deformity and concomitant symptoms such as pain or discomfort. Bother or distress may also exist and manifest as interference with intercourse, changes in confidence, and changes in interpersonal relationships. Urologists may find utility in using the Peyronie's Disease Questionnaire (PDQ) or other PD questionnaires, which have been shown to demonstrate valuable subjective data in conjunction with objective measurements.[7,8] Past medical history and family history are important to identify known risk factors and comorbidities associated with PD, including penile fracture or trauma, Dupuytren's contracture, plantar fibromatosis, diabetes, cardiovascular disease, ED, and low testosterone; however, most patients do not report an exact inciting event.

Physical exam should focus on the genitalia to assess for penile deformity, presence of palpable abnormalities, and location of pain or discomfort. Evaluation of the penis should be performed in both flaccid and erect states with baseline measurement of penile curvature documented based on visual estimate, home photography, and/or more objective measurements performed such as utilizing a protractor or goniometer.[9] While careful history and physical examination may be sufficient to diagnose PD and move towards medical management, current American Urological Association (AUA) guidelines recommend an intracavernosal injection test with or without duplex Doppler ultrasound prior to any invasive treatment (e.g., intralesional treatments, penile prosthesis placement, or surgery).[10] The intracavernosal injection test enables urologists to better assess the extent of penile deformity, plaque(s), and pain in the erect state, while the addition of duplex ultrasound can better characterize plaque size and/or density, differentiate between calcified and non-calcified plaques, and obtain information on the vascular integrity of the penis.

It is also important to clinically identify and categorize whether the patient presents during the active or passive phase of PD as this will guide subsequent management. The active phase is characterized by dynamic and changing symptoms with patients presenting with penile and/or glanular pain or discomfort with or without erection. Penile deformity and plaque may not be fully developed, distress may be present, and erectile function may be compromised. Importantly, some patients may experience painless deformity as well as intact erectile function. While invasive treatment is not advised during this phase, urologists should carefully plan with patients to educate them on their treatment options, expectations, and goals, as well as PD natural history and timeline. The following phase is the passive phase, during which symptoms have been clinically quiescent or unchanged for ≥ 3 months based on either patient report or clinician documentation. Pain with or without erection may still be present but is less common. Also, penile deformity is now stable and no longer progressive.

Understanding the natural history of PD enables urologists to better guide patients regarding disease progression and timeline, and patient expectations. Mulhall et al performed a study that followed 246 men with newly diagnosed PD who had no medical treatment.[11] The mean duration of PD at follow up was 18 months. Their results showed that all patients who initially reported penile pain had improvement; 89% of whom reported complete resolution at follow up. However, of the men who reported penile curvature, only 12% improved (mean change 15°), 40% remained stable, and 48% worsened (mean change 22°) at follow up. These results combined with more recent studies suggest that many or most patients will have resolution or improvement of penile pain over time without intervention, while curvature and/or other deformities are much less likely to improve naturally.[12,13] Therefore, patients should be counselled accordingly, and treatment options should be discussed to target patient goals. Treatments should not be offered in patients whose PD does not cause them bother, as the risks may outweigh the benefits.

Medical treatments

Oral and topical therapies

During the active phase of PD, the only medication class recommended by current AUA guidelines are oral non-steroidal anti-inflammatory drugs (NSAIDs), which can be offered to patients in need of pain management.[10] However, it can prove difficult to anticipatorily take NSAIDs before sexual activity, due to its often-spontaneous nature. Pentoxifylline (PTX), a nonspecific phosphodiesterase inhibitor, is another oral medication with limited but promising scientific data. Smith et al reported in a retrospective cohort study

that 92% of the PTX treatment group demonstrated plaque improvement/stabilization compared to 44% in the no treatment group.[14] Coenzyme Q10 (CoQ10) has also had newer data suggesting its efficacy and safety for PD treatment. Safarinejad performed a double-blind, placebo-controlled randomized study and found significantly reduced curvature and plaque size, and increased International Index of Erectile Function (IIEF) scores in the CoQ10 group compared to placebo, with no significant effects on pain.[15] Colchicine and potassium aminobenzoate have also been studied in the literature; however, data are limited with varying results, requiring further investigation with larger randomized controlled trials. As for other oral therapies, AUA guidelines recommend against the use of vitamin E, tamoxifen, procarbazine, omega-3 fatty acids, and combination vitamin E with L-carnitine due to the lack of compelling evidence suggesting their efficacies.[10] With any oral medication, patient compliance may prove to be an issue, thereby warranting appropriate patient counseling while determining the best treatment plan for these patients.

Limited studies have been performed evaluating topical therapies for PD. Fitch et al performed a randomized placebo-controlled pilot study which found that topical verapamil hydrochloride 15% gel improved curvature and reduced plaque compared to placebo at 9 months follow up.[16] Topical liposomal recombinant human superoxide dismutase has also been shown to improve pain, curvature, and plaque size.[17,18] Future studies with larger patient cohorts need to be performed to further investigate these potentially promising topical therapy options. Current guidelines do not suggest their use as a treatment for PD.[10]

Injection therapies

Intralesional injection therapy has been widely studied in the literature and include collagenase clostridium histolyticum (CCh), interferon-α2b, and verapamil. CCh targets collagen within plaques and works to break them down to improve curvature and deformities. Current AUA guidelines recommend CCh to be performed with clinician/patient modeling in PD patients during the passive phase with curvature 30°-90° in the dorsal, lateral, or dorsal/lateral planes with intact erectile function (with or without the use of medications).[10] These recommendations are based largely on the results of the double-blind, randomized, placebo-controlled IMPRESS (Investigation for Maximal Peyronie's Reduction Efficacy and Safety Studies) I and II trials which facilitated approval by the Food and Drug Administration.[19] The IMPRESS trials found significant improvement in penile curvature deformity with similar results when stratified by degree of baseline deformity (30°-60° or 61°-90°). Post hoc meta-analysis of the two trials revealed a mean 34% improvement in penile curvature in the CCh group compared to a mean improvement of 18.2% in the placebo treated men ($p < 0.0001$). Additionally, PDQ-bother score was significantly improved in the treatment group compared to placebo (-2.8 +/- 3.8 versus -1.8 +/- 3.5; $p = 0.0037$). These results strongly demonstrated the safety and efficacy of CCh for the treatment of passive phase PD, at least within the inclusion criteria specified.

Patients should be appropriately counseled on expectations, as CCh does not guarantee complete straightening of the penis. Additionally, due to the costs, side effects, and rigorous protocol, patients may elect to drop out early from treatment. Important adverse events identified included penile ecchymosis (80%), swelling (55%), pain (45%), hematoma (< 1%), and corporal rupture (< 1%). Therefore, patient reassurance and regular follow up with patients is crucial as patients are often scared after adverse events. Regarding the more serious adverse event of corporal rupture following CCh, there is ongoing discussion on whether to manage these patients similar to that of traumatic penile facture or with more conservative measures including observation and medical management.

Recent studies have further explored the utility of CCh. To investigate its safety and efficacy during the active phase, Nguyen et al performed a retrospective study and found no statistically significant differences in final change in curvature between active and passive phase patients (16.7° versus 15.6°; $p = 0.654$) and in treatment-related adverse events (11% versus 10%; $p = 0.778$).[20] These results suggest that CCh may produce similarly safe and effective outcomes in treating PD in both active and passive phases. Another study targeted shortening the treatment protocol to assess safety and efficacy. Abdel Raheem et al published their results from a prospective study of 53 PD patients who received 3 CCh injections 4 weeks apart with daily combination home modeling, stretching, and a vacuum device to mechanically stretch the plaque.[21] Their study showed significant improvements in IIEF (20.9 to 23.8; $p < 0.001$), PDQ-bother score (8.9 to 6.1; $p < 0.01$) and mean penile curvature (31.4% improvement; $p < 0.01$) after only 3 injections. These results suggest the treatment protocol may be shortened and refined with similarly effective results.

Interferon-α2b may also be a potential option and works by inhibiting fibroblast proliferation and increasing collagenase production, but may cause

adverse events including sinusitis, flu-like symptoms, and minor penile swelling. These adverse events tend to be short in duration (< 48 hours) and may be managed effectively with over-the-counter NSAIDs. Interferon-α2b has been studied for use in both active and passive phases. In a randomized prospective study, Inal et al showed in 30 men (early stage PD) that penile pain resolved after 6 months in more patients who were administered interferon-α2b alone (71%) or interferon-α2b + vitamin E (83.3%) compared to vitamin E alone (50%).[22] However, the study showed no statistically significant changes in both objective and subjective parameters. Furthermore, the study's sample size was small (10 per group) and there was no true placebo group. Current data is limited for use in treating PD during the active phase and more studies are required.

To assess the safety and efficacy of interferon-α2b during the passive phase, Hellstrom et al performed a single-blind, multicenter, placebo controlled, parallel study in a total of 117 consecutive PD patients.[23] Injections were administered biweekly for 12 weeks with the control group receiving 10 mL of saline and the treatment arm receiving $5x10^6$ U interferon-α2b. Interferon-α2b demonstrated significantly greater improvements compared to placebo in mean penile curvature (-13.5° versus -4.5°; $p < 0.01$), mean plaque size (-2.6 cm^2 versus -0.9 cm^2; $p < 0.001$), and mean plaque density assessed from questionnaires graded between 0 to 3 (-0.77 versus -0.23; $p < 0.05$). Interestingly, both the control group of this study as well as the IMPRESS trials demonstrated improvements at follow up, suggesting that the mechanical disruption performed by the needle upon injection may in and of itself assist plaque breakdown. In a separate study, Trost et al retrospectively analyzed 127 men (median history of PD of 2.0 years) treated with interferon-α2b and found that 54% responded to therapy with an overall mean improvement of 9.0° ($p < 0.001$).[24] These studies suggest that interferon-α2b may be administered to PD patients, with stronger data demonstrating its utility during the passive phase which is reflected in the current AUA guidelines.[10]

Verapamil works as a calcium channel blocker and increases collagenase activity. Adverse events may include hypotension, headache, penile bruising, dizziness, nausea, and pain at the injection site. The first published study exploring its use as an intralesional injection was performed by Levine et al in 1994 and later updated in 2002.[25,26] The authors published their experience with verapamil in 156 men during the passive phase (mean disease duration 17.7 months) with 140 patients completing treatment (10 mg biweekly injections over 6 months). Of the 140 patients, 60% had an objectively measured decrease in curvature (mean reduction 30°) with 62% reporting subjective improvement during follow up (mean 30.4 months). Positive results have also been demonstrated for use during the active phase. Arena et al showed in a study of 39 patients that 50% of those treated during the active phase experienced curvature improvement, compared to only 10.2% in the passive phase patient group.[27] These results suggest that verapamil may be more effective as an active phase treatment. Nevertheless, there have been no published studies of verapamil with placebo-controlled trials. Therefore, there is weak evidence demonstrating its efficacy and use. Due to this reason, it remains a conditional recommendation in treatment guidelines.[10]

External therapies

External energy therapies include penile low-intensity shockwave therapy (LiSWT), electromotive drug administration (EMDA) or iontophoresis, and penile traction therapy (PTT). AUA guidelines suggest that LiSWT may play a role during the active phase for pain management.[10] Palmieri et al performed a prospective, double-blind, placebo-controlled clinical trial which randomized PD patients (≤ 12 months) to receive either LiSWT (n = 50) or placebo (n = 50).[28] The study showed that at 24 weeks follow up, mean pain scores on a visual analog scale decreased more from baseline in the LiSWT group (5.5 to 0.46) than in the placebo/sham group (5.2 to 2.7). In a separate study, Palmieri et al conducted a prospective, randomized, controlled clinical trial comparing LiSWT alone to combination LiSWT + tadalafil 5 mg for management of patients with PD (< 12 months) and ED.[29] At 12 weeks follow up, mean visual analog scale score, mean IIEF, and mean quality of life score were significantly improved in both groups while mean plaque size and mean curvature were unchanged. Importantly, at 24 weeks there was a significantly higher mean IIEF and mean quality of life score in patients that received LiSWT + tadalafil, suggesting its potential use in the conservative management of patients with PD and ED during the active phase. Hatzichristodoulou et al replicated these findings of pain relief during passive phase treatment in a placebo-controlled, prospective, randomized, single-blind study.[30] Their study demonstrated a greater decrease in mean pain scores on a VAS in the LiSWT group (4 to 1.5) compared to placebo/sham (4 to 3). Additionally, a subgroup analysis of the 45 patients who experienced pain at baseline showed that 85% (17/20) of patients in the LiSWT group reported pain decrease compared to only

48% (12/25) in the placebo group (p = 0.013, RR=0.29, 95% CI 0.09-0.87). However, while these studies have demonstrated positive findings in terms of pain relief, none reported significant improvements in penile curvature or plaque size. Furthermore, Chitale et al reported no significant changes in IIEF, pain reduction, curvature, and plaque size in their prospective randomized controlled double-blind trial comparing limited shock wave therapy to sham treatment in 36 PD men (stable disease > 6 months).[31] Given its limited utility in treating only pain symptoms, which often spontaneously resolve in the natural history of PD, along with the associated risks and adverse events (i.e. localized petechial bleeding/bruising, urethral bleeding or transient hematuria, minor ecchymosis, increased pain), providers ought to thoroughly discuss the risks, benefits, and cost of LiSWT. Further investigation is needed, with current AUA guidelines giving a conditional recommendation for its use to improve penile pain while recommending against its use for reduction of penile curvature or plaque size.[10]

EMDA is an external energy therapy that involves using iontophoresis as a mechanism to transdermally deliver drug therapy to target tissues with minimal side effects. Greenfield et al performed a randomized, double-blind, placebo-controlled trial of 42 passive phase PD patients which compared EMDA verapamil to saline and found that there was no statistically significant difference between the two treatment groups at 3 months follow up.[32] Given poor evidence of efficacy, the AUA guidelines do not recommend EMDA with verapamil for treatment of PD.[10] However, scientific studies continue to explore various combination therapies with EMDA. In a prospective, randomized controlled study, Di Stasi et al looked at EMDA combination therapy with verapamil + dexamethasone.[33] After 6 weeks, the EMDA verapamil + dexamethasone study group demonstrated significant decreases in median plaque volume (824 mm to 348 mm) and in penile curvature (43° to 21°), whereas the control group demonstrated no significant changes. Additionally, the treatment group experienced significant permanent pain relief compared to transient pain relief in the control group. However, with only a single study and a small sample size, further randomized controlled studies with larger sample sizes are required before determining meaningful benefit.

PTT is a therapy that works through a mechanical means and has been studied for use in both active and passive phases. Levine et al performed the first study which used the FastSize Penile Extender (Aliso Viejo, CA, USA) in 11 men (mean PD duration 29 months), 8 of whom previously failed non-surgical treatments.[34] The traction therapy involved using the device 2-8 hours per day for 6 months. After 6 months, all men experienced reduced curvature (mean reduction 22°) and increased stretched penile length (up to 2.5 cm). Additionally, mean IIEF increased from 44.6 to 55 and there was no change in penile sensation or new ED in the treatment group. In another study, Gontero et al investigated PTT using the Andropenis (Andromedical, Madrid, Spain) penile extender in 15 patients with PD for over 12 months, curvature < 50°, and fibrous plaque diagnosed on physical exam or ultrasound.[35] Traction was performed for 5-9 hours per day for a total of 6 months. While the study reported an increase in mean stretched and flaccid penis length after 6 months (1.3 cm and 0.83 cm respectively), only 6/15 patients experienced improvement in penile curvature with nonsignificant decrease from mean baseline of 31° to 27° after 6 months (p = 0.059).

To explore the efficacy of PTT in the active phase, Martínez-Salamanca et al performed a nonrandomized prospective controlled trial comparing 55 active phase men who underwent PTT for 6 months to 41 active phase men who received no intervention.[36] Their results showed that PTT during the active phase significantly decreased mean curvature at 9 months (mean decrease 20°; p < 0.05), decreased pain (VAS score decrease from 5.5 to 2.5; p < 0.05), and improved erectile function, hardness, and ability to achieve penetration. Importantly, PTT was associated with sonographic plaque disappearance in 48% of patients and reduced the need for surgery in 40% of patients who would otherwise have been surgical candidates. While these studies demonstrated some positive results, the previously described regimens presented significant limitations. Patients may be reluctant to consider PTT due to the strict regimen with frequent and lengthy treatment times for 6 months, discomfort, and the presence of an apparatus on the penis.

As a result, the novel RestoreX (PathRight Medical Inc., Plymouth, MN, USA) PTT device was developed and studied to determine whether this therapy regimen could be made more accessible and attractive for patients.[37] In their study, Ziegelmann et al performed a randomized, controlled, single-blind, intent to treat trial in men with PD, with a total of 110 men randomized 3:1 to the PTT group (30-90 minutes per day for 3 months) or control group (no therapy for 3 months). At 3 months, PTT using RestoreX demonstrated significant improvements over the control in penile length (1.5 versus 0 cm; p < 0.001), curvature (-11.7° versus 1.3°; p < 0.01), and erectile function (IIEF-Erectile Function domain 4.3 versus -0.7; p = 0.01) among those with ED. This study demonstrated safe and effective PTT using a novel

device with a shorter treatment regimen. Additionally, Wymer et al reported in a separate study that RestoreX PTT may offer a more cost-effective method for achieving ≥ 20% curvature improvement compared with surgery or CCh.[38] While PTT has shown positive results in the scientific literature with promising developments on the horizon, current AUA guidelines do not include its use in their recommendations.[10] Further studies should be performed exploring PTT on a larger scale.

Surgical treatments

Penile plication

Historically, surgery has been considered the gold-standard treatment for PD with relatively high success rates (65%-96% achieving penile straightening).[38] Tunical plication surgery involves the placement of sutures on the side opposite of the plaque to "pull" the penis into a straighter shape. The surgery may be offered to patients who have adequate penile rigidity for coitus (with or without pharmacotherapy and/or vacuum device therapy). Several studies have been performed demonstrating its safety and efficacy as a simple and straightforward surgery with minimal chance of inducing ED or decreased sensation. Surgical technique may vary depending on plaque location and may involve midline incision, circumcision incision, or penile degloving. Furthermore, surgical plication options include corporoplasty techniques (i.e. Nesbit, Yachia) and nonincisional techniques. Various modifications have been made over the years to improve outcomes and avoid adverse events. Gholami and Lue published their results using a 16-dot plication technique in 132 consecutive patients, which demonstrated excellent and durable results with 93% of patients reporting straight erections at 6 months postoperatively.[39] Other studies have also pushed the limits in plication techniques and understanding. Once reserved only for noncomplex small degrees of penile deformity, newer studies have demonstrated the efficacy of penile plication in more complex deformities as well as those of different curvature types (dorsal, ventral, lateral). Adibi et al published their results in 43 patients with complex penile deformity (11 biplanar curvature, 32 severe curvature ≥ 60°) treated with plication surgery.[40] Their study utilized a 2 cm penoscrotal incision mobilized distally along the penile shaft without degloving. In the 11 men with biplanar curvature, median angle in the primary plane of curvature improved from 45° to 10°, with the secondary plane corrected from 35° to 5° using an average of 7 sutures. Among the 35 patients with severe curvature, plication was able to correct the median angle from 70° to 15° using an average of 11 sutures. In a separate study comparing the safety and efficacy of patients undergoing penile plication for different types of curvature, Chung et al performed a retrospective review with outcome data in patients with dorsal, ventral, and lateral curvature.[41] The study demonstrated that penile plication was safe and effective for correcting all directions of PD curvature with patient-completed satisfaction surveys at a mean of 15 months demonstrating equally high rates of satisfaction for penile curvature, penile rigidity, strength of erection, and overall satisfaction. Data revealed a similar number of sutures required for each group (8-9) to achieve similar curvature correction (37°-45°). Decreased penile length was reported subjectively, however objective length loss was small (mean length loss for all groups, 0.3 cm-0.8 cm). These studies demonstrate that plication can be a safe and effective surgical treatment option for PD in dorsal, ventral, lateral, biplanar, and severe curvatures.

Plaque incision or excision with or without grafting

Plaque incision or excision with or without grafting is an alternative surgical technique which can be offered to patients with adequate rigidity for coitus (with or without pharmacotherapy and/or vacuum device therapy). This surgery may be most applicable to patients with severe deformities, significant hourglass deformities, or plaque burden. Plaque incision or excision comes with increased risks, with studies reporting complication rates as high as 67% for postoperative ED and 20% for decreased sensitivity.[42,43] Interestingly, while these surgeries often preserve penile length, rates of penile shortening have been reported to range from 18% to 43%.[43,44] Nevertheless, the surgery has demonstrated durable and effective results with Wimpissinger et al reporting a 73% patient satisfaction rate with plaque incision and vein grafting at mean follow up of 156 months.[43] Sansalone et al also demonstrated high patient satisfaction rates of 97% at mean follow up of 20 months following plaque incision and grafting with bovine pericardium in 157 men.[45]

Grafting materials vary and include autografts, synthetic inert substances (e.g. Dacron, Gortex, silicone with silastic borders), allografts, xenografts, and collagen fleece. In a study comparing patient-perceived outcomes of plaque incision with saphenous vein grafting to corporeal plication, Kim et al reviewed the records of 67 patients at 1 year follow up.[46] Study results showed no differences between the two techniques regarding satisfactory straightness ($p = 0.13$), satisfaction with surgery ($p = 0.71$),

new use of erectile aids (p = 0.06), pain on erection (p = 0.12), or subjective penile shortening (p = 0.41). However, patients who underwent plaque incision with grafting had longer operative times (p = 0.0001) and were more likely to experience loss of rigidity (p = 0.03), inability to have intercourse (p = 0.05), and sensation loss (p = 0.0045). On the other hand, patients in the plication group were more likely to experience palpable nodules (p = 0.03). These results suggest that plication may yield similar results while maintaining fewer side effects. Nevertheless, plaque incision or excision with or without grafting provides an effective surgical option for patients with extensive plaque, severe or complex deformities, and/or for those who desire preservation of penile length.

Penile prosthesis

Penile prosthesis (PP) surgery may be offered to patients with concomitant PD with ED and/or penile deformity sufficient to impair sexual intercourse despite pharmacotherapy and/or vacuum device therapy. This surgery may offer patients a solution to both issues in one surgery as the insertion of PP may correct deformity without the need for other surgical interventions. Importantly, results from the PROPPER (Prospective Registry of Outcomes with Penile Prosthesis for Erectile Restoration) study demonstrated that inflatable PP (IPP) patients can produce high rates of patient satisfaction (> 80%) and device usage (> 88%), with decreased rates of depression (baseline 19.3% to 10.5% at 1 year [p = 0.02] and 10.9% at 2 years [p = 0.07]).[47]

Surgeons need to be prepared for adjunctive maneuvers since Levine et al determined in their single-center study that satisfactory straightening was accomplished in 4% (4/90) of patients with IPP alone while the remaining 79% (71/90) required IPP + modeling.[48] Manual modeling with the device inflation may correct deformities as the penis is bent in the direction opposite the curvature to help disrupt the plaque. Wilson and Delk published their results in a study of 138 patients treated with IPP insertion and manual modeling of the erect penis.[49] Their technique achieved successful straight, rigid erections in 86% (118/138) of patients with 90% (124/138) actually using their IPP without penile shortening or impaired sensation at mean follow up of 32 months. The most worrisome complication during modeling is urethral perforation, which occurred in their study in 4 patients (3%).

Combining IPP with penile plication or graft excision/incision have also been reported in the scientific literature, demonstrating safe, efficacious, and durable results in addressing severe curvatures and ED during the same case. Rahman et al reported complete correction in all 5 patients who received combined plication with IPP placement with no recurrence at mean follow up of 22 months.[50] Cormio et al reported their successful outcome in a patient 8 years after combined plication + IPP surgery (normal voiding function, successful intercourse, straight penis, IIEF-5 score 24).[51] In a retrospective review, Chung et al demonstrated high patient satisfaction and effective curvature correction following synchronous IPP placement and plication down from a mean of 39° to a mean < 5° in PD patients presenting with dorsal (n = 11), lateral (n = 2), and biplanar curvatures (n = 5).[52] In a study that evaluated IPP placement with tunica albuginea-relaxing incisions without grafting, Djordjevic and Kojovic reported complete penile straightening in 95% (59/62) of patients at median follow up of 35 months.[53]

Some patients who undergo IPP placement for ED have undiagnosed concomitant PD that is only identified intraoperatively due to prior history of incomplete assessment secondary to poor erection quality. Tausch et al demonstrated in a retrospective study that regardless of whether PD was identified preoperatively, synchronous plication/IPP or Yachia corporoplasty can be safely and effectively performed with satisfactory results.[54] These studies show that IPP alone, with modeling, or combined with other surgical techniques synchronously yield beneficial results.

Other potential treatments

Vacuum therapy

Vacuum therapy has been explored in the scientific literature and aims to treat PD through mechanical straightening of penile curvature. Raheem et al performed a study of 31 PD patients with mean disease duration of 9.9 months.[55] The treatment regimen involved using the vacuum device (Osbon ErecAid, MediPlus, High Wycombe, UK) for 10 minutes twice daily over a 12-week period. After 12 weeks, there was a clinically and statistically significant improvement in penile length, curvature, and pain. Notably, 21 patients demonstrated improved curvature (5°-25°), 7 had no change, and 3 had worsened curvature. Of the 31 patients, 51% (16/31) were satisfied with the outcome of therapy, with 15 undergoing subsequent surgical correction. These results suggest that vacuum therapy may be safe to use in both active and passive disease phase, may improve or stabilize PD curvature, and may reduce the number of patients requiring surgery. Nevertheless, larger studies need to be performed and current guidelines do not recommend its use as a stand-alone treatment option.[10]

Autologous platelet rich plasma

Autologous platelet rich plasma (PRP) injection have been used in other medical therapies and may be effective for use in PD by improving angiogenesis and wound healing. However, one concern with PRP is early washout, which may be avoided by using platelet rich fibrin matrix. In a preliminary study to assess safety and feasibility of platelet rich fibrin matrix injections for treatment of urologic conditions including PD, Matz et al reviewed data in 17 patients with a mean receipt of 2.1 injections per patient.[56] Of the 17 patients, 11 had PD with PRP injected with ultrasound into the plaque. While sample sizes were very small, 80% (4/5) PD patients with subsequent follow up (overall mean 15.5 months) reported subjective improvement in curvature. Adverse events in all 17 patients included mild pain (23.5%) and bruising (5.9%). To date, there exists only this one study exploring this therapy. As for stem cell therapy in treatment of PD, there have been promising published results, but only involving rat models.[57,58]

Conclusion

PD is a common condition that can potentially result in physical, emotional, and/or psychological distress. Patients may be embarrassed to seek professional help or may be unaware of their available treatment options. As a result, patients may not discuss their signs or symptoms unless directly asked. For these reasons, PD is likely underdiagnosed and therefore undertreated. Urologists should become comfortable with discussing and managing these issues with patients in order to properly diagnose patients, educate them on disease progression and timeline, target treatment goals, reach a shared decision regarding possible treatment, and manage expectations. Treatment options offered may vary based on practice resources and surgeon experience. In fact, due to the complex nature of managing and treating PD, the role may be best suited for experts with appropriate and specific experience, tools, and surgical skillset. As new medical and surgical treatments are being studied, the landscape of PD management may continue to evolve and should target the maximizing of patient satisfaction while minimizing adverse events. □

References

1. Dibenedetti DB, Nguyen D, Zografos L, Ziemiecki R, Zhou X. A population-based study of Peyronie's disease: prevalence and treatment patterns in the United States. *Adv Urol* 2011;2011:282503.
2. Arafa M, Eid H, El-Badry A, Ezz-Eldine K, Shamloul R. The prevalence of Peyronie's disease in diabetic patients with erectile dysfunction. *Int J Impot Res* 2007;19(2):213-217.
3. Mulhall JP, Creech SD, Boorjian SA et al. Subjective and objective analysis of the prevalence of Peyronie's disease in a population of men presenting for prostate cancer screening. *J Urol* 2004;171(6 Pt 1):2350-2353.
4. Kadioglu A, Oktar T, Kandirali E, Kendirci M, Sanli O, Ozsoy C. Incidentally diagnosed Peyronie's disease in men presenting with erectile dysfunction. *Int J Impot Res* 2004;16(6):540-543.
5. Devine CJ Jr, Somers KD, Jordan SG, Schlossberg SM. Proposal: trauma as the cause of the Peyronie's lesion. *J Urol* 1997;157(1):285-290.
6. Gonzalez-Cadavid NF, Rajfer J. Mechanisms of disease: new insights into the cellular and molecular pathology of Peyronie's disease. *Nat Clin Pract Urol* 2005;2(6):291-297.
7. Peyronie's Disease Questionnaire (PDQ) – US version. 2013 Auxilium Pharmaceuticals, Inc. Available from URL: http://www.auxilium.com/PDQ. Accessed April 21, 2020.
8. Hellstrom WJ, Feldman R, Rosen RC, Smith T, Kaufman G, Tursi J. Bother and distress associated with Peyronie's disease: validation of the Peyronie's disease questionnaire. *J Urol* 2013;190(2):627-634.
9. Ohebshalom M, Mulhall J, Guhring P, Parker M. Measurement of penile curvature in Peyronie's disease patients: comparison of three methods. *J Sex Med* 2007;4(1):199-203.
10. Nehra A, Alterowitz R, Culkin DJ et al. Peyronie's disease: AUA guideline. *J Urol* 2015;194(3):745-753.
11. Mulhall JP, Schiff J, Guhring P. An analysis of the natural history of Peyronie's disease. *J Urol* 2006;175(6):2115-2118; discussion 2118.
12. Grasso M, Lania C, Blanco S, Limonta G. The natural history of Peyronie's disease. *Arch Esp Urol* 2007;60(3):326-331.
13. Berookhim BM, Choi J, Alex B, Mulhall JP. Deformity stabilization and improvement in men with untreated Peyronie's disease. *BJU Int* 2014;113(1):133-136.
14. Smith JF, Shindel AW, Huang Y et al. Pentoxifylline treatment and penile calcifications in men with Peyronie's disease. *Asian J Androl* 2011;13(2):322-325.
15. Safarinejad MR. Safety and efficacy of coenzyme Q10 supplementation in early chronic Peyronie's disease: a double-blind, placebo-controlled randomized study. *Int J Impot Res* 2010;22(5):298-309.
16. Fitch WP 3rd, Easterling WJ, Talbert RL, Bordovsky MJ, Mosier M. Topical verapamil HCl, topical trifluoperazine, and topical magnesium sulfate for the treatment of Peyronie's disease--a placebo-controlled pilot study. *J Sex Med* 2007;4(2):477-484.
17. Riedl CR, Plas E, Vorauer K, Vcelar B, Wagner A, Pflüger H. Pilot study on liposomal recombinant human superoxide dismutase for the treatment of Peyronie's disease. *Eur Urol* 2001;40(3):343-348; discussion 348-349.
18. Riedl CR, Sternig P, Gallé G et al. Liposomal recombinant human superoxide dismutase for the treatment of Peyronie's disease: a randomized placebo-controlled double-blind prospective clinical study. *Eur Urol* 2005;48(4):656-661.
19. Gelbard M, Goldstein I, Hellstrom WJ et al. Clinical efficacy, safety and tolerability of collagenase clostridium histolyticum for the treatment of peyronie disease in 2 large double-blind, randomized, placebo controlled phase 3 studies. *J Urol* 2013;190(1):199-207.
20. Nguyen HMT, Anaissie J, DeLay KJ, Yafi FA, Sikka SC, Hellstrom WJG. Safety and efficacy of collagenase clostridium histolyticum in the treatment of acute-phase Peyronie's disease. *J Sex Med* 2017;14(10):1220-1225.
21. Abdel Raheem A, Capece M, Kalejaiye O et al. Safety and effectiveness of collagenase clostridium histolyticum in the treatment of Peyronie's disease using a new modified shortened protocol. *BJU Int* 2017;120(5):717-723.

22. Inal T, Tokatli Z, Akand M, Ozdiler E, Yaman O. Effect of intralesional interferon-alpha 2b combined with oral vitamin E for treatment of early stage Peyronie's disease: a randomized and prospective study. *Urology* 2006;67(5):1038-1042.
23. Hellstrom WJ, Kendirci M, Matern R et al. Single-blind, multicenter, placebo controlled, parallel study to assess the safety and efficacy of intralesional interferon alpha-2B for minimally invasive treatment for Peyronie's disease. *J Urol* 2006;176(1):394-398.
24. Trost LW, Ates E, Powers M, Sikka S, Hellstrom WJ. Outcomes of intralesional interferon-α2B for the treatment of Peyronie disease. *J Urol* 2013;190(6):2194-2199.
25. Levine LA, Merrick PF, Lee RC. Intralesional verapamil injection for the treatment of Peyronie's disease. *J Urol* 1994;151(6):1522-1524.
26. Levine LA, Goldman KE, Greenfield JM. Experience with intraplaque injection of verapamil for Peyronie's disease. *J Urol* 2002;168(2):621-625; discussion 625-626.
27. Arena F, Peracchia G, Di Stefano C, Passari A, Larosa M, Cortellini P. [Clinical effects of verapamil in the treatment of Peyronie's disease]. *Acta Biomed Ateneo Parmense* 1995;66(6):269-272.
28. Palmieri A, Imbimbo C, Longo N et al. A first prospective, randomized, double-blind, placebo-controlled clinical trial evaluating extracorporeal shock wave therapy for the treatment of Peyronie's disease. *Eur Urol* 2009;56(2):363-369.
29. Palmieri A, Imbimbo C, Creta M, Verze P, Fusco F, Mirone V. Tadalafil once daily and extracorporeal shock wave therapy in the management of patients with Peyronie's disease and erectile dysfunction: results from a prospective randomized trial. *Int J Androl* 2012;35(2):190-195.
30. Hatzichristodoulou G, Meisner C, Gschwend JE, Stenzl A, Lahme S. Extracorporeal shock wave therapy in Peyronie's disease: results of a placebo-controlled, prospective, randomized, single-blind study. *J Sex Med* 2013;10(11):2815-2821.
31. Chitale S, Morsey M, Swift L, Sethia K. Limited shock wave therapy vs sham treatment in men with Peyronie's disease: results of a prospective randomized controlled double-blind trial. *BJU Int* 2010;106(9):1352-1356.
32. Greenfield JM, Shah SJ, Levine LA. Verapamil versus saline in electromotive drug administration for Peyronie's disease: a double-blind, placebo controlled trial. *J Urol* 2007;177(3):972-975.
33. Di Stasi SM, Giannantoni A, Stephen RL et al. A prospective, randomized study using transdermal electromotive administration of verapamil and dexamethasone for Peyronie's disease. *J Urol* 2004;171(4):1605-1608.
34. Levine LA, Newell MM. FastSize medical extender for the treatment of Peyronie's disease. *Expert Rev Med Devices* 2008;5(3):305-310.
35. Gontero P, Di Marco M, Giubilei G et al. Use of penile extender device in the treatment of penile curvature as a result of Peyronie's disease. Results of a phase II prospective study. *J Sex Med* 2009;6(2):558-566.
36. Martínez-Salamanca JI, Egui A, Moncada I et al. Acute phase Peyronie's disease management with traction device: a nonrandomized prospective controlled trial with ultrasound correlation. *J Sex Med* 2014;11(2):506-515.
37. Ziegelmann M, Savage J, Toussi A et al. Outcomes of a novel penile traction device in men with Peyronie's disease: a randomized, single-blind, controlled trial. *J Urol* 2019;202(3):599-610.
38. Wymer K, Kohler T, Trost L. Comparative cost-effectiveness of surgery, collagenase clostridium histolyticum, and penile traction therapy in men with Peyronie's disease in an era of effective clinical treatment. *J Sex Med* 2019;16(9):1421-1432.
39. Gholami SS, Lue TF. Correction of penile curvature using the 16-dot plication technique: a review of 132 patients. *J Urol* 2002;167(5):2066-2069.
40. Adibi M, Hudak SJ, Morey AF. Penile plication without degloving enables effective correction of complex Peyronie's deformities. *Urology* 2012;79(4):831-835.
41. Chung PH, Tausch TJ, Simhan J, Scott JF, Morey AF. Dorsal plication without degloving is safe and effective for correcting ventral penile deformities. *Urology* 2014;84(5):1228-1233.
42. Chung E, Clendinning E, Lessard L, Brock G. Five-year follow-up of Peyronie's graft surgery: outcomes and patient satisfaction. *J Sex Med* 2011;8(2):594-600.
43. Wimpissinger F, Parnham A, Gutjahr G, Maksys S, Baierlein M, Stackl W. 10 years' plaque incision and vein grafting for Peyronie's disease: does time matter? *J Sex Med* 2016;13(1):120-128.
44. Da Ros CT, Graziottin TM, Ribeiro E, Averbeck MA. Long-term follow-up of penile curvature correction utilizing autologous albugineal crural graft. *Int Braz J Urol* 2012;38(2):242-247; discussion 248-249.
45. Sansalone S, Garaffa G, Djinovic R et al. Long-term results of the surgical treatment of Peyronie's disease with Egydio's technique: a European multicentre study. *Asian J Androl* 2011;13(6):842-845.
46. Kim DH, Lesser TF, Aboseif SR. Subjective patient-reported experiences after surgery for Peyronie's disease: corporeal plication versus plaque incision with vein graft. *Urology* 2008;71(4):698-702.
47. Khera M, Bella A, Karpman E et al. Penile prosthesis implantation in patients with Peyronie's disease: results of the PROPPER study demonstrates a decrease in patient-reported depression. *J Sex Med* 2018;15(5):786-788.
48. Levine LA, Benson J, Hoover C. Inflatable penile prosthesis placement in men with Peyronie's disease and drug-resistant erectile dysfunction: a single-center study. *J Sex Med* 2010;7(11):3775-3783.
49. Wilson SK, Delk JR 2nd. A new treatment for Peyronie's disease: modeling the penis over an inflatable penile prosthesis. *J Urol* 1994;152(4):1121-1123.
50. Rahman NU, Carrion RE, Bochinski D, Lue TF. Combined penile plication surgery and insertion of penile prosthesis for severe penile curvature and erectile dysfunction. *J Urol* 2004;171(6 Pt 1):2346-2349.
51. Cormio L, Massenio P, Di Fino G et al. Long-term results of combined tunica albuginea plication and penile prosthesis implantation for severe penile curvature and erectile dysfunction. *Case Rep Urol* 2014;2014:818623.
52. Chung PH, Scott JF, Morey AF. High patient satisfaction of inflatable penile prosthesis insertion with synchronous penile plication for erectile dysfunction and Peyronie's disease. *J Sex Med* 2014;11(6):1593-1598.
53. Djordjevic ML, Kojovic V. Penile prosthesis implantation and tunica albuginea incision without grafting in the treatment of Peyronie's disease with erectile dysfunction. *Asian J Androl* 2013;15(3):391-394.
54. Tausch TJ, Chung PH, Siegel JA, Gliga L, Klein AK, Morey AF. Intraoperative decision-making for precise penile straightening during inflatable penile prosthesis surgery. *Urology* 2015;86(5):1048-1052.
55. Raheem AA, Garaffa G, Raheem TA et al. The role of vacuum pump therapy to mechanically straighten the penis in Peyronie's disease. *BJU Int* 2010;106(8):1178-1180.
56. 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;59(1):61-65.
57. Castiglione F, Hedlund P, Van der Aa et al. Intratunical injection of human adipose tissue-derived stem cells prevents fibrosis and is associated with improved erectile function in a rat model of Peyronie's disease. *Eur Urol* 2013;63(3):551-560.
58. Gokce A, Abd Elmageed ZY, Lasker GF et al. Intratunical injection of genetically modified adipose tissue-derived stem cells with human interferon α-2b for treatment of erectile dysfunction in a rat model of tunica albugineal fibrosis. *J Sex Med* 2015;12(7):1533-1544.