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CLINICAL FOCUS: MENS HEALTH
REVIEW

Peyronie's disease: new paradigm for the treatment of a unique cause of erectile dysfunction

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ABSTRACT

Peyronie's Disease is an incurable condition of the tunica albuginea of the penis associated with scarring, plaque formation, and penile deformity on erection. It is often associated with erectile dysfunction. Recent data have supported a familial and genetic predisposition to this chronic condition. The etiology of Peyronie's Disease is unknown, but is likely associated with multiple micro traumas to the erect penis in men who are susceptible to the scarring typical of Peyronie's Disease. The treatment of Peyronie's Disease has improved over the past decade as a result of animal studies and the approval of new medications. In the acute phase of the condition, phosphodiesterase type 5 inhibitors have been shown to have some benefit and are supported by animal studies demonstrating reduced fibrosis of the penis in animal models of Peyronie's Disease. In the stable phase of the disease, newer injectable agents have shown great promise. Collagenase clostridium histolyticum is approved for the treatment of Peyronie's plaques by direct injection into the scarred tissue with data showing satisfactory safety and efficacy. Surgical procedures for penile straightening have been refined with improved outcomes in the past decade. For those men with erectile dysfunction and Peyronie's Disease, penile implants can restore erectile function and form. As a result of the new understanding of the risk factors for Peyronie's Disease and recent advances in treatment options, the algorithm for the treatment of Peyronie's Disease has improved outcomes for patients and their partners.

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Introduction

Peyronie's Disease (PD) is an often debilitating condition caused by fibrosis of the tunica albuginea (TA) of the penis resulting in difficulty with coitus in many patients. Over the past decade, the knowledge of the etiology, genetics, and treatment of PD has changed the approach to this condition that causes angst, depression, and disability in many men affected. Peyronie's Disease was first reported by Fallopius and Vesalius in correspondence in 1561 [1]. Earlier reports exist, but the first series of patients was reported by Francois Gigot de la Peyronie in 1743. Peyronie, often referred to as the father of French surgery, was the first surgeon to be physician to the royal court of France. He reported a series of five men with what he termed *induratio penis plastica* that consisted of 'rosary beads' in the penile shaft caused by irritation of the penis and best treated by bathing in the baths of Berege in Southern France. Little was known of the optimal treatment paradigm over the centuries and most men were told that there was no solution to their problem.

PD presents as fibrotic plaques of the TA causing penile deformities on erection. Plaques are usually unifocal (78–84%) and located on the dorsum of the penile shaft (46–62%) [2]. The plaques may occur ventrally or laterally. These dense scar tissue plaques cause deformities during erection including curvature, 'hour glass deformity' and multiple complex deformities. Curvature, usually, is directed to the side of the plaque and varies from minimal to more than 120 degrees. Patients also report penile shortening, often as much as one third to one half of pre-PD erectile length [3]. While the onset of the deformities is usually insidious, many patients report the acute appearance of curvature and deformity. In the early stages of PD, patients may experience pain in the penis, usually on erection and in the location of the plaque. This discomfort with erection resolves once the PD has become stable. While erectile dysfunction (ED) can occur with PD, erectile function is normal in the majority of patients.

The extent of curvature can make sexual intercourse difficult causing discomfort for patient and partner. Angles of curvature can be more than 90°; in one cohort approximately 20% of patients had curvature greater than 60° [3]. The erectile pain is likely due to inflammation associated with abnormal healing. A study of biopsies of 12 painful Peyronie's plaques showed inflammatory collections surrounding the plaques in more than two-thirds of cases [4]. Pain associated with the plaques generally resolves within several months of onset and resolution of tenderness is a sign of stabilization. The acute phase of the condition usually lasts between 6 and 18 months. Once the acute phase has stabilized, a chronic phase characterized by little pain, stable penile deformity, and stable plaque size signals the best opportunity for treatment. 20–40% of PD patients report ED with lack of tumescence or flaccidity distal to the plaque.

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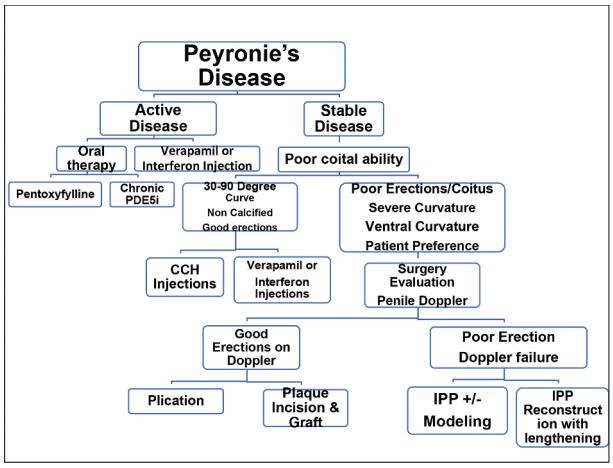

Figure 1. Peyronie's disease treatment algorithm.

PD also affects the quality of life, with 77% of afflicted men reporting psychological complaints and two-thirds of those reporting frequent concern over the condition [5]. PD can cause a negative impact on self-image, a reduction in sexual satisfaction, relationship problems, anxiety, stress, and depression. Spontaneous disease regression has been noted in 5–40% of cases, with one large series reporting 13% resolution. Pain will generally resolve over time. Curvature is less likely to improve without treatment. Reports of low testosterone in PD patients suggest that evaluation should include a morning total testosterone level to screen for hypogonadism [6].

PD is most common in middle-aged and older men. The prevalence of PD has been reported from 0.38% to 3.7% of 40- to 70-year-old men [7]. However, the age at onset has been reported from 18 to 80 years of age. The prevalence of PD noted in contemporary prostate cancer screening populations has been 3.7% to 8.9% [8]. Approximately 10% of men with ED have PD [2].

Etiology

The TA is composed of connective tissue surrounding the corpora cavernosa [9]. This anatomic structure is composed of an inner circular layer and an outer longitudinal layer than function in controlling venous outflow during erection. In the normal male, the TA is composed of bundles of collagen-containing elastic fibers in a regular, latticed pattern. TA in PD plaques, however, shows a dysregulated extracellular matrix, with increased collagen where the pattern is disorganized with a loss and fragmentation of elastic fibers, and significant fibrin deposition. These plaques which are an example of abnormal healing, have a disordered ratio of type III to type I collagen. Peyronie's plaques exhibit increased concentrations of fibroblasts and myofibroblasts. Once lesions become chronic and stable, they have little inflammation. Dystrophic calcification is present in one-third of plaques [9].

While there have been many theories of the etiology of PD, most cases are idiopathic and not associated with other disease states. Trauma, either single or multiple small injuries are agreed upon as the primary etiology of PD. Many patients, however, do not recall a specific traumatic event. As a result, most feel that multiple small traumatic events in susceptible individuals is the most likely cause of PD. Trauma to the TA during intercourse may cause micro-hemorrhage, fibrin extravasation, cellular infiltration, and an inflammatory response, inducing deposition of abnormal extracellular matrix. PD patients may have genetic tendency for abnormal wound healing or have connective tissue vasculogenic aberrations or autoimmune disorders[10]. Family history of PD is reported in 2–4% of men and an association with Dupuytren's contracture (DC) in 20% of patients [8]. Identical twins have been reported to have Peyronie's disease. In a study of patients with Paget's disease of bone, a condition characterized by abnormal bone turnover, 14–31% of the patients had PD and 23% had DC [11]. Age is a significant risk factor, with a prevalence of 1.5% in men aged 30–39 years and 6.5% in men older than 70 years [4]. Older men may be more susceptible to penile injury during coitus since erectile rigidity is decreased and the partially erect penis is more likely to buckle during coitus. Trauma to the penis is a common etiology of PD. There is a three-fold increased risk of PD in patients with prior genital or perineal trauma [4]. An association has been reported with urologic procedures including radical prostatectomy, urethral catheterization, and cystoscopy.

In 193 patients who had surgically corrected penile fractures and 150 with who had of taqaandan (the Middle Eastern cultural practice of forceful bending of the erect penis for detumescence) found only one case of PD. These findings add to the controversy about trauma and may indicate that trauma only with predisposing factors will produce PD. Association with hypertension, diabetes, and other risk factors for systemic vascular disease have been reported in several series. Transforming growth factor (TGF)-beta is suggested as a substance in fibrotic conditions like PD. TGF-beta is elevated in the TA of patients with PD [9].

The cause of ED in patients with PD is controversial. While penile deformity, pain, and psychologic factors may be the cause of ED in some patients, penile vascular derangements have been identified in 61–88% of men with PD and ED [8]. The TA plays an important function in the veno-occlusive mechanism of penile erection, and loss of the normal mechanical properties of the TA may contribute to inadequate venous control in the erectile mechanism and ED. Veno-occlusive dysfunction has been identified in 30–86% of PD patients with ED, while arterial dysfunction has been demonstrated in 44–52% in studies using penile Doppler examinations [2]. Because both veno-occlusive and arterial dysfunction are common and progressive in the aging male, identifying the exact cause for the ED associated with PD is difficult.

Diagnosis

The diagnosis of PD is by patient history and palpating a penile plaque on examination. Most plaques are easily palpable, typically larger than 1.5 cm, on the dorsum of the penile shaft and non-tender. Important medical history includes presenting symptoms, duration of deformity, coital functional disability, ED, penile length loss, pain, and stability of the lesion. History

of associated conditions such as Dupuytren's contracture, Lederhose disease, family history, diabetes, Paget's disease of bone, systemic vascular disease, and prior genitourinary surgery, trauma or instrumentation should be elicited. Patients should be asked about erectile function, including tumescence distal to the plaque, generalized lack of tumescence, physical inability for intromission due to the curvature, anxiety, and psychological impact. Discussion with the patient's partner is also helpful in assessing the impact of the PD. Documentation of plaque size and location are important in the physical examination. Reports of hypogonadism in PD patients suggest that a screening morning total testosterone should be assessed in these men at the time of diagnosis [12].

Imaging studies can evaluate PD and assist in choosing a treatment plan. Options for imaging include ultrasonography, X-ray using a mammography technique, computed tomography (CT), and magnetic resonance imaging (MRI). High-frequency ultrasonography is the best option for identifying plaque calcification and documenting the thickness of the TA [2]. Imaging is best used to evaluate ED and PD. Penile color Doppler ultrasound is performed following the pharmacologic induction of an erection using injectable intracavernosal vasoactive agents. Evaluation of erectile function is critical when considering surgical options as men with adequate erectile function may be candidates for penile straightening procedures alone, while those with poor erections will usually require penile prosthesis implantation [6]. After induction of an erection, ultrasound is used to evaluate arterial flow and venous leakage. Documenting the degree and location of curvature during erection with photographs allows for future comparison and patient counseling during treatment.

Treatment

Treatment for PD is designed to improve sexual function and produce a functional and comfortable erection for both patient and partner (Figure 1). Physicians must advise the patients that a completely straight erection is unlikely, and should stress that the goal of treatment is the recovery of coital function [8]. Treatment to restore coitus range from oral medications to surgical intervention. Patients usually prefer beginning with less invasive options prior to considering reconstructive surgery. Surgery is best delayed until resolution of the active, acute phase of the disease. Montorsi et al. recommend delaying surgery for at least 12 months from the end of the active phase before considering reconstructive surgery [13]. During the active phase, curvature, deformity and erectile function change and surgery before stabilization of the process may result in insufficient curvature restoration. Non-surgical options for both active and stable PD include oral agents, topical applications, intralesional injections, extracorporeal shockwave therapy (ESWT), and ultrasound.

Non-surgical treatment options for PD focus on limiting inflammatory and fibrotic processes that lead to abnormal wound healing and scar formation resulting in plaque and erectile deformity. Oral medications are desirable for the treatment of PD, but there are few evidence-based studies to support their effectiveness. Vitamin E, Colchicine, Potaba (potassium paraminobenzoate), Tamoxifen, l-Carnitine, Pentoxifylline, and PDE5 inhibitors have all been studied, however, none is able to show definitive clinical benefit[8]. Animal studies have suggested that phosphodiesterase type 5 inhibitors such as sildenafil can reduce plaque formation and propagation in a Peyronie's animal model [14]. Small, controlled clinical studies have supported the use of sildenafil or tadalafil in improving plaque formation especially in the acute phase of plaque formation [8]. While there are few double-blind, placebo-controlled studies of oral medications, there are direct plaque injection techniques that have shown more reliable results in well-designed clinical trials. Different from oral medications, injection therapies deliver intra-lesional agents aimed at limiting the inflammatory, fibrotic process by administering drug directly into the scar tissue. The calcium-channel blocker Verapamil has been used as it has the ability to inhibit fibroblast proliferation. Several randomized. Placebo-controlled studies in small numbers of patients have supported the effectiveness of verapamil. Unfortunately, the amount of benefit has varied with the series. Levine and colleagues have reported improvement in penile curvature using verapamil injection, with an improved ability for intercourse in 87% of patients [8]. Other studies have reported less curvature improvement (18%), but durable stabilization of curve and no disease progression in 60% of men, suggesting that verapamil may benefit some patients and prevent worsening of symptoms in the majority of men treated [8]. Interferon α-2b has been studied for inhibiting fibroblast activity. A double-blind, placebo-controlled clinical study reported statistically significant improvement in erectile curvature compared with placebo injections (14° vs. 5°). Another study, however, failed to show curvature improvement in their patients [8]. The most extensively studied and documented injectable therapy, collagenase *Clostridium histolyticum* (CCH), may be the most effective non-surgical PD treatment. CCH has been used successfully to treat Dupuytren's contracture, a fibrotic disease of the hand associated with PD, and works by breaking down collagen-based scar that forms the plaque and causes penile curvature. Administered by a series of injections into the plaque, two placebo-controlled, double-blind studies have shown significant improvement in erectile curvature compared with placebo injections (34% vs. 18% and 33% vs. 22%). As an additional primary end point in these studies, there was a statistically significant improvement in patient bother score using a clinically validated Peyronie's Disease questionnaire. Treatments usually require four sets of two injections each followed by home penile modeling. Data on CCH suggest mean improvements in penile curvature of 15–20° [15,16]. Recent studies of a penile traction device have documented improved outcomes when the traction device is combined with CCH [17]. An abbreviated treatment schedule was reported by Abdel Raheem and colleagues that limited the

injection numbers and performed the modeling procedure by the patient at home with equivalent results and reduced costs [18]. Similarly, a recent trial has documented improved outcomes with CCH, modeling and daily sildenafil use [8]. Unfortunately, the company that produces CCH has decided to focus sales and marketing from Peyronie's Disease and has ceased export to the UK and Europe depriving many anxious and appropriate candidates for CCH to be treated with less well-studied options [19,20]. Thus, while CCH represents a promising minimally invasive therapy for PD, those with significant curvature may not achieve functionally satisfactory results and may need surgical intervention.

Extracorporeal shock wave therapy (ESWT) at low intensity delivers directed ultrasound energy to the scar plaque has been reported as a possible treatment alternative, but should be considered, at best, investigational. The mechanism for a beneficial effect remains unclear. Since the presumed pathogenesis of PD is trauma to the TA it is curious that this treatment itself is traumatic. Side effects are few and may include local pain, bruising, and urethral bleeding which was reported in 7% of men in one large series. Uncontrolled studies of ESWT have provided contradictory results. Reported results include: decreased plaque size in 0–58%, reduced curvature in 0–74%, decreased pain in 56–100%, and improved coital function in 12–75%. A review of 4 RCTs and 1 meta-analysis assessed ESWT for PD was reported from the European Society of Sexual Medicine [18]. The trials reviewed had beneficial effects on pain, but showed no measurable effect on penile curvature or plaque size. The authors concluded that ESWT is safe and low morbidity, but the effectiveness for treatment of PD is not supported by available data. Patients reporting PD associated discomfort may have some improvement from ESWT, but no change was identified in disease progression.

The choice of a surgical procedure depends on physician counseling and patient preferences. Decision regarding surgery must be based on the patient's coital function, penile deformity examination, and erectile rigidity [2,6]. Three categories of surgical procedures are available for PD reconstruction. Corporoplasty, or penile plication, has the best outcome with regard to post-operative sexual satisfaction and preserved erectile function. Corporoplasty is reserved for patients with good erections and non-complex curvature of 60 degrees or less without hour-glass deformity [19]. Plication is carried out in the TA at a location opposite the plaque and curvature. Since these plication procedures can shorten the penile length on erection, these procedures are reserved for patients with adequate penile length [21]. Plaque incision and grafting procedures are used for more severe or complex curves, hour-glass deformities, and in men who have already suffered significant penile shortening secondary to PD, as these procedures will lengthen the tunica and usually preserve, but do not add length to the erect penis [6]. Graft material varies from autologous tissue transfers to manufactured materials. Recently, excellent results have been obtained with collagen fleece [6]. Men with satisfactory erectile function with or without supportive medications may be candidates for penile straightening procedures with tunical lengthening or shortening techniques. The value of proper preoperative assessment of erectile function is critical. Flores et al. reported incision and grafting procedures in men with pre-operative diminished rigidity treated with medical therapy, overall sexual satisfaction decreased significantly post-operatively. This lack of satisfactory erectile function was not identified in men undergoing corporoplasty [22]. Inflatable penile prosthesis (IPP) implantation is best suited for men with PD and poor erectile function, or men who prefer this a more reliable erection. While semirigid penile prostheses have been used successfully for men with PD, satisfaction rates in these men are less than those implanted with an inflatable device [23]. Baseline erectile function is important not only for the decision to proceed with IPP placement but also in deciding between corporoplasty and plaque incision and grafting. IPP placement has been successful in men with PD, but often modeling of the penis after IPP placement may be necessary to correct residual post implant curvature. Satisfaction rates for patients and partners with IPP in the presence of PD have been gratifying. [24] Nelson et al. highlight the significant psychosocial impact of PD which leads many men to significant depression and a poor self-image. Many men will have overly optimistic expectations for a surgical result that is not attainable [5]. Because of these exaggerated expectations, pre-operative discussions should to be honest and detail realistic expectations, surgical limitations and potential complications and alternatives.

Summary

PD is an incurable, sexually debilitating disease that results in penile deformity, coital difficulties, and significant psychological stress for patients and their partners. PD is more prevalent than previously thought, and its prevalence is likely to increase as populations age and more men seek treatment for ED. The condition remains enigmatic with only limited evidence and speculation as to its pathogenesis. Treatment of PD should be individualized and tailored to the patient's needs, goals and expectations, disease history, physical examination, and coital function [2]. While there are medical treatments, there are few with evidence-based data to support their safety and effectiveness. Randomized placebo-controlled trials support more recent advances in injectable therapies, especially CCH [15,16]. After PD has stabilized and less invasive options have failed, surgical correction is an option for motivated patients with stable PD and functional erectile impairment. Surgical reconstruction is a good option when proper treatment decisions are made, with the goal of return to sexual function following PD treatment. While there have been many advances in the understanding of the etiology of PD and newer treatment alternatives, there remains much work to do in the understanding and treatment of PD. Recent progress in injectable agents and improved options for surgical

reconstruction support that men should be encouraged to seek treatment for this physically and psychologically debilitating condition.

A practical treatment plan is management of the patient initially and during the acute phase of PD expectantly [2]. If the patient is relatively asymptomatic, reassurance and clinical follow-up may be all that is necessary. Because of the associated hypogonadism with PD, it is important to do a screening morning total testosterone level on PD patients. If the patient has progressive or symptomatic PD, more aggressive treatment is indicated. Choosing between the different treatment options will depend on the physician's clinical experience, interpretation of the available data and on the patient's comfort with different forms of therapy. Initial treatment in the active stage of PD can be with a daily PDE-5 inhibitor such as tadalafil. Treatment of stable curvature of less than 90 degrees is best with a course of CCH injections and home modeling. Treatment of concomitant ED can be with either oral or injectable erection-promoting agents or a vacuum erection device. Surgical intervention for penile straightening should be reserved for those with severe penile deformity that alters erectile function and who have failed less invasive options. Penile prosthesis implantation is used in patients with ED and PD who fail less invasive therapy and desire to resume sexual intercourse. Surgical intervention should be considered only after PD has stabilized for 6–12 months. With any treatment option, goals and expectations of treatment and adverse events should be discussed in detail with patients and partners.

Declaration of interest

The contents of the paper and the opinions expressed within are those of the authors, and it was the decision of the authors to submit the manuscript for publication.

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