

Peyronie's Disease

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Peyronie's disease is a psychologically and physically devastating disorder that is manifest by a fibrous inelastic scar of the tunica albuginea, resulting in palpable penile scar in the flaccid condition and causing penile deformity, including penile curvature, hinging, narrowing, shortening, and painful erections. Peyronie's disease remains a considerable therapeutic dilemma even to today's practicing physicians. Peyronie's disease (PD) is a psychologically and physically devastating disorder that is manifest by a fibrous inelastic scar of the tunica albuginea, resulting in palpable penile scar in the flaccid condition and causing penile deformity, including penile curvature, hinging, narrowing, shortening, and painful erections. In spite of multiple treatment options offered since Francois de la Peyronie described PD in 1743 [1], PD remains a considerable therapeutic dilemma even to today's practicing physicians.

History

Francois de la Peyronie was a French Barber Surgeon who practiced from 1693 until his death in 1747 [2]. His career was prolific; he acted as the commander of the medical corps under Louis XIV, founded the Royal Academy of Surgery in 1737, and became a famous surgeon in Paris, caring for prominent Parisians and the kings of Poland and Prussia [2]. His most famous

contribution to medical history is his classic paper on *induratio penis plastica* [1], describing “disfiguring knobs” [1] and “indurations” causing a bending of the penis. Other investigators throughout history have reported on PD, going as far back as Theoderic of Bologna in 1265 [3].

Etiology and molecular mechanisms

The etiology of PD is the subject of much scientific research. Historically described etiologies included the patient's sexual history or a history of “deviant behavior” [4,5]. Forceful penetration and penile trauma have long been thought to be causative factors [6], and although other investigators have questioned their causality [7], it is likely that they remain an important triggering or epigenetic event in the development of the disease. More contemporary thinking would consider PD as a disorder of wound healing and as such may be considered similar to the formation of hypertrophic scars. Recent investigations have focused on the mechanisms of wound healing, fibrosis, and scar formation and have correlated their findings to the Peyronie's population.

Normal wound healing can be divided into three distinct phases based on biochemical activity: the acute phase, characterized by hemostasis and inflammation; the proliferative phase, characterized by fibroblast and epithelial growth; and the remodeling phase, characterized by collagen breakdown and reorganization. An understanding of the typical biochemical events of each phase is necessary to approach a basic science study of this disorder of wound healing.

Tissue injury is inherent in the creation of wounds, and the body's response to blood vessel disruption is the central feature of the acute phase.

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Exposure of subendothelial collagen to platelets from broken blood vessels leads to platelet aggregation and activation of the coagulation cascade. Platelets release granules containing several locally active and chemotactic agents, including platelet-derived growth factor, transforming growth factor- β (TGF- β), and platelet-activating factor. The end result is activation of the coagulation cascade, fibrin deposition, and clot formation. The clot functions not only to provide hemostasis but also as a physical scaffold for the movement of acute cellular response elements into the damaged area.

Cellular response follows a consistent pattern, with neutrophils arriving first, attracted by chemotactic agents including TGF- β , tumor necrosis factor alpha, and interleukin-1 [8].

Macrophages follow neutrophil arrival by approximately 48 hours. They function in a similar fashion to phagocytose dead or injurious material and by destroying bacteria or other foreign cells via oxygen free radical reactions. In addition, macrophages strongly recruit other cellular elements by releasing TGF- β [9] and stimulate local tissue repair through the release of vascular endothelial growth factor, insulin-like growth factor, and endothelial growth factor.

The proliferative phase spans days 4 through 12 after injury, and it is during this phase that scar initially forms. Fibroblasts migrate to the site of injury, particularly via the action of platelet-derived growth factor. Their role is the production of collagen and the recreation of the extracellular matrix lost during injury. Although there are many types of collagen in the body, types I and III dominate wound healing. Type I collagen is the primary collagen of skin, whereas type III becomes more important in wound healing. Collagen deposition is dependent on several cofactors, including adequate amino acid supply and vitamin C, which serves as an electron donor during key synthesizing steps. Fibroblasts also produce glycosaminoglycans, the principle elements of which in wound healing are chondroitin sulfate and dermatan. The interaction of collagen and glycosaminoglycans remains an active area of research in the science of wound healing. Endothelial cells proliferate to form new capillaries via the stimulus of vascular endothelial growth factor.

The remodeling phase of wound healing begins during the proliferative phase and results in the final production of a smaller, potentially contracted scar. This phase is marked by a balance between matrix metalloproteinases (MMPs),

which break down collagen, and the formation of collagen by fibroblasts. MMPs are induced by IL-1 and are inhibited by tissue inhibitors of metalloproteinases (TIMP), of which there are two identified molecules (TIMP-1 and TIMP-2), and by fibrinolytic inhibitors such as fibrin/plasminogen activator inhibitor-1 (PAI-1) [10].

Further study of the molecular etiology of PD has unearthed several important growth factors, which may be divided into profibrotic and antifibrotic groups. Profibrotic factors include TGF- β 1, which is an activator of collagen I synthesis [11] and which is released by neutrophils and macrophages during the acute and proliferative phases of wound healing. El Sakka and colleagues [12] found that, in PD plaques, TGF- β 1 protein expression, as measured by western blot, was overexpressed as compared with control subjects. In addition, TGF- β 2 and TGF- β 3 expression was not enhanced, suggesting that TGF- β 1 overexpression may play a role in PD development. Subsequently, TGF- β 1 was used to induce PD in a rat model, further solidifying its role as a central modulator of collagen deposition in PD [13].

A second group of profibrotic enzymes include the fibrin/PAI-1 system. Plasmin breaks down the extracellular matrix directly and by activating MMPs to break down collagen. PAI-1 inhibits MMPs and plasminogen activator, which is an activator of plasmin [14]. Fibrin has been studied as an inducer of PD [15,16] and has been used as an inducer of PD in an animal model [17]. It has also been found that levels of TGF- β 1 and PAI-1 levels are increased in fibrin-induced PD plaques [16].

The major identified anti-fibrotic enzymes are the MMPs. Although many different MMPs have been discovered, there are a few that seem to be more relevant in PD research. Collagen I breakdown is mediated by MMPs 1 and 13, whereas for collagen III, MMPs 1, 3, 10, and 13 seem to be the most active. Studies are underway examining the possibility of fibrosis regression, particularly through the induction of the nitric oxide synthase pathway.

Recent work has further elucidated the molecular biology of PD and has unearthed potential targets for molecular-based therapies. Ryu and colleagues [18] evaluated the efficacy of a TGF- β 1 inhibitor in the treatment of induced PD in a rat model. The rats were injected with TGF- β 1 into the tunica albuginea, inducing a PD-like state. The rats were randomized into four groups: control, PD group without treatment, PD with saline

injections, and PD with IN-1130 injections. IN-1130 is a small molecule inhibitor of activin receptor-like kinase 5 and is a receptor for TGF- β 1. The rats with PD that were treated with IN-1130 showed significant improvement in curvature and fibrosis when compared with those receiving no injections or saline injections. The treatment group had a posttreatment curvature of 9.1° versus 23.0° and 32.6° for the no injection and saline injection groups, respectively.

Del Carlo and colleagues [19] investigated the role of MMPs and TIMPs in the pathogenesis of PD using harvested plaque from patients who have PD. PD tissue samples were found to have diminished or absent levels of MMP 1, 8, and 13 when compared with matched perilesional tunica. PD fibroblasts were cultured with soluble MMPs and TIMPs after treatment with TGF- β or IL-1 β . They found that IL-1 β stimulation increased the production of MMPs 1, 2, 8, 9, 10, and 13 in PD fibroblasts, whereas TGF- β increased the production of only MMP 10 and decreased the production of MMP-13, suggesting that the abnormal PD fibroblasts can be induced to make MMPs.

It is possible that a genetic predisposition toward impaired wound healing and PD exists. Qian and colleagues [20] compared gene expression profiles in samples taken from PD tunica albuginea plaques, Dupuytren's contractures, and normal palmar fascia and found several gene family similarities between the PD and Dupuytren's groups, including MMP-2, MMP-9, and thymosins TM β 10 and TM β 4.

Epidemiology

Epidemiologic data on PD are limited and inconsistent. The first published epidemiology report on PD was by Pokley in 1928 [21] and consisted of 550 patients. The historically accepted (although likely incorrect) prevalence of 1% in the American male population was popularized by studies from Ludvik and Wasserburger [22] and Devine [23]. In 1991, Lindsay and colleagues [24] reported an overall prevalence of 0.38% based upon hospital record review, estimating that at that time there were 423,000 men in the United States who had PD and that approximately 32,000 new cases occur annually. The mean age at diagnosis in their population was 53 years, with a highest incidence reported for the group 50 to 59 years of age. Sommer and

colleagues [25] examined prevalence in the European population. Eight thousand men from Cologne, Germany were surveyed, and 3.2% reported a self-diagnosed palpable penile plaque. Their largest incidence (6.5%) was found among patients who were 70 years of age and older. In addition, 8.4% of men presenting for prostate cancer screening were found to have objective evidence for PD [26]. These studies suggest that the true prevalence of PD may be as high as 10%. Despite these more recent findings, many physicians, including urologists, believe incorrectly that 1% is the correct prevalence rate [27]. It is possible that reported rates of prevalence are falsely low, given patients' unwillingness to report such an embarrassing condition.

Controversy exists as to the age of presentation of PD. Although PD is thought to be a disease primarily of older men, there is research to suggest that PD occurs in younger men and may warrant more aggressive early therapy. PD has been reported in patients as young as 18 years [28]. In addition, in this study [28], patients presenting under the age of 40 were found to have a lower rate of concomitant erectile dysfunction (ED), were more likely to recall a specific traumatic event, were more likely to present during the acute phase of the disease, and were more likely to have multiple plaques and more complicated curvatures. Tefekli and colleagues [29] report an 8.2% prevalence of PD in men under 40 years of age. They also found that younger patients presented most often during the acute phase of the disease, had generally smaller curvatures (<60°), and had an ED rate of 21%. Briganti and colleagues [30] compared 20 patients under 40 years of age who had PD with 28 patients over 40 years of age who had PD and found that the younger patient group had significantly different International Index of Erectile Function scores and subjective loss of penile length. In addition, the younger patients were more likely to present during the acute phase of PD. More recently, Mulhall and colleagues [31] found that men younger than 40 years of age who had PD were more likely to present at earlier stages of the disease, were more likely to have diabetes, and were more likely to have multiple plaques as compared with patients over 40 years of age who had PD. These younger patients may benefit from treatment to minimize disease progression.

PD has historically been thought to be a disease with spontaneous resolution [32]. More recent reports have disproved this theory. In 1990, Gelbard and colleagues [33] surveyed 97 men who had PD

and found that, over a follow-up course of 3 months to 8 years, 47% felt that their disease had not changed, 40% felt that their disease was worse, and 13% felt that there was spontaneous gradual improvement. Similarly, in 2002 Kadioglu and colleagues [34] retrospectively reviewed 63 patients who presented with acute PD and were followed for 6 months without treatment. Thirty percent of patients felt that their disease worsened, whereas 67% felt that their disease was stable. Only two patients were found to have spontaneous improvement. In the largest published study looking at the natural history of untreated patients who had PD, Mulhall and colleagues [35] reviewed 246 men who presented within 6 months of the onset of PD and were followed for a minimum of 12 months without treatment. At a mean of 18 months of follow-up, 40% of patients who had curvature remained stable, 48% worsened, and only 12% improved. PD is a naturally progressive disease, with low rates of spontaneous resolution. In spite of this published information, survey data have revealed that primary care physicians and urologists believe that PD has a high rate of spontaneous resolution [27]. Men who present with active PD and compromising deformity should be managed with treatment that may offer deformity improvement or stabilization, not “watchful waiting,” in contrast to those men who have disease that does not interfere with function because they can be reassured and followed expectantly.

Evaluation of the patient who has Peyronie’s disease

Thorough evaluation of the patient who has PD is essential not only to diagnose the disease correctly but also to guide treatment. No universally accepted standardized evaluation for the PD man exists, nor has a validated questionnaire been developed. A suggested guideline for initial evaluation of the patient who has PD, including history, physical examination, and imaging analysis, has been published [36] and is outlined below. Subjective and objective data gathering remains discordant among clinicians and investigators, making the interpretation of clinical trial data confusing at best. The most efficacious mechanism for the evaluation of the patient who has PD may be via subjective and objective assessments specifically geared toward the application of known PD etiologies.

The subjective assessment begins with the patient interview. History should be focused on the onset and duration of symptoms, the patient’s presenting signs and symptoms, and the presence or absence of pain. It is useful to elucidate whether the patient continues to experience pain at the time of the initial evaluation because this may represent acute phase of the disease. Pain may be present with palpation, erection, or during coitus and should be differentiated because this may indicate a different degree of acute inflammation. The patient’s subjective curvature deformity should be noted. Up to 90% of men may present with ED as their presenting complaint, given that ED may be their most bothersome symptom. It is important to know what prior PD therapies the patient has undergone because such information may help guide future treatment.

A detailed past medical and sexual history should be part of the initial evaluation of every patient who has PD. Medical history should focus on personal or family history of wound-healing disorders, including Dupuytren’s contracture, which is reported in up to 20% of patients who have PD. Any risk factors for ED, such as dyslipidemia, atherosclerotic disease, history of tobacco use, and diabetes, should be queried. Patient’s baseline erectile function should be assessed using a validated questionnaire. Although a validated PD questionnaire is in development, the International Index of Erectile Function may be used to gauge the patient’s baseline sexual function.

The objective evaluation begins with the physical examination. Although the focus should be on the genital examination, an examination of the hands or feet is appropriate given the patient’s history. Measurement of penile length is critical because the loss of penile length is not only a known complication of PD but is also a source of great concern among patients. The penis should be measured stretched in its flaccid state dorsally from pubis to corona or meatus. The suprapubic fat pad should be compressed during measurement. Objective evaluation of curvature is best performed using penile duplex ultrasound after pharmacologic stimulation to produce a full erection equal to or better than the patient’s at home. Simple erection induction in the office allows objective assessment of deformity. Duplex ultrasound allows assessment of vascular flow rates, the degree of curvature as measured with a protractor, the presence and location of Peyronie’s plaque(s), and the presence of any hinge effect. In

addition, the degree of plaque calcification can be assessed. Autophotography should not be used as the sole means for curvature measurement because this modality can be inconsistent and inaccurate.

The final portion of the PD evaluation is objective assessment of the patient's erectile capacity and penile sensation. During duplex ultrasound the patient should be asked to grade his pharmacologic erection as compared with home erections. Biothesiometry is recommended to assess penile sensation. Using the distal phalanx of the index fingers as positive control and the ventral surface of bilateral thighs as negative control, the point at which vibratory sensation is achieved should be measured on the mid shaft bilaterally and on the glans.

Nonsurgical therapy for Peyronie's disease

Since the first description of PD in the literature, physicians have been searching for medical therapy options with little confirmed success. Consistent successful medical therapies continue to evade the practicing urologist, although current research into the molecular pathophysiology of PD may lead to a medical cure. Several nonsurgical options are available and may stabilize or reduce deformity and improve sexual function. The evaluation of their efficacy has been compromised by small clinical trials and without, in most cases, placebo control. Data outcomes are difficult to interpret with an absence of a validated questionnaire and in a disease in which spontaneous improvement has been noted in 5% to 12% of patients [31–34]. The nonsurgical options for treatment of the pain and curvature of PD, including oral, topical, intralesional, external energy, and combination therapies are presented below and in Table 1.

Oral therapies

Vitamin E

Vitamin E was the first oral therapy to be described for the treatment of PD [37]. Vitamin E is a fat-soluble vitamin that is metabolized in the liver, excreted in bile, and is thought to have antioxidant properties in humans. Oxidative stress and the production of reactive oxygen species is known to be increased during the acute and proliferative phases of wound healing because neutrophils and macrophages produce these reactive oxygen species [38], and the inflammatory phase of wound healing has been shown to be

prolonged in patients who have PD [39]. Thus, a biochemical mechanism does exist for vitamin E use. Gelbard and colleagues [33] compared vitamin E therapy with the natural history of PD in 86 patients. No significant differences were found between the two groups in terms of curvature, pain, or the ability to have intercourse. In 1983, Pryor and Farell [40] performed a double-blind, placebo-controlled crossover study evaluating vitamin E for the treatment of PD in 40 patients. No significant improvements were noted in plaque size or penile curvature. We do not recommend vitamin E for the treatment of PD because there is no evidence of benefit in placebo-controlled trials.

Colchicine

Colchicine is an antigout medication that inhibits fibrosis and collagen deposition primarily through its inhibition of the inflammatory response. Due to these factors, colchicine has been used as primary oral therapy for PD and in combination with other modalities. Akkus and colleagues [41] administered an escalating dose of colchicine in a nonrandomized, nonplacebo controlled fashion to 19 patients who had PD over a 3- to 5-month period. Thirty-six percent of patients noted a reduction in curvature, and 63% noted an improvement in the palpable plaque. Seventy-eight percent of those patients that experienced painful erections before treatment had resolution of their symptoms. Kadioglu and colleagues [42] treated 60 patients who had PD using 1 mg of colchicine twice daily, with a mean follow-up of 11 months. They found significant improvements in pain in 95% of men; however, 30% of patients reported improved curvature, whereas 22% of patients reported worsened curvature. Safarinejad performed a randomized, placebo-controlled trial of Colchicine in 2004 with 84 men [43] and found that Colchicine was no better than placebo at improvement of pain, curvature angle, or plaque size as measured by ultrasound. We do not recommend colchicine because of its lack of demonstrated efficacy in placebo-controlled trials. The agent is also associated with gastrointestinal distress, including diarrhea, and with rare aplastic anemia.

Potassium aminobenzoate

Potassium aminobenzoate is a member of the vitamin B complex that is believed to increase the activity of monoamine oxidase in tissues, thereby decreasing local levels of serotonin and thus

Table 1
Nonsurgical therapies for Peyronie's disease

Treatment	Mechanism of action	Comments
Oral		
Vitamin E	Antioxidant that theoretically reverses or stabilizes pathologic changes in the tunica albuginea.	Limited side effects, low cost. Efficacy not proven.
Colchicine	Inhibits fibrosis and collagen deposition.	Mixed reports of efficacy in noncontrolled trials. Single randomized controlled trial failed to show benefit. May cause GI disturbances including severe diarrhea.
Potassium aminobenzoate	Member of the vitamin B complex, thought to increase the activity of monoamine oxidase, thereby decreasing local serotonin levels, which may contribute to fibrogenesis.	Significant reduction in plaque size but not curvature. Expensive and difficult to tolerate due to GI side effects.
Tamoxifen	May reduce TGF- β release from fibroblasts and may block TGF- β receptors, resulting in diminished fibrogenesis.	Efficacy not proven. Side effects may include alopecia.
Carnitine	Believed to inhibit acetyl coenzyme-A.	Efficacy not proven. More investigation is needed.
L-Arginine	Amino acid substrate in the formation of nitric oxide, which is thought to be lacking in PD tissue.	Improvement in plaque size and collagen/fibroblast ratio in a rat model. Well tolerated.
Pentoxifylline	Nonspecific phosphodiesterase inhibitor that may reduce collagen levels in PD plaques.	Improvement in plaque size and collagen/fibroblast ratio in a rat model.
Topical		
Verapamil	Increases extracellular matrix collagenase secretion through fibroblast inhibition and decreases collagen and fibronectin synthesis and secretion. Decreases fibroblast proliferation	When administered topically the drug does not seem to penetrate into the tunica albuginea.
Intralesional		
Steroids	Anti-inflammatory and cause reduction in collagen synthesis.	Treatment with steroids is discouraged by the authors. Effects are unpredictable and may cause atrophy and distortion of tissue planes.
Collagenase	Breakdown of collagen.	Statistically significant improvement in curvature has been noted in men who have mild to moderate disease.
Verapamil	Same as topical verapamil.	Improvements in plaque volume, pain, and curvature have been reported in controlled and noncontrolled trials.
Interferons	Decrease the rate of proliferation of fibroblasts in Peyronie's plaques in vitro. Reduce production of extracellular collagen and increase production of collagenase.	Recent encouraging results with reports of improvement in curvature and pain. Dosing regimens and side effect profiles yet to be determined.

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Table 1 (continued)

Treatment	Mechanism of action	Comments
External energy		
Penile ESWT	ESWT-induced inflammatory response with resultant plaque lysis, improved vascularity, and the creation of contralateral scarring.	No statistically significant improvement noted in curvature, plaque size, or pain.
Electromotively administered verapamil with or without dexamethasone	Electric current may have some beneficial effect on wound healing.	Objective improvements of plaque size and curvature have been noted. Adverse effects include erythema at electrode site.
Combination therapy		
Vitamin E and colchicine	Synergistic effect possible.	Improvements in curvature and plaque size have been noted.
ESWT with intralesional verapamil injection	Synergistic effect possible.	Significant improvement in plaque size compared with placebo.
Intralesional verapamil with oral carnitine or tamoxifen	Synergistic effect possible.	Statistically significant subjective improvement in curvature, plaque size, and erectile function in patients treated with carnitine and intralesional verapamil.
Penile traction devices		
fsPhysioMed penile extender	Stretching of contracted tissue may result in the formation of new connective tissue.	Early results demonstrate improvement in curvature, increase in length, and improvement in hinge effect. Side effects were limited to mild discomfort with the device.

Abbreviations: ESWT, electroshock wave therapy; GI, gastrointestinal; PD, Peyronie's disease.

possibly decrease fibrogenesis. This effect has been demonstrated in vitro with PD tissue. Potassium aminobenzoate is used for other conditions, including scleroderma, dermatomyositis, and pemphigus. Zarafonatis and Horrax [44] first described the use of potassium aminobenzoate for the treatment of PD, and a subsequent European study published in 1978 reported a 57% improvement rate with 9% complete resolution in a pooled cohort of 2653 patients [45]. This study did not include a control or placebo group. In 1999, Weidner and colleagues [46] published a randomized, placebo-controlled trial of potassium aminobenzoate given 3 g orally four times per day for 1 year in 103 men. The only significant difference found between the two groups was plaque size, which has not been shown to correlate with a decrease in penile curvature. A 2005 follow-up study by Weidner and colleagues [47] suggested that the use of potassium aminobenzoate may protect against progression of PD plaques. Potassium aminobenzoate is expensive and has low tolerability due to gastrointestinal side effects. It should be dosed at 3 g orally four times per day. We do not recommend the use of potassium

aminobenzoate because of its lack of evidence regarding its efficacy in the treatment of PD.

Tamoxifen citrate

Tamoxifen is a nonsteroidal antiestrogen that acts by competing with estrogen binding sites in target tissues. Tamoxifen affects the release of TGF- β from fibroblasts and blocks TGF- β receptors, thus potentially reducing fibrogenesis [48,49]. In 1992, Ralph and colleagues [48] investigated tamoxifen in 36 patients who had recent-onset PD (duration <4 months). Eighty percent of patients reported a reduction in pain, 35% reported a subjective reduction in curvature, and 34% reported a decrease in plaque size. A follow-up study in 1999 by Teloken and colleagues [50] failed to show any statistically significant difference between tamoxifen and placebo, and there was a reported increase of alopecia in the active treatment group. We do not recommend the use of tamoxifen.

Carnitine

Carnitine is a naturally occurring participant in metabolism. Carnitine facilitates the entry of

long-chain fatty acids into muscle mitochondria, which are used as energy substrate. Carnitine is thought to inhibit acetyl coenzyme-A, which may aid in the repair of damaged cells. Biagiotti and Cavallini examined the use of carnitine for the treatment PD in 2001 [51]. Forty-eight men were divided into two groups to receive tamoxifen at 20 mg twice daily for 3 months or acetyl-L-carnitine 1 g twice daily for 3 months. The men taking carnitine saw greater improvement in curvature and had statistically significant improvement in pain. In addition, the patients taking carnitine reported far fewer side effects as compared with tamoxifen. More study is needed to elucidate the role of carnitine in the treatment of PD.

L-arginine

L-arginine is an amino acid that, when catalyzed by nitric oxide synthase, combines with oxygen to form nitric oxide. Inducible nitric oxide synthase is expressed in the fibrotic plaques of PD, and long-term suppression of nitric oxide synthase exacerbates tissue fibrosis [52]. In 2003, Valente and colleagues [52] reported that L-arginine, given daily in the drinking water of a rat model with TGF- β 1-induced PD plaques, resulted in an 80% to 95% reduction in plaque size and in the collagen/fibroblast ratio. In addition, L-arginine was found to be antifibrotic in vitro. This suggests that L-arginine, as a biochemical precursor of nitric oxide, may be effective in reducing PD plaque size.

Pentoxifylline

Pentoxifylline is a nonspecific phosphodiesterase (PDE) inhibitor. Valente and colleagues [52] found that normal human and rat tunica albuginea and PD plaque tissue express PDE5A-3 and PDE4A, -B, and -D. In their in vitro study, PD fibroblasts were cultured with pentoxifylline and were found to have increased cAMP levels and reduced collagen I levels as compared with control subjects. Pentoxifylline given orally to a TGF- β 1-induced PD rat model resulted in decrease in PD plaque size and collagen/fibroblast ratio. Brant and colleagues [53] reported a single case report of successful PD treatment using pentoxifylline alone. Further studies are required to definitively examine pentoxifylline for the treatment of PD; however, its known biochemical effect and early success in animal models make it an attractive option for oral therapy.

Topical therapies

Verapamil

Interest in topical verapamil for the treatment of PD has followed its success as an intralesional agent (see below). One study demonstrated that tunica albuginea tissue concentrations of verapamil are not achievable through topical application [54]. A recent three-arm trial without a known placebo demonstrated benefit with topical verapamil [55], but this study was significantly compromised [56]. Thus, the use of verapamil as a topical agent for PD is not recommended.

Intralesional therapies

Steroids

The powerful anti-inflammatory effect of steroids made them early investigated agents for intralesional therapy of PD. In 1954, Bodner and colleagues [57] reported improvement in 17 patients treated with intralesional hydrocortisone and cortisone. In 1975, Winter and Khanna [58] showed no difference between patients treated with dexamethasone injections and the natural history of the disease. In 1980, Williams and Green [59] published a prospective study using intralesional triamcinolone. All patients were observed for 1 year after study enrollment. During that time, only 3% of patients reported improvement. Triamcinolone was administered every 6 weeks for 36 weeks; 33% of patients reported improvement, particularly in pain and plaque size. The use of intralesional steroids is discouraged due to the side effects of local tissue atrophy, fibrosis, immune suppression, and lack of objective measures of benefit.

Collagenase

Collagenase was first studied in vitro by Gelbard and colleagues [60] in 1982. A subsequent clinical trial by that group [61] demonstrated subjective improvement in 64% of patients within 4 weeks of treatment. A decade after their initial study, they published their findings of a double-blind trial in 49 men [62]. Statistically significant improvement in curvature was noted in the collagenase treated group; however, improvement was seen only in patients who had less than 30° curvatures and plaques of less than 2 cm. Larger-scale controlled trials of collagenase are in development.

Verapamil

Verapamil is a calcium-channel blocker that has been shown in in vitro studies to inhibit local

extracellular matrix production by fibroblasts, reduce fibroblast proliferation, increase local collagenase activity, and affect the cytokine milieu of fibroblasts [63,64]. In 1994, Levine and colleagues [65] reported on 14 men who underwent biweekly intralesional injections of verapamil for 6 months. Significant improvement in plaque-associated narrowing was noted in all patients, and curvature was improved in 42%. The first randomized, single-blind trial of intralesional verapamil was published in 1998 [66]. Significant differences were noted in terms of erection quality and plaque volume. A trend toward improvement in curvature was noted. As a follow up, Levine and Estrada reported on 156 men enrolled in a prospective, nonrandomized trial of patients who had PD with a mean follow up of 30.4 months [67]. A local penile block was performed with 10 to 20 mL 0.5% bupivacaine, followed by injection of 10 mg verapamil diluted in 6 mL sterile normal saline (total volume 10 mL) into the Peyronie's plaque using one to five skin punctures but with multiple passes through the plaque. The goal was to leave the drug in the needle tracks, not to tear or disrupt the plaque. Injections were administered every 2 weeks for 12 total injections. Eighty-four percent of patients with pain achieved complete resolution, 62% were found on objective measurement to have improved curvature ranging from 5° to 75° (mean 30°), and only 8% of patients had measured worsening of curvature. More recently, Bennett and colleagues [68] administered six intralesional injections (10 mg in 5 mL) every 2 weeks to 94 consecutive patients who had PD. Follow-up was at 5.2 months after completion of the sixth injection. Eighteen percent of patients (n = 17) were found to have improved curvatures (average improvement of 12°), 60% (n = 56) had stable curvature, and 22% (n = 21) had increased curvature (average increase of 22°). All patients who had pretreatment penile pain had improvement at follow-up. The authors suggest that these data support intralesional verapamil for the stabilization of PD. It may be that six injections provides stabilization but is insufficient to accomplish reduction of curvature. We recommend a trial of six injections with each injection occurring every 2 weeks. If no improvement is noted, the therapy may be terminated, the verapamil dose can be increased to 20 mg, or interferon (IFN) injections may be offered. We consider verapamil to be contraindicated in patients who have ventral plaques or extensive plaque calcification.

Interferons

Duncan and colleagues [69] reported in 1991 that IFNs decrease the rate of proliferation of fibroblasts in Peyronie's plaques in vitro, reduce the production of extracellular collagen, and increase the activity of collagenase. Initial studies performed by Wegner and colleagues [70,71] demonstrated low rates of improvement but a high incidence of side effects, including myalgia and fever. In 1999, Ahuja and colleagues [72] reported on 20 men who received 1×10^6 units of IFN- α -2b biweekly for 6 months. All patients reported softening of plaque, 90% of patients presenting with pain had improvement, and 55% had a subjective reduction in plaque size. Dang and colleagues [73] administered 2×10^6 units to 21 men biweekly for 6 weeks and found objective curvature improvements in 67% and improvement in pain in 80%. Seventy-one percent of patients reported improvement in ED symptoms. In 2006, Hellstrom and colleagues [74] reported on a placebo-controlled, multicenter trial of 117 patients who underwent biweekly injections of 5×10^6 units for a total of 12 weeks. Average curvature in the treatment group improved 13°, versus 4° in the placebo arm, and 27% of patients in the treatment group had measured improvement, versus 9% of saline group. Pain resolution was noted in 67% of the patients receiving treatment versus 28% for patients receiving placebo. IFN therapy requires further investigation to adequately determine efficacy, dosing regimens, and side-effect profiles before its routine use in patients who have PD.

External energy therapies

Penile electroshock wave therapy

Local penile electroshock wave therapy (ESWT) has been suggested to be helpful. Various hypotheses about its mechanism of action exist, including direct damage to the plaque resulting in an inflammatory reaction with increased macrophage reaction leading to plaque lysis, improved vascularity resulting in plaque resorption, and the creation of contralateral scarring of the penis resulting in "false" straightening [75]. Hauck and colleagues [76] randomized 43 men to ESWT or oral placebo for 6 months. No significant effect was noted in terms of curvature, plaque size, or subjective improvement in sexual function or rigidity. More recent work from a German group [77,78] randomized 102 men to ESWT or to receive placebo shocks.

There was no statistically significant difference found between the groups for plaque size, improvement of deformity, or sexual function post-treatment. ESWT cannot be recommended as therapy for PD.

Iontophoresis

Iontophoresis involves the transport of ions through tissue by means of an electric current. Several studies have investigated the efficacy of topically applied verapamil with or without dexamethasone with enhanced penetration using iontophoresis [79–82]. In 2002, Levine and colleagues [83] confirmed that verapamil was found within the exposed tunica albuginea by examining surgically retrieved tunica albuginea from patients after a single intraoperative exposure during plaque incision and grafting surgery. Di Stasi and colleagues [82] recently reported on a prospective, randomized study of 96 patients treated with 5 mg verapamil plus 8 mg dexamethasone using iontophoresis versus 2% lidocaine delivered electromotively. Forty-three percent of patients in the verapamil/dexamethasone group noted objective improvement in plaque size and curvature; no changes were noted in the lidocaine group. In 2007, Greenfield and colleagues [84] reported on the use of 10 mg verapamil versus saline iontophoresis. Patients were assessed using papavarine-induced erections before and 1 month after treatment. Sixty-five percent of patients in the verapamil group demonstrated improvement in curvature, versus 58% in the saline group. Mean curvature improvement was 9.1° in the treatment group versus 7.6° in the saline group, which is not as robust as intralesional verapamil injections. In addition, the electric current may have some beneficial effect on wound healing, which is supported in the dermatologic literature [85]. Further investigation into iontophoresis is ongoing.

Combination therapy

Vitamin E and colchicine

A placebo-controlled study by Preto Castro and colleagues [86] randomized 45 patients to receive vitamin E and colchicine or ibuprofen. Statistically significant improvements in curvature and plaque size were noted in the treatment arm. Patients in the treatment arm reported a greater decrease in pain, although this did not reach statistical significance.

Electroshock wave therapy with intralesional verapamil injection

In 1999, Mirone and colleagues [87] prospectively examined two groups of patients who had PD: one group was treated with ESWT, and the other group received ESWT and perilesional verapamil injections. A 52% improvement in plaque size by ultrasound was noted in the ESWT-only group compared with 19% for the combination therapy. A follow-up study by the same investigators involving 481 patients demonstrated a 49% improvement in plaque size among those treated with combination therapy [88].

Intralesional verapamil with oral carnitine or tamoxifen

In 2002, Cavallini and colleagues [89] randomized 60 men to receive intralesional verapamil plus oral carnitine or intralesional verapamil plus oral tamoxifen. Statistically significant subjective improvements in curvature, plaque size, and erectile function were found in the carnitine group. No difference in improvement of pain was found between the two groups.

Penile traction devices

The use of tissue expanders has long been a mainstay of treatment in the orthopedic, oral-maxillofacial, and plastic surgical fields. It is well documented that gradual expansion of tissue results in the formation of new bone and connective tissue. Recently, initial work was done to evaluate the efficacy of a penile extender device (fsPhysioMed; FastSize LLC, Aliso Viejo, CA) for the treatment of PD. An initial pilot study at our institution of 10 patients found that daily use of the fsPhysioMed device resulted in a 33% improvement in curvature (from an average curvature of 51° to 34°), an increase in penile length ranging from 0.5 to 2.0 cm, and an improvement in hinge effect in all those with advanced narrowing or indentation. No patients noted recurrence or worsening of curvature, and there was no incidence of local skin changes, ulceration, loss of sensation, or worsening of curvature. Long-term and larger studies are needed before penile extender devices can be recommended for all patients who have PD.

We favor a multimodal approach to nonsurgical therapy for PD. All patients are given pentoxifylline 400 mg orally three times a day, with L-arginine 1000 mg twice a day. Patients are encouraged to use the fsPhysioMed device 2 to 8 hours per day for 6 months and are offered

verapamil injections as a means to improve curvature and pain.

Surgical treatment of Peyronie's disease

Surgery remains the gold standard treatment for PD. Surgery should be performed only when the disease is stable enough to ensure long-term efficacy. In general, surgery should be considered only when disease duration is 9 months to 1 year and when the disease has remained stable for at least 6 months.

Preoperative history, physical examination, and duplex ultrasonography are essential to formulating a treatment plan. A treatment algorithm was developed at Rush University Medical Center in Chicago, IL, based on the patient's erectile function, degree of curvature, and presence of hinge effect (Fig. 1) [90]. In brief, if rigidity is adequate for intromission with or without the use of pharmacotherapy and if the patient has a simple curve less than 60° and no hourglass or hinge effect, the patient is offered a plication procedure. If the patient has a complex curve greater than 60° or presence of destabilizing hourglass or hinge effect, he is offered a grafting procedure. Patients whose rigidity is inadequate for intromission despite oral pharmacotherapy are offered penile prosthesis with manual molding. Informed consent is critical before the initiation of any therapy for PD, particularly surgical correction. The risks of reduction of rigidity, diminished penile sensation, delayed ejaculation, shortening of the penis, and persistent or recurrent curvature should be carefully discussed with the patients and carefully documented in the medical record. It may also be wise to discuss with patients the expected changes in penile shape consistent with the early postoperative period.

PD – Surgical Algorithm

- When rigidity adequate +/- pharmacotherapy

- 1) Tunica plication techniques
 - Simple curve < 60 degrees
 - No destabilizing hourglass or hinge effect
- 2) Partial Excision and Grafting
 - Complex curve >60 degrees
 - Destabilizing hourglass or hinge effect

Fig. 1. Surgical algorithm for Peyronie's disease.

Surgery for PD generally falls into two categories: plication procedures for less severe disease and grafting procedures for significant (>60°) curves or the presence of hinge effect. It is beyond the scope of this article to detail all the available and practiced surgical techniques. Instead, the Rush University (Chicago) procedures of Tunica Albuginea Plication and plaque incision with Tutoplast (Coloplast, Minneapolis, MN) human pericardial grafting are detailed herein. Other published outcomes are presented in Tables 2 and 3 [91–105].

Tunica albuginea plication

An artificial erection is created in the operating room using 60 mg of papavarine and infusion of saline using an infusion pump. A circumcising incision is made 1.5 to 2 cm proximal to the corona, and the penis is degloved, exposing Buck's fascia to the base of the penis. Hemostasis is best achieved using bipolar current to avoid injury to the sensory nerves.

For ventral curves, the segment of Buck's fascia overlying the deep dorsal vein is opened, and the vein opposite the point of maximum curvature is excised. Circumflex and perforating veins are ligated using 4-0 silk ties, and the lateral neurovascular bundles are carefully elevated to expose the dorsum of the tunic. A pair of transverse incisions, each 1.0 to 1.0 cm in length and separated by 0.7 to 1.5 cm, is made directly over the septum. The incision is carried down sharply with the scalpel through the longitudinal tunical fibers, leaving the circular fibers intact. The intervening tunica is thinned to reduce the bulk of the plicated tissue. The tunica is plicated using 2-0 braided polyester suture (Tevdek; Teleflex Medical, Fall River, MA) in an inverting vertical mattress fashion, thus burying the knot; typically a single central plication suture is placed. The plication is reinforced with several 3-0 PDS sutures (Ethicon, Somerville, NJ) placed in a Lembert fashion. Penile straightness is rechecked by recreating an artificial erection using saline. Two to three plications are usually sufficient, although as many as six plications may be necessary.

For dorsal curves, Buck's fascia is opened longitudinally on both sides of the urethra, and the plication incisions include the thick ridge of tunica adjacent to the urethra bilaterally. Plication sutures are placed in the same fashion as for ventral curves.

Table 2
Published plication data

Author	Date of publication	Patient no.	Procedure type	% Straight	% with ED	Diminished sensation (%)	Mean follow-up duration (mo)
Montague et al [91]	1999	28	Modified corporoplasty (transverse closure of longitudinal corporal incisions)	89	4	Not reported	24.1
Gholami et al [92]	2002	132	16-dot plication technique	85	3	Not reported	31
Syed et al [93]	2003	50	Nesbit plication	90	Not reported	21	84
Savoca et al [94]	2004	218	Nesbit plication	86.3	13	11	89
Rolle et al [95]	2005	50	Nesbit plication	100	0	Not reported	Not reported
Brock et al [96]	2006	23	Minimally invasive intracorporeal plaque incision	91	Not reported	4	25
Greenfield et al [97]	2006	68	Tunica albuginea	99	7.3	4	29

Abbreviation: ED, erectile dysfunction.

Once satisfactory straightening has been reached, Buck's fascia is reapproximated using running 4-0 chromic suture, and the skin is reapproximated with 4-0 chromic sutures on a cutting needle in a horizontal mattress fashion. Xeroform (Tyco Health Care, Mansfield, MA) dressing is placed over the suture line and covered with sterile gauze. A Cobandressing (3M, St. Paul, MN) is lightly wrapped from the glans to the base of the penis.

The dressing is left in place for 3 days, at which time the patient is instructed to remove it at home. Patients are instructed to return for their initial follow-up visit 2 weeks after surgery. From weeks 2 to 6, patients are instructed in massage and stretch rehabilitation, which is undertaken for 5 minutes twice daily. Sexual activity is allowed 6 weeks postoperatively. Based upon the recent report by Moncada and colleagues [106], for patients undergoing surgical reconstruction, the use of an external penile traction device is recommended beginning 2 to 3 weeks postoperatively. It should be applied daily for up to 12 hours for 3 months to reduce postoperative shortening.

A review of long-term follow-up data for the Tunica Albuginea Plication procedure was recently performed [107]. Ninety patients were reviewed, with an average follow-up of 72 months.

Ninety-three percent of patients reported resolution of their curvature, with only 2% of patients reporting a recurrence of their curvature postoperatively. Twenty-eight percent of patients developed noted diminished rigidity, but 88% of patients were still capable of intromission with the use of oral phosphodiesterase-5 inhibitors. Sixty-eight percent of patients felt that their sensation was unchanged, and 98% report continued ability to achieve orgasm. In terms of penile shortening, which is a known complication of plication surgery, 74% of patients subjectively felt that their penis was shorter; however, objective, office-based data demonstrated that the majority (82%) of patients did not lose length.

Peyronie's plaque incision/partial excision and human pericardial tissue grafting

Penile reconstruction in the face of severe deformity demands plaque incision or partial excision with the placement of graft tissue over the resulting defect. Many different graft tissues are available, from autologous vein, dermal, or fascial transfer to commercially available "off-the-shelf" materials. Concerns regarding all grafting procedures include graft contracture, curvature recurrence, neurovascular injury, and impotence.

Table 3
Published graft data

Author	Date of publication	Patient no.	Procedure type	% Straight	% with ED	Diminished sensation (%)	Mean follow-up duration (mo)
Gelbard et al [98]	1996	69	Plaque incision and temporalis fascia grafting	74	14	Not reported	Not reported
Lue et al [99]	1998	112	Plaque incision with venous grafting	96	12	10	18
Hatzichristou et al [100]	2002	17	Tunica albuginea-free grafting	100	0	Not reported	39
Egydio et al [101]	2002	33	Tunica albuginea incision and bovine pericardial grafting	87.9	Not reported	Not reported	19
Levine et al [102]	2003	40	Tunica albuginea incision and human pericardial grafting	98	30	Not reported	22
Kalsi et al [103]	2005	113	Plaque incision with venous grafting	86	15	Not reported	12
Breyer et al [104]	2007	19	Porcine small intestine submucosa Graft	63	53	Not reported	15
Hsu et al [105]	2007	48	Plaque incision with venous grafting	90	5	Not reported	Not reported

Abbreviation: ED, erectile dysfunction.

The ideal graft material should be readily available, should possess enough compliance to function with erections, and should have a high rate of efficacy with a low complication rate [108]. Although the ideal graft material has yet to be confirmed, our preference is the Tutoplast processed human pericardium.

An artificial erection is created in the operating room using 6 mg of papavarine and a saline infusion pump. The penis is degloved via a circumcising incision initiated 1.5 cm proximal to the corona. When correcting a dorsal curvature, the neurovascular bundle is elevated over the area of maximum curvature, and Buck's fascia is incised bilaterally and longitudinal to the urethra. In the absence of hinge effect, a simple transverse incision should be made centered over the area of maximum curvature and performed to the 3 and 9 o'clock positions on the shaft bilaterally. Longitudinal extensions of this incision can be made at a 30° angle to the transverse incision, creating the modified "H" incision and thus resulting in a rectangular defect. In the presence of hinge effect, indentation, or extensive calcification, this tissue should be excised before graft placement.

Upon incision or partial excision of the plaque, the penis is placed on stretch, and 4-0 PDS

(Ethicon, Somerville, NJ) stay sutures are placed in the four corners of the defect. The penis's stretched length should be remeasured at this point in the operation; it will likely be 1 cm longer than preoperatively. The stay sutures are used to stretch the defect to affect an accurate measurement of the defect in the longitudinal and transverse directions. Another stay suture is placed at the 12 o'clock position. The Tutoplast processed pericardial graft should be secured to the tunica in a running fashion, leaving approximately 10% extra to account for any minor graft shrinkage. The artificial erection is recreated, and the penis is inspected for residual deformity. Additional grafting or plication measures may be taken at this time. A recent analysis demonstrated that adding a plication does not compromise postoperative rigidity or cause significant shortening [109]. The graft is secured to septal fibers using two or three simple 4-0 PDS sutures. Buck's fascia is reapproximated using 4-0 chromic suture (Ethicon, Somerville, NJ), and the penile skin is reapproximated with horizontal mattress sutures of 4-0 chromic on a cutting needle. The same dressing as for the Tunica Albuginea Plication procedure is used, with Xeroform gauze, a dry sterile dressing, and Coban dressing.

The Coban dressing is removed on postoperative day 3, and the patient is seen in the office on postoperative day 14. At that time the patient is instructed on penile massage and stretch therapy as a means to aid in recovery. Small subgraft hematomas are not routinely aspirated unless they are a source of significant postoperative pain, and our experience is that the hematomas resorb with time, causing no residual effect. The use of penile traction devices is encouraged beginning 2 or 3 weeks postoperatively. These patients are encouraged to use a low-dose phosphodiesterase inhibitor nightly on postoperative days 10 to 50 as pharmacologic erectile rehabilitation [109].

A recent review of our long-term results of Tutoplast grafting for severe PD was recently performed [107]. One hundred eleven patients undergoing our grafting procedure were retrospectively reviewed, with an average follow-up of 58 months. Ninety-two percent of patients remained satisfactorily surgically straightened. There was some curvature recurrence in 12%. Thirty-five percent of patients noted diminished postoperative rigidity, but 76% of patients were able to achieve intromission with PDE-5 inhibitors. Ninety percent of these patients were taking PDE-5 inhibitors before their operation. Although 65% of patients felt that they lost length, flaccid stretched penile length measurements in the office demonstrated an average gain of 0.2 cm. Sensation remained intact in the majority of patients, with 89% reporting an ability to achieve orgasm.

Straightening with penile prosthesis

Patients presenting with PD and ED can achieve curvature straightening and definitive mechanical erections through the placement of a penile prosthesis. The risks of ED development after surgical correction of PD are well known and described, and all men who have baseline ED, vascular comorbidities, or severe curvatures likely requiring significant plaque excision and grafting should be counseled to consider penile prosthesis. Prosthesis choice depends on the patient and surgeon; the medical literature supports the use of semirigid implants [110,111], two-piece implants [112,113], and three-piece implants [114,115], although patient satisfaction seems to be best with inflatable devices [116]. Our treatment algorithm involves placement of penile prosthesis followed by manual molding and, if necessary, a relaxing tunical incision with or without patch grafting (Fig. 2). The prosthesis should be placed in the usual fashion.

PD – Prosthesis Algorithm

- When inadequate rigidity

Penile Prosthesis Placement

- IPP alone (not Ultrex)
- With modeling
- With incision
- With incision and grafting (when defect >2 cm)

Fig. 2. Prosthesis algorithm for Peyronie's disease.

After closure of the corporotomy incisions, the prosthesis should be inflated, demonstrating curvature. The cylinder tubing is clamped to protect the pump, and the penis should be bent in a direction opposite the curvature and held in that configuration for 60 to 90 seconds. The cylinders should be then filled with more saline, and the procedure should be repeated until adequate straightening (residual curve $\leq 30^\circ$) is achieved. The cylinders should then be emptied and filled to approximately 75% rigidity, at which point penile straightness should be reassessed. If residual curve $> 30^\circ$ persists, one option is to consider a relaxing tunical incision after elevating the overlying Buck's fascia. If the defect is 2 cm or greater, it should be grafted (we prefer Tutoplast processed pericardium) to prevent cylinder herniation or recurrent cicatrix contracture. Regular use of the prosthesis by the patient (once completely healed from surgery) helps to maintain penile straightness because the prosthetic cylinder acts like an internal tissue expander.

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