Review Article

Peyronie's disease: What's around the bend?

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ABSTRACT

Introduction: Peyronie's disease (PD) is a fibrotic diathesis of the tunica albuginea that results in penile plaque formation and penile deformity, negatively affecting sexual and psychosocial function of both patients and their partners. In this review, we discuss the PD literature and PD treatment options, with special emphasis on potential future therapies.
Methods: The PD literature was reviewed, and articles of interest were identified using keyword search in PubMed. Articles evaluating investigational and novel PD treatments were emphasized.
Results: Existing PD treatment modalities are diverse and include oral, topical, intralesional, mechanical, and surgical therapies. Surgical treatment has high success rates and is indicated in men with significant, stable deformity. The United States Food and Drug Administration-approved intralesional collagenase *Clostridium histolyticum* injection therapy is a minimally invasive option with demonstrated efficacy in PD. Other nonsurgical therapies have been reported, including Botox and stem cell therapy, but these currently have little or equivocal evidence to support their efficacy.
Conclusions: Further research is essential to develop novel, safe, and effective minimally invasive PD treatment options. This work is ongoing, with the promise of specific, targeted, and highly effective therapies on the horizon.

Key words: Peyronie's disease, plaque incision and grafting, tunical plication

INTRODUCTION

Peyronie's disease (PD) is a fibrotic diathesis of the penis often leading to penile deformity that can be associated with pain, impaired ability to have sexual intercourse, shame, depression and/or anxiety, and decreased quality of life.[1-3] PD typically presents during the fifth decade of life, with a mean age of presentation of 52–57 years.[4-7] The estimated overall prevalence of PD varies widely, with rates ranging from 0.39% to 13.1%,[4,5,8] and even higher in certain sub-populations. For example, up to 16% of men after radical prostatectomy may develop PD.[9] François Gigot de la Peyronie, the French physician and surgeon to King Louis XV, is credited with first describing PD in 1743.[10] However, the first report of PD may date back even further, to Theodoric Borgognoni of Bologne during the 13th century.[11] Despite PD's long and storied history, consensus regarding its management is lacking, and relatively few therapies with definitive evidence of efficacy exist. In light of PD's high prevalence and its significant impact on affected men and their partners, a better understanding of this disease process, as well as more effective treatment options, are essential. This review addresses the etiology, diagnosis, and treatment of PD, with special emphasis on potential future PD therapies.

ETIOLOGY, PATIENT ASSESSMENT, AND TREATMENT: WHAT WE KNOW SO FAR

Although the etiology of PD is multifactorial and incompletely understood, penile trauma is widely believed

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to be an important contributing factor.[12,13] Penile trauma resulting in PD may either be acute and severe (e.g., sustained during an accident or surgical procedure), or repetitive microtrauma such as that which commonly occurs during sexual intercourse. While all sexually active men are exposed to some level of penile trauma during sexual activity, few develop PD, suggesting that other factors, including a man's genetics, likely contribute to PD pathogenesis. A personal history of nongonococcal urethritis[13,14] and smoking[13,15] are potential risk factors for PD, as is having a sexual partner with a history of inflammatory diseases of the genital tract,[13] fibromatous lesions of the genital tract,[13] or a history of genital tract surgery.[13,14]

Hypogonadism is prevalent in men with PD, suggesting that low testosterone (T) may also represent a PD risk factor. A recent study evaluating 121 men with PD reported hypogonadal T levels (<300 ng/dL) in 74.4% of the cohort.[16] It has also been suggested that hypogonadal men with PD may have greater penile curvature than eugonadal PD patients.[16,17] Similarly, high rates of low T were observed in men with PD and erectile dysfunction (ED) in a recent study, although low T and degree of penile curvature were not correlated.[18] Another study failed to show a difference between T levels in men with PD compared to controls, although the study was likely underpowered.[19] Interestingly, adrenal androgens were significantly lower in the PD group when compared with controls, suggesting that androgen deficiency may play a role in PD pathogenesis because androgens modulate the matrix metalloproteinases (MMP) that are essential in normal wound healing. There is no direct evidence for a causal relationship between hypogonadism and PD, nor is there evidence that testosterone therapy ameliorates PD symptoms. As such, T is not currently considered a treatment for PD. However, the literature does support a relationship between androgen levels and PD, and screening for low T should be considered in men with PD, with initiation of testosterone therapy for symptomatic hypogonadism.

Management of PD may include counseling, nonsurgical therapies, and surgical intervention. The Peyronie's Disease Questionnaire (PDQ) is a recently developed and validated tool that measures psychosexual impact of PD in men, and represents the first PD-specific self-reported assessment tool.[20] The PDQ is highly reproducible[21] and sensitive to changes in men with PD,[22] making it an invaluable tool for baseline assessments in new PD patients and for measuring PD treatment outcomes.

Scores of nonoperative treatments for PD have been utilized over the centuries since PD was first reported, the vast majority with minimal or equivocal success based on small retrospective or single-arm prospective studies. A list of these agents, proposed mechanism of action, and the level of evidence available for each is provided in Table 1.[23]

Interferon (IFN) α2a and α2b have been evaluated in multiple observational studies for potential benefit in PD patients with stable, noncalcified plaques,[24-31] as well as in one randomized controlled trial (RCT) demonstrating efficacy[32,33] and one RCT showing no benefit, which was likely underpowered.[34] Guidelines for treatment of PD from the European Association of Urology conclude that intralesional IFNα2b is potentially effective in PD treatment.[35] The 2015 AUA guidelines also conclude that IFNα2b is effective for some PD symptoms and may be administered to patients with PD (moderate recommendation; evidence strength grade C), after appropriate counseling regarding potential adverse events, such as flu-like symptoms and penile swelling. However, further evidence in the form of another adequately powered RCT is necessary before IFNα2b can be definitively recommended for PD treatment.

Intralesional collagenase *Clostridium histolyticum* (CCH) is a relatively recent addition to the PD treatment armamentarium, and is unique among nonsurgical options in that its safety and efficacy are supported by rigorous evidence from several RCTs.[77-81] These studies demonstrated a significantly greater improvement in penile curvature and PD symptom bother in CCH-treated men compared to placebo-treated men, while effects on pain and erectile function were similar in both groups. CCH is the only pharmacologic agent currently approved by the United States Food and Drug Administration (US FDA) for the treatment of PD. The recent AUA guidelines support CCH administration in combination with modeling for the reduction of curvature in patients with stable PD with curvature between 30° and 90° (moderate recommendation; evidence strength B).

Surgery represents an excellent treatment option when penile deformity is severe enough to interfere with sexual intercourse and has been stable for 3–6 months.[121] Ideally, any associated pain should resolve prior to operative intervention,[112] as pain tends to reflect active disease with ongoing inflammation and may limit surgical success. Surgical intervention may involve: (1) Tunical plication alone when there is adequate penile length and curvature <60°, (2) plaque incision/excision with or without grafting when penile length is inadequate and/or curvature is more severe or associated with deformities including hourglass or hinging, or (3) placement of inflatable penile prosthesis with or without adjuvant maneuvers, such as penile modeling, in the setting of concomitant ED that is unresponsive to treatment.[34] Surgery is safe in appropriately selected patients, with efficacy rates approaching 100% in some series.[108,109] However, there remains considerable interest in identifying effective nonoperative treatments for PD, as these would limit adverse events associated with surgery and may allow treatment during the active phase of disease, potentially modifying and attenuating the overall disease course. To develop such treatments, however, a

Table 1: PD treatment options[23]

Treatment	Proposed mechanism of action in PD	Level of evidence in humans•	Placebo or no treatment control	Grade of evidence•
Systemic (oral)				
Procarbazine[36-38]	Cytotoxic alkylating agent (?anti-inflammatory)	IV (against)	No	C (against)
Vitamin E[33,37,39-43]	Antioxidant (↓ROS)	IB (against)	Yes	B (against)
Propionyl-L-carnitine[43]	↓Ca^{2+} in endothelial cells	IB (against)	Yes	B (against)
Acetyl-L-carnitine[44]	↓Ca^{2+} in endothelial cells	IB	No	C
Tamoxifen[44-46]	Modulation of TGF-β1 secretion by fibroblasts	IB (against)	Yes	B (against)
Omega-3 fatty acids[47]	Anti-inflammatory	IB (against)	Yes	B (against)
Pentoxifylline[48-50]	Nonspecific PDE-inhibitor → ↑NO, ↓TGF-β1 expression	V	No	D
L-arginine[50]	Precursor of NO	NA (animal only)	Yes	NA
Sildenafil[50,51]	PDE5 inhibitor; may ↓collagen and ↑apoptosis index within plaque	NA (animal only)	Yes	NA
Tadalafil[52]	PDE5 inhibitor; may ↓collagen and ↑apoptosis index within plaque	IB	No	C
Colchicine[53-56]	Anti-microtubule (anti-inflammatory)	IB (against)	Yes	B (against)
Potaba[57,58]	↑tissue O_2 uptake, ↑GAG† secretion, ↑MAO‡ activity	IB	Yes	B
Coenzyme Q10[59]	Antioxidant (↓ROS), ↓TGF-β1 expression	IB	Yes	B
Peironimev®[60]	Multiple antioxidants (↓ROS), ↑ tissue O_2 uptake, ↑GAG† secretion, ↑MAO‡ activity	IB	No	C
Transdermal				
Verapamil (EMDA or topical gel)[61-65]	Ca^{2+} channel antagonist; may ↓collagen synthesis and/or ↑collagenase activity	IB (mixed)	Yes	C
Dexamethasone (EMDA w/verapamil)[61,62,65]	Steroid (anti-inflammatory)	IB	Yes	B
LrhSOD* (topical)[66,67]	Antioxidant (↓ROS)	IB (for pain only)	Yes	B (for pain only)
Intralesional				
IFNα2a[28]	↓fibroblast proliferation → ↓collagen synthesis	IV	No	D
IFNα2b[23-27,29-33]	↓fibroblast proliferation → ↓collagen synthesis	IB	Yes	C
Verapamil[65,68-76]	Ca^{2+} channel antagonist; may ↓collagen synthesis and/or ↑collagenase activity	IB (mixed)	Yes	B-C
CCH[77-82]	Clostridial collagenase	IB	Yes	A
LrhSOD[83-85]	Antioxidant (↓ROS)	IV	No	D
OnabotulinumtoxinA (Botox®)[86]	↓connective tissue growth factor expression	IV	No	D
Iloprost[87]	↓TGF-β and platelet activity, ↓leukocyte migration, ↓adhesion molecule expression, vasodilation	IV	No	D
Decorin[88]	↓TGF-β activity	Animal only	Yes	NA
Ad HDAC2 shRNA[89,90]	Epigenetic modification of gene expression	Animal only	Yes	NA
Stem cells[91,92]	Regeneration of healthy tissue, exact mechanism unclear	Animal only	Yes	NA
Nonpharmacologic, nonsurgical				
ESWT[40,52,93-96]	Direct damage to plaque and/or ↑vascularity 2/2 heat →plaque lysis[95]	IB (for pain only)	Yes	B (for pain only)
Penile traction therapy[97,98]	Mechanical straightening and/or lengthening	IV	No	D
Vacuum erection device therapy[99,100]	Mechanical straightening and/or lengthening	IV	No	D
RT[101-103]	Unknown (cytotoxic, ?anti-inflammatory)	III (against)	Yes	C (against)
Hyperthermia therapy[104]	Unknown (possible modulation of heat-shock proteins,[104] ?↑vascularity 2/2 heat[95])	IB	Yes	B
Surgical				
Tunical albugineal plication[105-107]	Tunical shortening (side opposite plaque)	IV	No	D

Contd...

Table 1: Contd...

Treatment	Proposed mechanism of action in PD	Level of evidence in humans•	Placebo or no treatment control	Grade of evidence•
Plaque incision/excision and grafting[107-111]	Tunical lengthening (side of plaque)	IV	No	D
IPP (with possible penile modeling, tunical plication, or plaque incision/excision and grafting)[110-120]	Mechanical straightening (w/or w/o plaque manipulation, tunical shortening or lengthening procedures)	IV	No	D

•Highest level/grade of evidence available, which is predominantly in favor of treatment unless otherwise indicated as "mixed" or "against". Many of these studies, even RCTs, are difficult to interpret given comparison of multimodal treatment regimens against each other rather than single agents against placebo. In addition, most studies involve few patients, and many agents have studies both in favor of as well as studies against efficacy (i.e., showing no difference between comparison groups), further complicating interpretation, †GAG=glycosaminoglycans, ‡MAO=monoamine oxidase, *SOD=superoxide dismutase, PD=Peyronie's disease, lrhSOD=Liposomal recombinant human superoxide dismutase, Ad-HDAC2 shRNA=Adenovirus encoding silencing histone deacetylase 2 small hairpin mRNA, RT=Radiotherapy, IPP=Inflatable penile prosthesis, TGF-β=Transforming growth factor-beta, NA=Not available, RCTs=Randomized controlled trials, PDE=Phosphodiesterase, CCH=Collagenase *Clostridium histolyticum*, NO=Nitric oxide (Table adapted with permission from reference 23)

comprehensive molecular understanding of PD pathogenesis and its natural history is required. An algorithm for the treatment of PD is provided in Figure 1.[23]

FUTURE DIRECTIONS

Considerable interest remains in identifying novel minimally invasive PD treatment options. OnabotulinumtoxinA (Botox®) can reduce fibrosis in cell culture and in animal models of hypertrophic scars/keloids,[122-125] prompting a prospective cohort study to evaluate its potential in the setting of PD.[86] Following a single intralesional injection of 100U Botox®, investigators reported a significant decrease in penile plaque size and curvature, as well as a significant improvement in International Index of Erectile Function-5 (IIEF-5) score. However, this study only evaluated a small number of patients ($n = 22$) and lacked a placebo control group, limiting the conclusions that could be drawn.

Additional investigational agents for PD treatment include liposomal recombinant human superoxide dismutase (lrhSOD, also known as orgotein),[66,67,83-85] iloprost,[87] and Peironimev-Plus®.[60] The use of intralesional lrhSOD has only been described in observational studies,[83-85] while topical lrhSOD has been evaluated in one observational study[66] and one crossover RCT with promising results.[67] In the RCT, penile pain improved significantly in the treatment as compared to the placebo group. Decreases in penile curvature and plaque size were also observed, although these outcomes were not evaluated until after crossover, limiting a true efficacy comparison against placebo. Iloprost is a prostacyclin analog recently tested as a potential intralesional PD therapy, chosen because of its anti-transforming growth factor (TGF)-β activity in fibroblasts.[87] Additional potentially beneficial effects of prostacyclin include vasodilation, activation of fibrinolysis, and inhibition of platelet function, leukocyte migration, and cell adhesion molecule expression. Improvement in penile curvature was observed in 29% of 38 treated patients, but these data are difficult to interpret given the lack of a placebo comparison group. Peironimev-plus® is an oral supplement containing multiple antioxidants (Vitamin E, para-aminobenzoic acid, propolis, blueberry anthocyanins, soja isoflavones, muira puama, damiana, and *Persea americana*), several of which have been individually reported as possibly effective in PD treatment in small retrospective case series. A single study evaluating the efficacy of Peironimev-plus® included 64 men randomly assigned to one of the two treatment arms: (1) Perilesional verapamil injection + verapamil iontophoresis + Peironimev-plus® or (2) verapamil injection + verapamil iontophoresis.[60] The group receiving daily Peironimev-plus® and verapamil had significant improvements in penile plaque size, curvature, and IIEF score as compared to patients receiving verapamil alone. However, the absence of a placebo control group and lack of strong evidence supporting verapamil's efficacy in PD treatment limit the ability to interpret these data. Future well-designed, adequately powered RCTs are needed to determine the efficacy of lrhSOD, iloprost, and Peironimev-Plus® in PD. As such, these agents cannot be recommended for routine clinical use at this time.

Basic science research probing the molecular causes of PD has expanded in recent years, leading to an improved understanding of the underlying pathophysiology of PD that can inform future therapeutic efforts and improve clinical outcomes. A recent study characterized and compared the transcriptional signatures of human PD plaque, unaffected tunica albuginea, and corpora cavernosa cells in culture.[126] Several genes were found to be expressed at significantly higher levels (2.7–29.8-fold above baseline) in PD cells, including insulin-like growth factor-1, smooth muscle actin γ-2, myogenic factor 5, α-cardiac muscle actin 1 (ACTC1), periostin (POSTN), type III collagen (COL3A1), and MMP3, thereby identifying these as potential therapeutic targets. Genetic evaluation of PD plaque-derived fibroblasts in comparison with unaffected tunica albuginea demonstrated karyotype defects preferentially in plaque-derived fibroblasts, supporting a potential genetic etiology in affected men.[127] However, no specific genes have been causally linked to PD to date, despite the fact that PD can be inherited in autosomal dominant fashion.[128] HS-173,

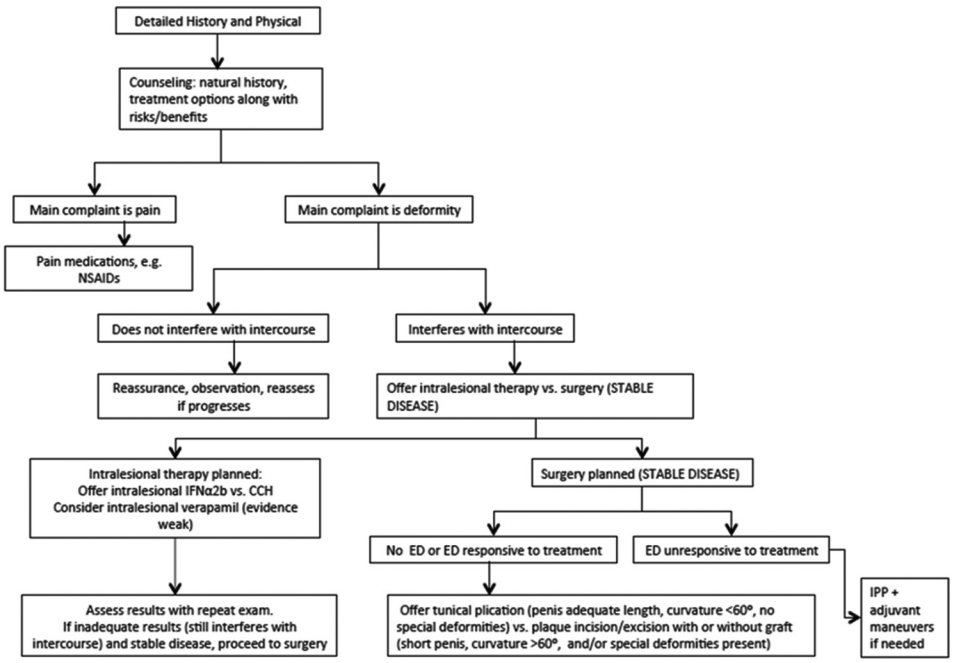

Figure 1: Peyronie's disease treatment algorithm[23] (Figure adapted with permission from reference 23)

a novel imidazo [1,2-a] pyridine derivative that inhibits phosphoinositide 3-kinase (a downstream effector of TGF-β), may represent a candidate therapy for treating PD and other fibrotic diseases.[129] This small molecule inhibits growth and induces apoptosis in PD plaque-derived fibroblasts. Further investigation is warranted, with future work to include animal studies to demonstrate a benefit beyond the cell culture dish.

Animal models of PD using intra-tunical injection of profibrotic agents such as fibrin TGF-β[130] permit more rigorous testing of potential PD treatments prior to investigation in humans. PD animal models have been employed to study the possible therapeutic benefits of decorin, a proteoglycan with anti-TGF-β activity,[88] and adenovirus encoding silencing histone deacetylase 2 small hairpin mRNA (Ad-HDAC2 shRNA).[89] Intracavernous treatment with decorin prevents tunical thickening and collagen disorganization seen in the untreated PD model rats.[88] Maximal intracavernosal pressure and mean duration of erection were significantly increased in the treatment group. Epigenetic modifications, including histone acetylation and deacetylation, are known to play a role in fibrotic diatheses,[131] and small interfering RNA against HDAC2 has been shown to have antifibrotic effects on PD cells in culture.[90] *In vivo*, rats treated with Ad-HDAC2 shRNA exhibited regression of plaque and decreased inflammatory cell infiltration when compared to controls (untreated or treated with adenovirus encoding scrambled shRNA).[89]

Stem cells represent another potential future PD therapy. Stem cell use in a TGF-β-induced animal model of PD was first reported in 2013.[91] The investigators performed intralesional injection of either human adipocyte-derived stem cells (ADSCs) or buffer vehicle as control, demonstrating a significant objective improvement in erectile function (as measured by intracavernosal pressure over mean arterial pressure) in the treatment group as compared to control. Decreased fibrosis was apparent in the treatment group by histological and immunohistochemical examination, and was quantified using Western blot of the fibrotic markers collagen III (decreased 69.9% in treatment animals compared to control) and elastin (decreased 47.7%). A subsequent study confirmed the benefits of ADSCs in a PD rat model,[92] with improved erectile function and downregulation of fibrotic change in the ADSC groups, both for what they termed prevention (injection of ADSCs vs. vehicle together with TGF-β1) and treatment (injection of ADSCs vs. vehicle 30 days after injection of TGF-β1). While these studies suggest a potential benefit for ADSCs during the active phase of PD, further research is needed to elucidate the exact therapeutic mechanisms of ADSCs, and human trials are essential prior to widespread clinical application. Subcutaneous fat may be harvested from patients with active PD to permit autologous stem cell derivation for investigational intralesional treatment.

Ultimately, evidence of the efficacy and long-term safety of stem cell therapies, together with the other molecular or genetic therapies discussed above, will be required, particularly in light of the possibility of neoplastic risk with some of these treatment approaches.[132] Nevertheless, recent advances in our understanding of the molecular basis of PD and the application of novel molecular therapies

herald the beginning of a new era in PD treatment – one of precision medicine. Future advances will enable not only the identification of additional specific treatment targets, but also of susceptible men to which specific, effective therapies can be targeted. In more completely understanding PD pathogenesis, as well as the relationship of PD with environmental factors and other comorbidities, an individualized, holistic, highly effective approach to treatment and prevention of further morbidity can be undertaken. While additional basic science and clinical research are required to completely understand all facets of PD, recent progress is encouraging and suggests a bright future for medicine's approach to this potentially devastating condition.

CONCLUSIONS

PD has a long history in the literature, and myriad minimally invasive therapies have been used, albeit few have demonstrable efficacy. CCH is the only nonsurgical treatment option rigorously shown to be safe and effective in the treatment of PD, and is thus currently the only US FDA-approved nonsurgical treatment for PD. Ongoing research may yield additional therapeutic options, although a more complete understanding of PD pathogenesis and genetic predisposition is needed. Numerous therapies have been tried in humans, including IFN-α2, Botox®, lrhSOD, iloprost, and Peironimev-Plus®, among others. However, rigorous clinical trial data are currently lacking to demonstrate true efficacy of the majority of these therapies. Other potential cell-based and small molecule therapies have been studied *in vivo* (decorin, HDAC2 shRNA, stem cells) and *in vitro* (HS-173), and recent studies have identified several novel potential therapeutic targets. Our expanding knowledge regarding the molecular pathophysiology of PD will inform future clinical and translational research, leading to minimally invasive treatment options that can be targeted to appropriately selected men. Ultimately, this will lead to improved outcomes for our patients, ushering in an era of precision medicine in the treatment of PD.

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Conflicts of interest

There are no conflicts of interest.

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