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PEYRONIE'S DISEASE: A REVIEW OF ETIOLOGY, DIAGNOSIS, AND MANAGEMENT

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Abstract

Peyronie's Disease (PD) is a superficial fibrosing disorder of the penis resulting in plaque formation and penile deformity. Once considered rare, PD has more recently been found in up to 13% of men, and can negatively affect sexual and psychosocial function of both patients and their partners. While the etiology of PD is unclear, it is thought to result from an inciting traumatic event followed by aberrant fibrosis or dysregulated wound healing. The evaluation of men presenting with PD includes a detailed history and physical exam, focusing on the penis in both the flaccid and erect states. PD is often associated with erectile dysfunction (ED), as well as several other comorbidities. Laboratory testing is not needed to diagnose PD, although given the associations between PD and systemic diseases including hypogonadism, diabetes, and cardiovascular disease, screening and work-up for these conditions in men with PD may be warranted. Treatment modalities for PD are diverse and include oral, topical, intralesional, mechanical, and surgical therapies. Oral, topical, and mechanical therapies generally have little evidence supporting their efficacy. Several intralesional therapies, including interferon α2b and collagenase *Clostridium hystiolyticum* have demonstrated efficacy in the treatment of PD. Surgical treatment, indicated in men with significant, stable deformity, includes plication of the tunica albuginea, plaque incision/excision and grafting, and placement of inflatable penile prosthesis (IPP) with or without additional maneuvers to achieve desired results, and has high success rates.

Keywords

Peyronie's disease; Duplex Doppler ultrasound; Tunical plication; Plaque incision and grafting; Intralesional therapy; Oral Peyronie's disease therapy; Dupuytren's disease; Ledderhose disease; Genetics

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Compliance with Ethics Guidelines

Conflict of Interest

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INTRODUCTION

Peyronie's Disease (PD) is a superficial fibrosing condition of the penis characterized by the presence of fibrotic plaques often leading to penile deformity, with or without concomitant pain. Men with PD most commonly present in their sixth decade of life, with a mean age of 52-57 years old.[1-4] PD impacts sexual function and is also associated with psychosocial distress in patients and their partners. Once thought to be rare, PD now has a reported prevalence of up to 13.1% in adult men.[5]

François Gigot de la Peyronie, the French physician and surgeon to King Louis XV, is credited with the initial description of the disease.[6] However, several written reports precede la Peyronie's seminal publication, dating back to Theoderic Borgogni of Bologne in the 13th century.[7] Despite its long history, a complete understanding of the etiologies and natural history of PD remain elusive, and clear-cut patient treatment algorithms are lacking. La Peyronie treated his patients with topical mercury without success, then reported complete resolution in one patient after treatment in the holy water of a French thermal spa at Barèges.[8] Since that time, a plethora of surgical and non-surgical treatments have been described, all with a scientific basis, although defining efficacy with most treatments has been challenging due to suboptimal or small studies.

Given the high prevalence of PD and its significant impact on affected men, a better understanding of PD is essential. The purpose of this review is to synthesize and summarize the current understanding of PD etiology, diagnosis, and management.

PREVALENCE AND SIGNIFICANCE

The prevalence of PD is variable between studies, ranging from 0.39% in a population of men from Rochester, Minnesota[3] to 3.2% based on a survey of 4,432 subjects from the Cologne region of France.[4] A large, web-based survey of 11,420 subjects estimated PD prevalence in the U.S. at 0.5-13.1%, with variability due to differences in PD diagnostic criteria.[5] The prevalence of PD has also been studied in various sub-populations. In 2004, Mulhall et al. reported a PD prevalence of 8.9%, with PD diagnosed by the presence of a palpable plaque on physical exam, in a cohort of 534 men undergoing prostate cancer screening.[9] Subsequently, Tal et al. reported PD in 15.9% of 1,011 men after radical prostatectomy.[10] El-Sakka observed 7.9% of 1,440 men being evaluated for ED with concomitant PD,[1] using strict PD diagnostic criteria including the presence of a palpable nodule or penile curvature observed after intracorporal injection of prostaglandin E1. Arafa et al. reported a high proportion (20.3%) of 206 diabetic men with ED as also having PD, identifying diabetes as a potential PD risk factor.[11]

In addition to physical symptoms, which can limit sexual function, PD can cause significant psychosocial distress for patients and their partners.[12-14] Feelings of shame and embarrassment often accompany the physical symptoms of PD, with up to 81% of men reporting "emotional difficulties."[13] These feelings may persist or worsen with progression of the disease; depression has been reported in up to 48% of men.[12] The negative psychological impact of PD on patients and their partners is not always apparent to clinicians, and must be considered when approaching the patient with PD. Only recently has

psychosocial function in men with PD been evaluated using validated methods. In 2008, Nelson et al. used two questionnaires to evaluate the psychosocial status of 92 men with PD: The Center for Epidemiological Studies Depression scale (CES-D) and the Mental Health subscale of the Short Form-36 (SF-36), which assesses quality of life.[12] Remarkably, 48% of men in the cohort were depressed based on the CES-D, and the incidence of depression did not vary with length of time from PD diagnosis up to >18 months, suggesting a lack of adjustment to the PD diagnosis. The PD cohort also had a significantly lower average Mental Health subscale on the SF-36 compared to the general male population, indicating overall worse mental health in these men. The first PD-specific questionnaire, the Peyronie's Disease Questionnaire (PDQ), was developed and validated by Hellstrom et al. in 2013.[15] The PDQ assesses the severity of both physical and psychological symptoms of PD, as well as symptom bother. Such tools are invaluable in the comprehensive assessment of the patient with PD, fostering the multidisciplinary approach that is necessary to best treat the multifaceted nature of this disorder.

ETIOLOGY AND MODIFIABLE RISK FACTORS

The etiology of PD is multifactorial and incompletely understood. The most prevalent etiological theory implicates penile trauma, including both acute traumatic events as well as repetitive microtrauma such as that which occurs during intercourse, as the inciting event for PD.[16] Multiple other risk factors can also predispose to development of PD (TABLE 1).

It is important to point out that data on modifiable PD risk factors come almost entirely from retrospective studies, limiting their generalizability. Modifiable risk factors for PD include a personal history of nongonococcal urethritis, genital and/or perineal trauma, and iatrogenic trauma such as urethral catheterization, cystoscopy, or transurethral resection of the prostate.[16,17] Radical prostatectomy is also associated with increased risk of PD, with a 15.9% incidence of PD observed in men following radical prostatectomy.[10] An increased risk of PD in men with sexual partners having a history of inflammatory diseases of the genital tract,[16] fibromatous lesions of the genital tract,[16] and surgery on the genital tract has also been reported.[16,17] While a history of smoking has been implicated as a PD risk factor,[16,18] it is unclear whether this is related to the amount of smoking. The impact of alcohol use in PD is unclear, with one study supporting an association,[16] and another, larger study failing to show a relationship.[18] Possible associations with diabetes, hypertension, and/or other cardiovascular conditions have been suggested,[11,16] but other studies have failed to corroborate these findings.[17,18]

Hypogonadism is also a possible risk factor for PD.[19] Recent work suggests a high prevalence of hypogonadism in men with PD, with one study observing hypogonadal testosterone (T) levels (<300 ng/dL) in 74.4% of 121 PD patients.[19] In hypogonadal men with PD, penile curvature may be greater than in men with PD and normal T levels.[19,20] While yet another study observed similarly high rates of low T levels in men with PD and ED, no correlation between low T and degree of penile curvature was observed.[21] In contrast, yet another study failed to show a difference between T levels in men with PD compared to controls, although the study was small and likely underpowered.[22] Interestingly, significantly lower adrenal androgen levels in the PD group compared to

controls were observed, leading to a hypothesis that hypogonadism or androgen deficiency may play a role in PD pathogenesis because androgens modulate matrix metalloproteinases that are important in normal wound healing. If these androgens are deficient, the risk of PD increases.

Erectile dysfunction (ED) has been observed in up to 32% of men presenting with PD.[23] However, it is unclear whether one condition precedes the other or if they occur synchronously. Of note, fibrosis of corporal cavernosal blood vessels has been implicated in both the development of vasculogenic ED as well as PD, providing a potentially unifying pathogenic mechanism.[24-26] In men with both PD and ED, it is important to consider that both organic and psychogenic factors may contribute to both conditions, which can impact treatment approaches.[27] In summary, while numerous risk factors have been implicated in the development of PD, additional work is required to strengthen these associations. Furthermore, a more complete understanding of the molecular pathways that may link these disease states is essential in establishing and expanding the growing network of interactions between PD and other conditions.

HISTOPATHOLOGY AND MOLECULAR BIOLOGY

The tunica albuginea, a fascial structure surrounding the penile corpora cavernosa, provides both the pliancy of the penis when flaccid as well as its rigidity when erect.[28] Normal tunica albuginea consists of an organized lattice of elastin and collagen arranged around the penile corpora in inner circular and outer longitudinal layers, each consisting of multiple sublayers.[28] PD is characterized by focal tunical fibrosis, resulting in plaque formation and penile curvature or deformity due to the decreased pliancy of the tunica albuginea involved with plaque, with or without penile pain.[4] Ultrastructural and histologic changes in the tunica have been described in animal models of PD, as well as in biopsy and cadaveric specimens from patients with PD. These changes include collagen deposition in abnormally dense clumps and disordered, fragmented, sparse elastin fibers.[28-30] The abnormal presence of fibrin[28,29,31] or ossification in a linear configuration[29] may also be seen. In one series, fibrin deposition was seen in 95% of PD plaque samples and in no controls.[31] Increased peri-tunical cellularity has also been described in PD patients, which may manifest as a perivascular lymphocytic infiltrate surrounding the tunica or may involve the tunica itself.[29] These histopathologic changes are thought to develop from abnormal inflammation and wound healing.[4,32-36] Trauma to the microvasculature of the erect penis and subsequent fibrin extravasation may initiate wound healing, which in susceptible patients is thought to progress to fibrosis and plaque formation.[31]

The cellular and biochemical changes that occur in normal wound healing and in PD have been studied in cell culture and in animal models. In the setting of trauma, extravasation of fibrin initiates the release of multiple cytokines, including transforming growth factor β (TGFβ) and plasminogen activator inhibitor 1 (PAI1), and an increase in reactive oxygen species (ROS), which stimulates differentiation of fibroblasts into myofibroblasts (FIGURE 1).[37,38] TGFβ is a secreted protein that promotes tissue repair and inflammation, can induce monocyte infiltration and angiogenesis, and can modulate other inflammatory mediators.[39] TGFβ also stimulates the synthesis of extracellular matrix components (ECM) including

collagen, while concurrently inhibiting ECM degradation by proteases.[39] Myofibroblasts synthesize collagen and are important in normal wound healing.[37] During normal wound healing, myofibroblasts differentiate, help to repair the wound, and then undergo apoptosis. In abnormal wound healing, however, the persistence of myofibroblasts may cause continued accumulation of collagen, leading to fibrosis.[37] While myofibroblasts are common in PD plaques from humans and animal models, they are rarely seen in normal human tunica albuginea.[40] Nitric oxide (NO) is a potent antifibrotic mediator and can decrease collagen deposition and myofibroblast number in culture, possibly by inhibiting myofibroblast differentiation or by promoting apoptosis. [41]

Rat PD models have been developed using injection of profibrotic agents, including cytomodulin (a synthetic heptapeptide with TGFβ-like activity)[39] and fibrin[42] into the tunica albuginea. A rat model developed by El-Sakka et al. compared incision of the tunica albuginea followed by suture repair to animals receiving a sham operation.[43] Histopathological changes similar to those seen in the acute phase of PD were observed in rats undergoing tunical incision from 6 hours to 8 weeks after injury. Transient elevations in TGFβ1 were observed in some of the rats 6 hours to 3 days after injury, with resolution by 8 weeks after injury. These tunical changes in test rats were more consistent with normal wound healing than a Peyronie's-like plaque formation, indicating that a single event in otherwise normal animals may not be sufficient to induce PD. Trauma alone may not be sufficient to induce plaque formation in an otherwise normal organism, and genetic factors have been linked to PD, suggesting that a predisposition to fibrosis may be necessary to cause disease.

GENETICS

While all sexually active men are exposed to some level of penile trauma as a result of sexual activity, few develop PD. Multiple small, retrospective studies showed an association between PD and various histocompatibility antigens (HLA-B7,[44] HLA-A1, B8, Cw7, DR3, and DQw2,[45] and HLA-DQ5[46]), suggesting a genetic predisposition to PD. A variant of PD with autosomal dominant inheritance was described in 3 pedigrees by Nyberg et al., further supporting a genetic link.[47] An association between the autosomal dominant form of PD and HLA-B7 was noted, with HLA-B7 present in 90% of men with PD in the study. However, other published reports, including a more recent prospective study of 154 consecutive PD patients,[48] have failed to show an association between PD and HLA subtypes.[49,50]

PD has also been associated with Duputyren's disease (DD), a superficial fibrotic diathesis that involves the palmar fascia, resulting in fibrotic nodules and hand contractures. The two conditions often occur coincidentally, with one study observing a 21% incidence of DD in a cohort of 134 PD patients, as compared with 0% in a control group of equivalent size.[17] A strong association with DD was also noted in the autosomal dominant form of PD, in which 78% of PD-affected individuals concurrently suffered from DD.[47] A more recent case-control study by Bjekic et al. revealed a 39% rate of DD in their PD population (n=82), compared to 1.2% in the 246 controls ($p<0.01$).[16] Family history of DD was also a significant risk factor, present in 9.8% of cases compared with 0% of controls ($p<0.001$).

Multiple genes that promote fibrosis have increased expression in both PD and DD plaques when compared to normal control tissues using gene expression microarray analyses.[51] These upregulated genes include matrix metalloproteinases (MMP2, MMP9), matrix metalloproteinase activators (thymosins TMβ10, TMβ4), osteoblast-specific factors (OSF-1), and genes involved in myofibroblast differentiation (RhoGDP dissociation inhibitor 1). These genes that are common to both conditions further suggest that both PD and DD may have a common etiology that is influenced by genetics.

MALIGNANT POTENTIAL

While no association between PD and malignancy in humans exists, a link between fibrotic conditions and malignancies has begun to emerge. Cell proliferation and chromosomal instability are well-known hallmarks of malignancy, playing an important role in every phase of cancer from malignant cell transformation and progression/invasion, to development of intra-tumor heterogeneity with clonal resistance to various cancer therapies. Fluorescence *in situ* hybridization (FISH) has demonstrated chromosomal instability in fibroblast cultures derived from DD lesions, with numerical (autosomal trisomies and monosomies, gain or loss of Y chromosome) and structural (insertion/deletion) chromosomal abnormalities described.[52,53] FISH has also shown chromosomal instability in fibroblasts derived from human PD plaques.[54] Perhaps most strikingly, fibroblasts derived from human PD lesions can result in tumors when injected into immunodeficient mice[55]. While not related directly to PD, a recent study observed an increased frequency of certain malignancies in DD families when compared with controls, but failed to establish any statistically significant differences in cancer rates between the groups.[56] The same study also reported that of 20 polymorphisms in 12 cancer susceptibility genes studied, one (D312M variant of Xeroderma Pigmentosum complementation group D (XPD) gene, also known as Excision Repair Cross Complementing Rodent Repair Deficiency group 2 (ERCC2))[57] was significantly associated with DD (OR 1.75, p=0.004).[56] *XPD/ERCC2* polymorphisms have also been linked to an increased risk of bladder cancer.[58,59] Thus, dysregulation of cellular replication or senescence that predisposes to PD or DD plaque formation may result in malignancy, although further investigation is necessary to define this relationship in humans.

NATURAL HISTORY AND PRESENTATION

Although PD was initially described over 250 years ago,[6] its natural history has only recently been studied in detail. Williams and Thomas were the first to report on the natural history of PD during the 1970s, observing spontaneous symptom resolution in 50% of the patients in a small cohort.[60] This high PD resolution rate has not been confirmed in subsequent studies. Twenty years later, Gelbard et al. reported a spontaneous resolution rate of only 13%, with 47% of patients remaining stable and 40% worsening over time.[61] Berookhim et al. reported a 12% improvement rate in untreated men with uniplanar PD, with time to presentation of ≤ 6 months and younger age as predictors of improvement.[62] Perhaps more significantly, 67% of men in this cohort remained stable, and 21% worsened during the follow-up period of at least 12 months. Another study observed a 30%

progression rate in 307 men with PD over 8 months, with resolution occurring in only 0.65% of cases.[63]

PD most commonly affects men in the sixth decade of life,[23] with mean age at diagnosis ranging from 52-57 years.[1-4] However, PD may present at any time in adulthood, and patients as young as 21 years old have been reported.[2] The hallmark of PD is acquired penile deformity, which must be differentiated from congenital penile curvature and normal anatomic variants. PD-related deformity consists of curvature during erection, with associated findings including loss of flaccid stretched penile length, tunical indentations or hourglass deformity with erection, and buckling or penile instability on minimal axial loading despite maximal erection.[23] Unlike congenital penile curvature, in which ventral curvature predominates, curvature in PD may be in any direction, and may be uni- or biplanar. However, PD-related penile curvature is most commonly dorsal, with one study reporting dorsal curvature in 72% of patients,[23] and others citing lower dorsal curvature rates (30% dorsal + 12% dorsolateral).[2] Patients with dorsal curvature tend to present with more severe curvature than other PD patients.[2]

The natural history of PD is often divided into *acute* and *chronic* phases. The *acute phase* is characterized by progression of penile deformity and may be associated with pain in the erect and/or flaccid states. The length of the acute phase varies from 6-18 months.[23] In contrast, the *chronic phase* of PD is defined by stability of penile deformity for at least 3-6 months,[64,65] with improvement in or resolution of pain.[64] Mulhall et al. observed that pain improved in all patients and resolved in the majority within 12 months of PD presentation, with 89% of men being pain free at last follow-up with a mean follow-up of 18 months.[23]

Subjective loss of penile length is a common complaint, reported by 84% of patients undergoing expectant PD management. In one study, which followed 246 men with PD, mean stretched penile length decreased from 12.2 cm on initial assessment to 11.4 cm after a mean of 14.5 months follow-up ($p=0.035$).[23]

EVALUATION

Obtaining a detailed history and performing a thorough physical exam is the lynchpin of the PD diagnosis and lays the foundation for the treatment approach. The specific timing of symptom onset, presence of potential inciting incidents, including a history of penile trauma, progression or stability of the deformity, and interference with intercourse should be noted (TABLE 2). Since PD can negatively impact a man's psychosocial status and relationships, obtaining information regarding mood and relationship status can prompt mutidisciplinary therapeutic approaches.

Physical examination of the penis should be performed in both the flaccid and erect states to ensure that the physician understands the anatomic impact of the PD, and the patient corroborates what he has experienced outside of the clinical setting. Objective measurement of penile curvature is essential given that patient report of curvature is inaccurate.[66] In the flaccid state, the clinician should determine stretched penile length and note palpable penile plaque location and size. Men should also be examined with the penis erect, which can be most effectively accomplished using intracavernosal injection of vasoactive substances[67].

Concurrent use of duplex Doppler penile ultrasound allows for objective evaluation of plaque size, location, and calcification, and aids in determination of ED etiology if ED is concurrently present. Ultrasonography after intracavernosal injection is the most accurate assessment tool to determine type and degree of PD deformity and is preferred over photographs or vacuum erectile device (VED)-assisted erection.[23] Accurate assessment of penile deformity is invaluable in treatment planning and in evaluating treatment results. Furthermore, given the association of PD with DD, as well as Ledderhose disease, a fibrosing disorder of the plantar fascia, examination of the palms of the hands and soles of the feet, looking for nodules and/or contractures, can be helpful.

Laboratory testing is not necessary for PD diagnosis. However, given the possible association between PD, diabetes mellitus and cardiovascular disease,[11,16] screening for these comorbidities should be considered in at-risk PD patients. In men with both PD and ED, laboratory evaluation for ED risk factors, as well as evaluation of serum hormones and the hypothalamic-pituitary-gonadal axis should be performed (reviewed in [68]). Serum hormone evaluation in men presenting with PD and hypogonadal symptoms may also be useful.

TREATMENT

Treatment of PD utilizes both medical and surgical approaches, and includes a diverse group of systemic and locally administered drugs. Approaches to PD have included observation, small molecule and biologic drugs administered orally, topically, and intralesionally, mechanical therapies, and surgery. Counseling and observation alone may be appropriate for patients with minimal curvature that does not impede sexual intercourse and with no ED;[69] other patients will elect to proceed with treatment. It is important to note that most treatment methods have little evidence in the literature supporting their efficacy. Clinicians should also consider the psychosocial impact of PD, and refer affected, as well as their partners if appropriate, to a mental health specialist and/or sex therapist.

Surgical intervention should be avoided during the acute phase of PD, as the risk of progression or recurrence of curvature during this phase may interfere with optimal outcomes.[65] Penile deformity and any associated ED should be stable for at least 3-6 months prior to surgical intervention to avoid progressive disease after surgical treatment.[64] Resolution of penile pain should ideally be observed as well,[65] as pain most frequently accompanies active disease and may indicate persistent inflammation. While medical or minimally invasive treatments have traditionally been viewed as most effective during the acute phase,[69] these may be tried at any time in the disease course (FIGURE 2).

Systemic Drugs

Numerous systemic drugs have been evaluated in the treatment of PD including procarbazine, vitamin E, propionyl-L-carnitine, acetyl-L-carnitine, tamoxifen, omega-3 fatty acids, interferon-α2a (IFNα2a), interferon-α2b (IFNα2b), pentoxifylline, L-arginine, sildenafil, colchicine, coenzyme Q10, and potassium paraaminobenzoate (POTABA). While most of the above have little proven efficacy , we highlight available evidence for each drug, with the intention of guiding clinicians towards the use of drugs that may have efficacy, and

restrict our discussion to drugs that have been evaluated in humans (TABLE 3). It is important to note that many of these medications have been combined with others, and these combinations have not been thoroughly vetted or have also failed to show a beneficial effect.

Procarbazine was evaluated historically for PD treatment, but did not appear to have efficacy in improving curvature or reducing plaque.[70-72] Adverse effects, including gastrointestinal symptoms, headache, and anxiety, are common.

Multiple studies have evaluated oral *vitamin E* in treatment of PD, alone or in combination with other treatments.[71,73-76] The free-radical scavenging effect of vitamin E provides the theoretical basis for its use in PD[77] although no strong evidence that it provides benefit exists. Hashimoto et al. saw no difference in pain relief, curvature improvement, plaque size reduction, or ED improvement between the vitamin E and no-medication groups in a retrospective review of 31 patients.[74] A small, randomized prospective study by Inal et al. failed to show any difference between three treatment groups: vitamin E alone, intralesional IFNα2b alone, or combination therapy in 30 men.[75] A larger double-blind, randomized, placebo-controlled study of 236 men by Safarinejad et al. revealed no significant improvements in pain, decreases in penile curvature or changes in plaque size between any of four treatment arms, including placebo, vitamin E alone, propionyl-L-carnitine alone, or vitamin E and propionyl-L-carnitine together.[76] Only one study of combination therapy evaluating vitamin E and extracorporeal shock wave therapy (ESWT) in 35 patients observed a significant decrease in penile curvature compared to vitamin E alone.[73] However, these results have not been reproduced. As such, vitamin E is not recommended treatment in the European Association of Urology (EAU) 2012 PD guideline.[78]

Tamoxifen may act through modulation of TGFβ1 secretion by fibroblasts.[78-81] Its first application in PD was in 1992 in a small cohort of 35 men, with results demonstrating improvements in pain, penile deformity, and plaque size.[80] However, this study was limited by the absence of a control group, and a subsequent randomized controlled trial (RCT) by Teloken et al. failed to show a difference in improvements in pain, curvature, or plaque size in the tamoxifen group relative to placebo.[68] A randomized study comparing acetyl-L-carnitine to tamoxifen was published in 2001, suggesting that acetyl-L-carnitine was safer and more effective than tamoxifen, with a greater decrease in penile curvature in the acetyl-L-carnitine group (7.5 degrees vs. 0.5 degrees), and significantly more patients reporting improved pain (90% vs. 50%).[79] However, only 48 men were included in the study, which lacked a placebo control group. The 2012 EAU guidelines do not recommend tamoxifen for PD treatment based on available data.[78]

Omega-3 fatty acids have been evaluated in the setting of PD in a recent large RCT.[82] No differences in pain, penile curvature, or plaque size were observed between treatment and placebo groups.

Coenzyme Q10 has been evaluated in a single RCT with 93 patients in each arm (treatment vs placebo).[83] Plaque size and penile curvature both decreased in the treatment group and slightly increased in the placebo group (both p=0.001). Additional studies are needed to confirm efficacy.

Pentoxifylline is a non-specific cyclic adenosine monophosphate (cAMP) phosphodiesterase inhibitor[78,84] that attenuates TGFβ1-stimulated collagen deposition in cultured cells derived from human PD plaques.[85] *L-Arginine*, a precursor of NO synthesis, pentoxyfylline, and *sildenafil* all decrease collagen I expression in fibroblast cultures derived from human PD plaques as well as in rats.[86] Pentoxifylline use for PD treatment in humans has only been described in a single case report, which suggested that the patient's penile curvature improved as a result of pentoxyfylline use rather than the sildenafil he was concomitantly taking.[87] Despite promising results in cell culture and animal models, L-Arginine and sildenafil have not yet been evaluated for efficacy in PD patients.

Colchicine is an antimicrotubule agent[88] that decreases collagen deposition and elastic fiber fragmentation in a rat model of PD.[89] A small pilot study in 24 PD patients treated with colchicine appeared promising,[90] as did a subsequent study in 60 patients.[91] However, neither of these studies included comparison or control groups. A more recent RCT conducted in 84 patients failed to show any significant differences between colchicine and placebo in improvement in pain, penile curvature, or plaque size.[92]

Potassium Paraaminobenzoate (POTABA) may have an anti-inflammatory effect by enhancing oxygen uptake, fibroblast glycosaminoglycan secretion, and monoamine oxidase activity.[78,84] It was first introduced as a possible PD treatment in 1959, based on *in vitro* studies showing decreased collagen expression in treated fibroblasts.[93] The effects of POTABA were more recently studied in a RCT of 103 patients, which reported a response rate of 74.3% in the POTABA group and 50% in the placebo group (p=0.016), with significantly larger decrease in plaque size observed in the treatment group during the 12 month study period.[94] Pre-existing penile curvature did not improve with POTABA, but the authors concluded that the drug appeared to stabilize the disease, as curvature did not worsen in treated patients, whereas it did in placebo patients. There were no differences in penile pain between the two groups. This study is difficult to interpret, however, given the small sample size in each arm, the variability of PD symptom progression in the absence of treatment in men with PD more generally, and the significant improvements observed in placebo groups in other studies. As a result, confirmatory studies supporting POTABA are needed.

Transdermal And Intralesional Therapy

Verapamil has been studied in men with PD using electromotive drug administration (EMDA; either alone or in combination with dexamethasone),[95-98] via injection into PD plaque (with or without concurrent oral therapies),[98-108] via EMDA and injection together,[109,110] and as a topical gel.[111] The results of these studies are mixed and difficult to interpret, and in spite of the numerous studies investigating verapamil in PD, evidence of its efficacy remains weak. Multiple observational studies support efficacy of intralesional verapamil in stabilizing or reducing curvature, although all of these studies lacked control groups.[99,102-105] However, two RCTs both failed to demonstrate a significant difference in outcomes between intralesional verapamil and placebo control.[107,108] The EAU guidelines state that intralesional, EMDA, and topical verapamil therapies may be efficacious in treatment of PD.[78]

Intralesional[112-114] liposomal human recombinant superoxide dismutase (lhrSOD, a.k.a. orgotein) use in PD has only been decribed in observational studies.[112-114] Topical lhrSOD has been described in one observational study[115] and one crossover RCT,[116] with promising results. In the test phase, pain improved significantly in the treatment group compared to placebo. Curvature and plaque size both improved; however, these outcomes were not evaluated until after crossover. Therefore, no statement can be made comparing lrhSOD to placebo for these outcomes. Only 59 patients received the treatment between both studies. Thus further work is needed to confirm efficacy.

Multiple observational studies of intralesional *IFNα2b* and *IFNα2a* have supported a possible benefit in patients with stable PD with noncalcified plaques.[117-124] Stronger evidence for the use of IFNα2b comes from a RCT, which demonstrated significant improvement in penile curvature, plaque size, penile pain, and penile hemodynamics in the treatment arm compared to placebo control.[125,126] A second RCT compared results of patients treated with IFNα2b alone, vitamin E alone and combination therapy.[75] No significant differences were seen between any of these groups, although the study may have not been adequately powered, with only 10 patients per arm. Intralesional IFNα2b is considered potentially effective in PD treatment by the EAU guidelines.[78]

Intralesional collagenase *Clostridium histolyticum* (CCH) is a biologic agent consisting of 2 syngergistic microbial collagenases, and was recently approved by the U.S. Food and Drug Administration for the treatment of PD in men with palpable plaque and stable penile curvature of >30 degrees.[127] Evidence for the efficacy and safety of this agent is strong, with multiple large RCTs supporting the clinical benefit of CCH in PD,[127-131] including the Investigation for Maximal Peyronie's Reduction Efficacy and Safety Studies (IMPRESS) Trial[128] and a subsequent subgroup analysis.[127] These studies demonstrate significantly greater improvement in penile curvature and PD symptom bother score in the treatment arm compared to placebo, with effects on pain and erectile function similar to placebo. An average improvement of 34% in penile curvature, equivalent to −17.0±14.8 degrees of curvature, was observed in the treatment arm, in comparison with 18% (−9.3±13.6 degrees) in the placebo arm ($p < 0.0001$). Inclusion criteria for the IMPRESS trial included stable disease, dorsal curvature between 30 and 90 degrees, and intact erectile function with or without use of phosphodiesterase 5 inhibitors. Patients with isolated hourglass deformity, calcified plaque, plaque proximal to penile base, or ventral penile curvature were excluded. Adverse effects were relatively uncommon, and few serious adverse events including penile hematoma and penile rupture were reported, supporting the overall safety of CCH in the treatment of PD. To maintain optimal outcomes and safety, CCH can only be administered by physicians who receive specialized training.

Mechanical and Other Non-Surgical Therapies

A diverse group of non-surgical therapies have been studied in the setting of PD, including ESWT, penile traction therapy, vacuum erectile device (VED) therapy, radiation therapy, and hyperthermia therapy.

ESWT has been evaluated in numerous observational studies and several randomized trials, both placebo controlled[132-134] and uncontrolled.[135] No randomized studies support a benefit

of ESWT in improving penile curvature or plaque size. Two RCTs of ESWT reported decreased pain in the treatment group compared to placebo/sham.[133,134] A randomized, uncontrolled trial showed similar large improvements in pain using a visual analog score (baseline score of 5 decreasing to 0.4 after treatment) in both the ESWT and ESWT + tadalafil treatment groups.[135] Another RCT showed similar improvements in pain in the treatment and placebo groups. However, both groups had a low baseline pain level, which limited the ability to distinguish differences after treatment.[132] These studies suggest that while ESWT may not effectively treat penile deformity in PD, it may expedite the resolution of PD-related pain. However, it is unclear whether the trauma associated with extracorporeal shock waves may resulting in lasting damage or progressive penile deformity over time.

Potential benefits of *penile traction therapy* regimens of 2-8 hours per day have been investigated in observational studies, with decreases in penile curvature in treatment groups over time.[136,137] However, these studies were small (10 and 15 patients, respectively) and lacked control groups. In addition, penile traction therapy may be uncomfortable and inconvenient, given the overall long duration of daily treatment needed.

In 2010, Raheem et al. reported a decrease in penile curvature, improvement in penile length, and decrease in pain associated with a 12 week course of *VED therapy* in 31 PD patients.[138] The authors concluded that VED use may stabilize or improve penile curvature and decrease the need for surgical treatment. An earlier study evaluated use of the VED for penile lengthening after cirumferential tunical incision and venous grafting.[139] This study included only 4 patients who used a VED daily for 6 months starting one month after surgery, with increases in penile length in all four patients. One patient was noncompliant with the VED, but nonetheless gained 1 inch in penile length 6 months after surgery. The remaining 3 patients gained 2 inches each at 18-month follow-up. Interestingly, *de novo* PD following VED use has been described in two case reports, and is thought to be secondary to trauma associated with VED use.[140,141] While relatively few studies evaluating the use of VED in men with PD are available, the risks associated with VED use are few. Thus, a trial of VED therapy in men with PD, with or without other treatments, is reasonable.

Local hyperthermia therapy may be effective in men with PD, though the mechanism of action is unknown. Perugia et al. evaluated local hyperthermia therapy compared with intralesional verapamil in a randomized uncontrolled trial with 30 patients in each of two arms, and no control group.[106] Hyperthermia therapy consisted of 30 minutes of local treatment biweekly for 5 weeks, with significantly reduced plaque size and penile curvature observed when compared with intralesional verapamil. While these preliminary data are promising, additional studies are needed to confirm a benefit of hyperthermia therapy in men with PD.

Radiation therapy in treating PD has been evaluated only with observational studies, with only one including a control group, and with varying dosing regimens between studies.[142-144] These studies observed response rates of 29-47% of patients with improved curvature and 50%-69% with pain improvement.[143,144] However, these results are of limited value in the absence of comparison groups. The only study with a comparison group was performed by Furlow et al. in 1975 and observed more symptomatic improvement in the

radiotherapy group, with no difference in overall outcomes between radiotherapy and nontreatment groups.[142] Given the known risks of radiation exposure and the lack of compelling evidence for benefit, radiotherapy is not recommended in the treatment of PD.

Surgical Treatment

Surgical intervention is indicated in men with bothersome penile deformity that limits sexual intercourse and has been stable for at least 3-6 months, with options including tunical plication, plaque incision or excision with grafting, and insertion of inflatable penile prosthesis (IPP) with or without concurrent modeling, plication, or plaque incision/grafting.

Tunical plication is considered first-line surgical treatment to correct curvature in the stable PD patient with good erectile function with or without the use of pharmacologic or vacuum aids, adequate penile length, curvature <60 degrees, and absence of hourglass, hinge, or other atypical deformities.[78] Use of plication in patients with shaft narrowing or hinge defects, as well as curvatures ≥60 degrees, has nevertheless been reported.[66] Success rates of tunical plication, as defined by improvement in or resolution of penile curvature, range from 92%-99%, and serious adverse events are rare.[66,145,146] Patients must be appropriately counseled to expect penile shortening after plication.[66,146,147] In a series of 68 PD and 34 chordee patients, Greenfield et al. reported an average loss of 0.36 cm in penile length (2.4% of preoperative length), with a range of 0 to 2.5 cm.[66] Mean loss of penile length was directly related to degree of curvature, with greater loss of length in men with more significant curvature (4% in men with ≥60 degree curvature, 2% in men with curvature 45-59 degrees, and 1% in men with <45 degree curvature). The potential for altered penile sensation postoperatively should also be discussed, and has been reported in up to 8.8% of men.[66,148] While often transient, altered sensation may persist in the minority of men.[148]

Plaque incision or excision with grafting is another option in patients with good erectile function, and may be performed concurrently with tunical plication. Grafting has been reported with several materials, including cadaveric pericardium,[146,148-150] autologous temporalis fascia,[151] autologous buccal mucosa,[152] autologous venous patch,[147,153] autologous dermis,[148] autologous rectus fascia,[147] and porcine small intestinal submucosa.[148] No evidence is available to support efficacy of one graft material over another. Reported success rates, as defined by improvement in or resolution of penile curvature, range from 60-100%, and serious adverse events are rare.[146-148,152,153] Penile shortening was reported in 22.4% of patients in one series[153] and transient glans anesthesia in approximately 20% of patients.[148] Erectile function may be compromised postoperatively in a relatively small proportion of patients, with one study observing an 8.6% rate of *de novo* ED postoperatively.[147]

While men with good erectile function benefit from direct address of the PD plaque, in men with PD and concurrent ED unresponsive to medical therapy, placement of an IPP with penile modeling or plaque incision/excision and grafting is the preferred approach. Penile modeling is performed after placement of the IPP by grasping the penis and bending it in the direction opposite the curvature for 90 seconds while the IPP is inflated.[154] Significant improvements in curvature can be achieved after 1-3 repetitions of this sequence. Reported

success rates are 88-100%.[147,149,150] Penile plication may also be performed concurrently if needed to obtain desired results.[147,155]

CONCLUSIONS AND FUTURE DIRECTIONS

Peyronie's disease was once considered rare, but is now known to be more common than previously appreciated. PD is associated with significant psychosocial distress in patients and their partners, and consideration to both the physical and psychological ramifications of PD should be given during evaluation and treatment. Diagnosis of PD is based on detailed history and physical exam, and workup includes penile assessment in the flaccid and erect states to accurately assess plaques and curvature. The etiology of PD is not fully understood, but is likely related to trauma followed by abnormal wound healing. Interestingly, the predisposition to fibrosis and abnormal wound healing has a genetic basis in some affected men. Myriad nonsurgical modalities have been evaluated for PD treatment including pharmacologic, biologic, and mechanical therapies, the majority with unclear efficacy. Of the medications currently in use, CCH is the only FDA-approved drug for treatment of PD, and improves penile curvature and symptom bother. Surgical repair is indicated in men with significant, stable penile curvature, generally after failure of nonsurgical treatment approaches, and includes penile plication and plaque incision/excision and grafting with or without the placement of an IPP. Alternative nonsurgical treatments are continuously being investigated. Recently, intralesional decorin (proteoglycan)[156] and human adipose-derived stem-cell therapy[157,158] have shown promising results in animal models. Further research is needed to determine whether these agents will prove to be safe and effective in humans. An improved understanding of the factors predisposing to PD, including genetic factors, and the links between ED and other comorbid conditions in humans, including malignancy, is necessary to better inform patient risk stratification, as well as long- and short-term approaches to health maintenance.

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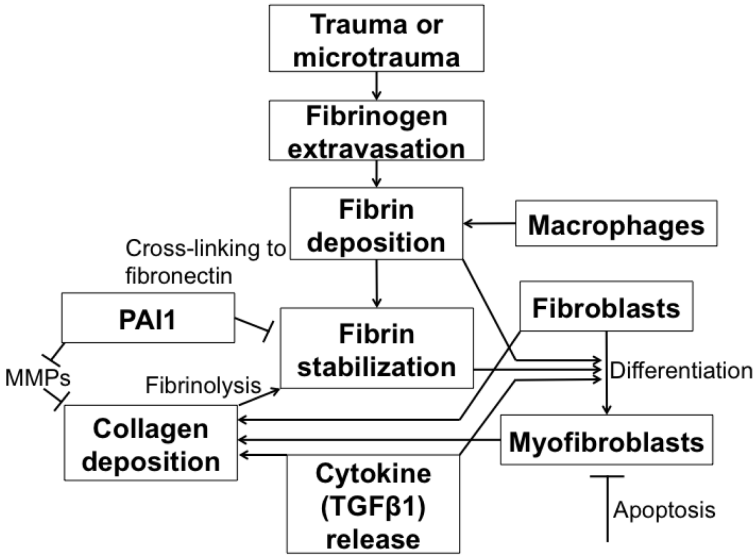

Figure 1.

Histopathology of Peyronie's Plaque Formation (adapted from [37])

[Place text below underneath Figure 1]

MMPs – matrix metalloproteinases

PAI1 – plasminogen activator inhibitor 1

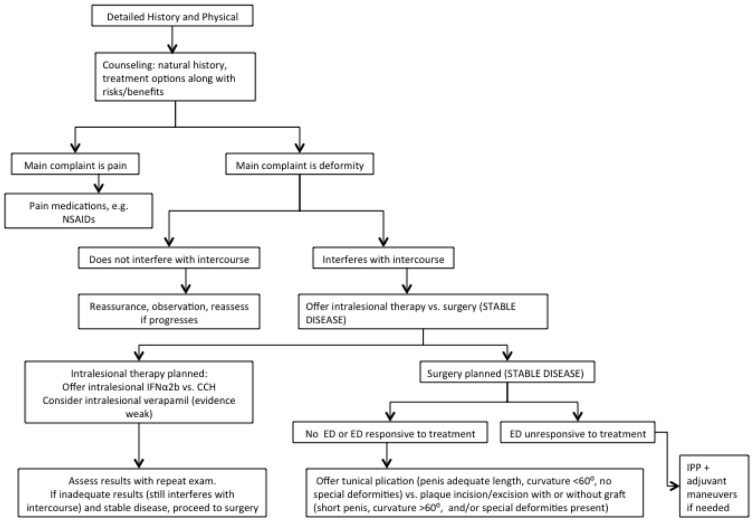

Figure 2.
Peyronie's Disease Treatment Approach

Table 1

Modifiable Risk Factors for Peyronie's Disease

Acute penile trauma or microtrauma
Penile / genital trauma from urologic procedures (e.g. Foley catheterization, cystoscopy, transurethral resection of the prostate, radical prostatectomy)
History of nongonococcal urethritis
History of inflammatory diseases or fibromatous lesions of the genital tract in sexual partner(s)
Smoking
Hypogonadism
?Diabetes
?Hypertension and other cardiovascular disease risk factors
?Alcohol use

Table 2

Essential Elements of the Peyronie's Disease History and Physical Examination

History	Flaccid Penile Exam	Erect Penile Exam (w/ Doppler US)
Onset and progression of symptoms: establish acute versus stable phase	Palpable plaque(s)? Location, size.	Palpable plaque(s)? Location, size.
Penile Deformity: Palpable plaque? Direction and degree of curvature. Impedes intercourse? Presence of hourglass deformity, hinge defect, other anomaly?	Stretched penile length	Plaque(s) visible by US? Location, size, calcification.
Penile Pain? Location, timing (flaccid, erect and/or with penetration), severity/progression	Tenderness to palpation? Location, severity.	Penile Deformity: Degree and direction of curvature. Uniplanar or biplanar? Hourglass deformity? Hinge defect? Other anomaly?
Presence of ED? If yes, pre-existing or new with PD symptoms? Validated questionnaire: IIEF†		Tenderness to palpation? Location, severity.
History of penile trauma? (urologic procedure/surgery, penile fracture, etc.)		
History of sexually transmitted infections?		
Other medical and surgical history. Diabetes, hypertension, cardiovascular disease.		
Social history: Sexual history, smoking/tobacco history, other recreational drug-use		
Family history of PD or DD?		
Assess distress, overall mood Consider using PDQ		

† IIEF: international Index of Erectile Function

Table 3

Drugs and Biologic Agents Used in Peyronie's Disease Treatment

Treatment	Proposed Mechanism of Action in PD	Recommended	Recommended AGAINST?
Systemic (Oral)			
Procarbazine	Cytotoxic alkylating agent (?anti-inflammatory)	No	Yes
Vitamin E	Anti-oxidant (↓ROS)	No	No
Propionyl-L-carnitine	↓Ca^{2+} in endothelial cells	No	No
Acetyl-L-carnitine	↓Ca^{2+} in endothelial cells	No	No
Tamoxifen	Modulation of TGF-β1 secretion by fibroblasts	No	Yes
Omega-3 fatty acids	Anti-inflammatory	No	No
Pentoxifylline	Non-specific PDE-inhibitor → ↑NO, ↓TGF-β1 expression	No	No
L-arginine	Precursor of NO	No	No
Sildenafil	PDE5-inhibitor; may ↓collagen and ↑apoptosis index within plaque	No	No
Colchicine	Anti-microtubule (anti-inflammatory)	No	Yes
POTABA	↑ tissue O_2 uptake, ↑GAG† secretion, ↑MAO‡ activity	No	Yes
Coenzyme Q10[83]	Anti-oxidant (↓ROS), ↓TGF-β1 expression	No	No
Transdermal			
Verapamil (EMDA or topical gel)	Ca^{2+} channel antagonist; may ↓collagen synthesis and/or ↑collagenase activity	No	No
Dexamethasone (EMDA w/ verapamil)	Steroid (anti-inflammatory)	No	Yes
Liposomal recombinant human SOD* (topical)	Antioxidant (↓ROS)	No	No
Intralesional			
IFNα2a	↓fibroblast proliferation → ↓collagen synthesis	No	No
IFNα2b	↓fibroblast proliferation → ↓collagen synthesis	Yes	NA
Verapamil	Ca2+ channel antagonist; may ↓collagen synthesis and/or ↑collagenase activity	Yes	NA
Collagenase Clostridium histolyticum	Clostridial collagenase	Yes	NA
Liposomal recombinant human SOD	Antioxidant (↓ROS)	No	Yes
Non-pharmacologic, non-surgical			
ESWT	Direct damage to plaque and/or ↑vascularity 2/2 heat → plaque lysis[159]	Yes	NA
Penile traction therapy	Mechanical straightening and/or lengthening	No	No
Vacuum erection device therapy	Mechanical straightening and/or lengthening	No	No
Radiotherapy (RT)	Unknown	No	Yes
Hyperthermia therapy	Unknown (possible modulation of heat-shock proteins,[160] ?↑vascularity 2/2 heat[159])	No	No
Surgical			
Tunical albugineal plication	Tunical shortening (opposite side of plaque)	Yes	NA
Plaque incision/excision and grafting	Tunical lengthening (side of plaque)	Yes	NA

Treatment	Proposed Mechanism of Action in PD	Recommended	Recommended AGAINST?
IPP (with possible penile modeling, tunical plication, or plaque incision/excision and grafting)	Mechanical straightening (w/ or w/o plaque manipulation, tunical shortening or lengthening procedures)	Yes	NA

† GAG: glycosaminoglycans

‡ MAO: monoamine oxidase

* SOD: superoxide dismutase