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REVIEW ARTICLE

Current insights and future directions in Peyronie's disease management: A narrative review

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Abstract

Peyronie's disease (PD) is an inflammatory and fibrotic disease which results in disfiguring and often distressing penile curvature deformity, affecting up to one in nine men in the United States, and between 0.3% and 13.1% of men globally. It progresses through an acute phase, associated with pain, as the fibrosis develops. In the quiescent phase, penile pain ceases and deformity stabilizes. The precise etiology remains unknown despite ongoing work to elucidate the biological underpinning. The diagnosis is guided by history and physical examination. Except for ultrasonography, imaging is not routinely recommended. Current management is predicated on symptomatic control and slowing progression in the acute phase, and correction of bothersome curvature in the stable phase. Most nonsurgical treatment options are poorly supported by available evidence, with the exceptions of traction therapy and certain intralesional injections. Surgical treatment, considered only after stabilization, is guided by severity and the presence or absence of erectile function and is highly individualized. Investigations are ongoing into several areas, including the exact biological mechanisms leading to plaque formation and failure of resolution; the effects of co-existing systemic disease; the role of imaging in diagnosis and surgical planning; combination and regenerative nonsurgical therapies; and improvements in surgical techniques. As diagnostic accuracy improves and targeted treatments become available, management of PD will become progressively tailored to an individual's particular disease. In this review, we summarize the current knowledge regarding PD, including etiology and epidemiology, diagnosis, management, cutting-edge research, and future directions in care of this condition.

KEYWORDS

injection, penile prosthesis, Peyronie's disease, plication, regenerative medicine, traction, tunical lengthening

1 | INTRODUCTION

Peyronie's disease (PD), also known as induratio penis plastica, refers to penile deformity with erection generated by a fibrous scar in the tunica albuginea of the corpus cavernosum. It is associated with curvature, narrowing, and/or shortening of the penis, pain, and significant psychological harm[1]. While the medical literature contains references to what may have been PD as early as the thirteenth century[2], the disease process is named for Francois de la Peyronie, a French surgeon to Louis XIV who reported a series of several patients with penile nodules and curvature in 1743[3]. The precise epidemiology is unclear due to under-reporting, but

survey data places prevalence estimates in the United States adult male population at 0.7% to 11.0%[4]. Certain conditions such as erectile dysfunction and diabetes mellitus are associated with higher incidences[5]. The estimates for worldwide prevalence range from 0.3% to 13.1%[6].

The natural history of the disease includes two phases—the active or acute phase, and the stable or chronic phase. These can be clinically distinguished by both pain and stability in the degree of curvature[7]. However, the precise distinction between the two remains a matter of debate[8]. Typically, the presence of pain is considered a hallmark of acute disease, though certainly pain is a suggestive measure, and discomfort due to the physical deformity can persist even in stable disease. Similarly, the length of time after which the disease is considered stable can range from 3 months to 12 months[9].

Current management paradigms follow two main principles. The first is that treatment is offered only for men who are bothered by the disease. The second is that the acute phase is managed with pain control and supportive treatment, while definitive interventional treatment is reserved for stable disease only[10,11]. The management paradigm currently in use, based on the American Urological Association (AUA) guidelines as well as available recent data, is summarized in Figure 1.

In this work, we will summarize the current thinking on diagnosis, etiology, and management. We will also explore cutting-edge work being done in this field to direct future diagnosis and management.

2 | GUIDELINES REVIEW

The AUA guidelines for the evaluation and management of PD can be summarized in three sections: diagnosis/initial evaluation; treatments; and "what not to do"[12].

2.1 | Diagnosis and initial evaluation

These statements emphasize the importance of a thorough history to investigate the nature of deformity, the degree of impairment with intercourse, the presence of pain, and overall distress. Also discussed is the obligation for physical examination with particular attention to palpable abnormalities. It is considered mandatory for in-office examination to include an induced erection, with or without a concomitant Doppler ultrasound. The guidelines caution that only those clinicians with the appropriate experience and tools to provide care should counsel and treat patients with PD.

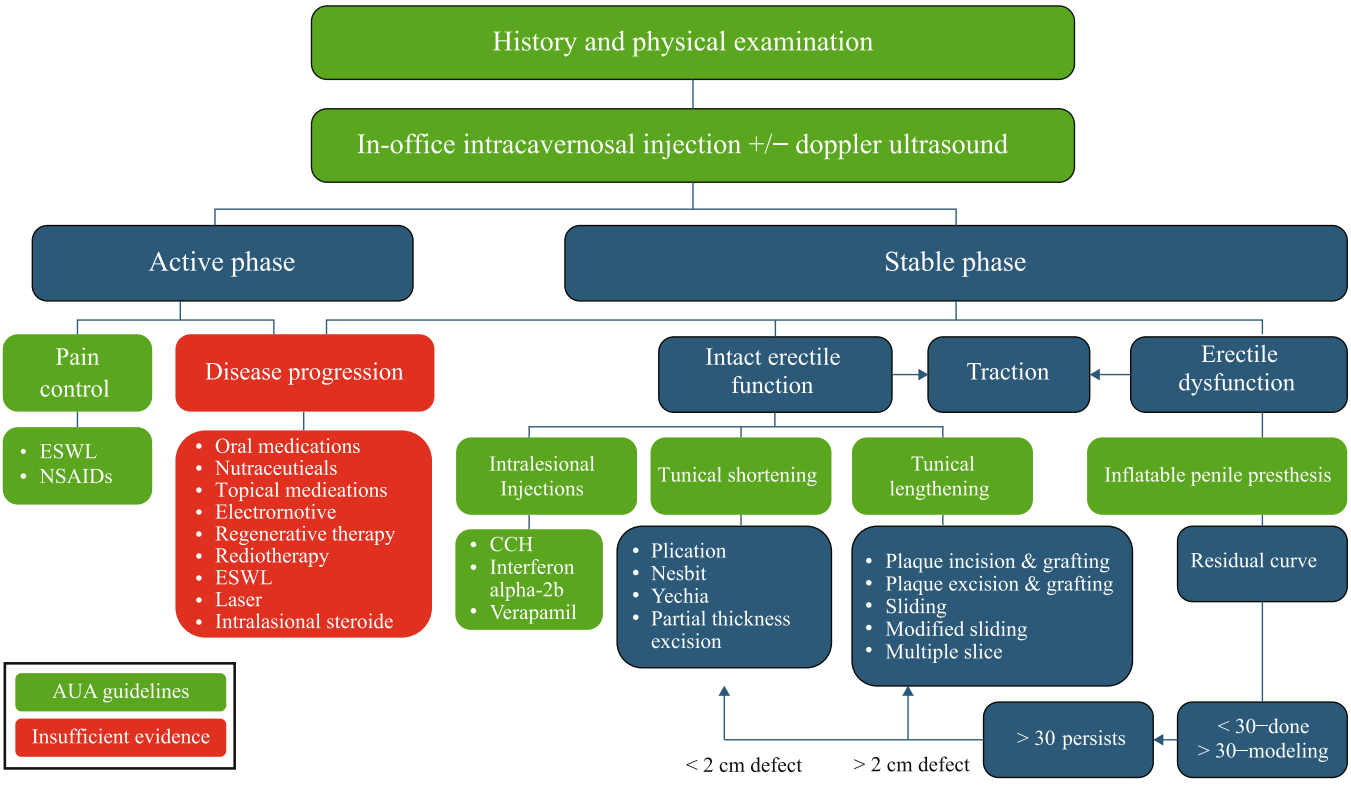

FIGURE 1 Treatment paradigm and visual summary of the AUA Guidelines. AUA, American Urological Association; CCH, collagenase Clostridium histolyticum; ESWL, extracorporeal shockwave therapy; NSAID, nonsteroidal anti-inflammatory drug.

2.2 | Treatment

Treatment of PD depends on the disease state and the degree of distress. For the management of pain in the acute phase of disease, guidelines recommend nonsteroidal anti-inflammatory agents. No other oral agent is specifically recommended; the only other treatment for pain discussed as acceptable is extracorporeal shockwave therapy (ESWT). For the management of bothersome stable phase disease, various options may be considered, in part dependent on the presence of erectile function (including that achieved with medication or vacuum devices). Several interventional or "intralesional" medications are considered acceptable, with clinicians having the option to offer collagenase Clostridium histolyticum (CCH); interferon alpha-2b; or verapamil. CCH has particular limitations including intact erectile function and curvature between 30° and 90°. Surgical options include tunical plication or plaque incision/excision with grafting in patients with intact erectile function, or inflatable penile prosthesis placement with erectile dysfunction or severe penile deformity.

2.3 | What not to do

There are several sanctions stated in the guidelines with regards to which treatments should not be offered, mainly for lack of sufficient evidence. These include all oral therapies, electromotive therapy, and radiotherapy. ESWT is discouraged with the notable exception that it may be offered for penile pain. Surgical reconstruction should not be offered except in stable disease.

2.4 | Other guidelines

The European Urological Association (EUA), Canadian Urological Association (CUA), and International Society for Sexual Medicine (ISSM) have published guidelines on the management of penile curvature and/or PD[13–15]. One study compared the guidelines for areas of consensus and discordance. The investigators found a high degree of concordance among the various guidelines. Regarding diagnosis, guidelines agree that history and physical examination is mandatory; intracavernosal injection is the gold standard for evaluation of curvature and deformity; and counseling regarding the limitations of the current literature is needed. With regard to treatment, the guidelines agree that oral medications should not be recommended; ESWT may be used for penile pain only, not to address deformity; intralesional injections are an option for those who do not wish to undergo surgery; surgical treatment should only be offered in the stable phase of disease; and erectile function (with or without use of medications or vacuum therapy) determines candidacy for either plication or grafting procedures versus prosthetic implantation[16].

3 | ETIOLOGY

Once thought to be caused by deviant sexual behavior, prolonged ungratified sexual desire, or infidelity[17], contemporary thinking considers the disease to be generated by microtrauma in patients with certain biological susceptibilities[18-20]. Essentially, repeated episodes of penile microtrauma during intercourse lead to the formation of fibrotic tissue in the tunica albuginea with subsequent penile deformation.[1,21] One risk factor is erectile dysfunction; less than complete rigidity may contribute to weak points along the penile shaft such that fracture is more likely to occur than with either full rigidity or rigidity insufficient for penetration at all[22]. However, the process of aberrant wound healing is thought to be required for the microtrauma to eventually result in fibrotic plaque. Evidence suggests many or most cases of penile trauma, even severe trauma such as fracture, do not result in PD[23].

Support for a genetic basis arises from several areas. First, the association with similar connective tissue diseases such as Dupuytren's contracture, Ledderhose disease, and tympanosclerosis has been well documented[24–27]. Based on these associations, the immune system has been proposed as a major modulatory factor, with inflammation thought to play a role in genitourinary fibrotic diseases in general and PD in particular[28]. Oxidative stress and other inflammatory conditions, including insulin resistance, nonalcoholic fatty liver diseases, and even COVID-19 infection, have been reported in conjunction with PD[29–31]. Other conditions including hypogonadism, chronic prostatic inflammation, and benign prostatic obstruction have all been recently proposed as risk factors based on the higher incidence of PD in patients with these conditions[32–34]. Nevertheless, there remains to be seen mechanistic evidence of causation in all these cases.

Epidemiological data has also suggested a genetic component. One study demonstrated a higher rate of average relatedness in cases with PD compared to matched controls out to the fifth-degree relatives using a large population database[35]. In addition, many genetic factors, including human leukocyte antigens, single nucleotide polymorphisms, karyotypic abnormalities, and genetic expression changes, have been associated with or linked to PD; however, despite advances in genetic technology no genetic factors have been definitively shown to be part of an underlying etiology[36].

4 | DIAGNOSIS

A careful history and physical examination are crucially important. The clinical history will assist in distinguishing between active and stable disease, as well as identify comorbid conditions which may impact treatment (such as erectile dysfunction or hypogonadism).

The Peyronie's Disease Questionnaire has been validated to quantify psychological and physical symptoms, penile pain, and symptom bother[37]. It has also been validated in various languages including Spanish, Italian, and Danish, and has been shown to reliably report improvements after treatment[38–41].

The physical examination may disclose a palpable plaque. However, curvature assessment via autophotography, smartphone or tablet-based applications, or induced erection in the office is necessary to complete the physical examination. Assessment of both curvature severity and direction is required for optimal treatment planning[42]. Of note, induced erection is preferred as autophotography has been demonstrated to be less reliable and may even underestimate true curvature severity[43]. In particular, intracavernosal injection is preferred to both stimulation and vacuum-generated erection as it has been shown to provide a more full erection and properly estimate the true degree of curvature[44].

Goniometry, defined as the art and science of measuring joint ranges, has historically been used to assess curvature on either photography or examination, though accurate assessment is difficult with low interrater reliability[45]. In addition, complex abnormalities including volume-loss deformity such as hourglass deformity may not be fully assessed simply by goniometry and plaque assessment. Three-dimensional computational analysis has been used to improve accuracy of penile deformity and volume measurement, though this has yet to see widespread clinical use[46].

Ultrasonography is a highly useful adjunct to the examination for several reasons[47]. First, not all plaques may be palpable, including punctate, ventral, or septal plaques[48,49]. Additionally, Doppler ultrasound can be used to characterize comorbid erectile dysfunction when performed along with induced erection[50]. Ultrasound has even been demonstrated to be capable of assessment of corporal fibrosis, which could play a role in surgical decision making[51]. Elastography has been used to characterize plaque tissue, and may be helpful in monitoring treatment changes[52].

5 | THERAPY—NONSURGICAL

A wide range of nonsurgical or conservative management options for PD are commonly used, whether effective or not. Several reviews have summarized the existing body of evidence for these options, including an assessment of the available randomized and/or controlled designs[53–62]. We will discuss oral medications, mechanical treatments, topical therapies, intralesional injections, radiotherapy, and regenerative treatments. In the following individual sections, allusion to use of medications or existing studies without specific references refer to the aforementioned reviews.

5.1 | Oral medications

Generally, oral medications are poorly efficacious with regard to improvements in curvature severity, plaque size, erectile function, or pain, with conflicting or unreproduced results in randomized studies. Popular oral medications among practicing urologists include vitamin E (tocopherol), para-aminobenzoacidic potassium, tamoxifen, colchicine, and L-carnitine, phosphodiesterase type 5 inhibitors (especially common in practice among European urologists), coenzyme Q10, procarbazine, pentoxifylline, propoleum, prostacyclin, and omega-3 fatty acids[63,64]. The unifying rationale behind use of these anti-inflammatory medications in PD stems from in vitro studies showing the effectiveness of many of these medications on fibrotic and inflammatory processes[65]. As a result, these medications tend to be prescribed in the acute phase for their ostensible benefit in inflammation reduction. While early observational studies demonstrated improvement in various disease parameters, randomized controlled studies invariably fail to reliably demonstrate improvements in angulation, plaque size, erectile function, or pain, possibly because of heterogenous populations. For example, a case series reported in 1948 was the first to describe the effects of vitamin E in 23 patients with PD, finding marked improvements in plaque size or even complete disappearance of plaques in most patients[66]. Also noted was improvement with pain. However, a controlled crossover study in 1983 was performed with 40 patients found no significant improvements in plaque size or curvature[67]. More recently, a randomized controlled trial of 236 patients in 2007 compared vitamin E, L-carnitine, and combination treatment to placebo, finding similar proportions of patients with declines in pain, degree of curvature, and plaque size in all four groups[68]. As a result, the AUA guidelines reference these studies to recommend against oral treatment with vitamin E.

Nevertheless, the more commonly prescribed medications, such as vitamin E, have little or no harmful side effects, and therefore can play a role in psychological support. The only oral medications recommended in any guideline are nonsteroidal anti-inflammatory drugs for pain control. Further investigations, especially into combination treatments using oral medications, will continue as the etiology of PD is better described.

5.2 | Mechanical therapy

Mechanical treatments such as traction and vacuum devices ought to have a role based on their mechanism of action, and the data has indeed borne out promising prospective results. These therapies work by remodeling the extracellular matrix of the plaque. Essentially, repeated stretching forces induce signal transduction pathways that lead to reorganization and lengthening of

fibrotic plaques[69,70]. Penile traction therapy has been evaluated in two prospective randomized trials. One trial used the Penimaster PRO device[69], while the other used the RestoreX device[70]. Both trials showed improvements in curvature, stretched penile length, and questionnaire scores. Side effects were mild, typically discomfort or glans numbness. In addition, to use as monotherapy for patients hesitant to undergo more invasive treatments, traction may have a role in length preservation pre- or postoperatively or as a combination treatment with intralesional injections. While vacuum devices are hypothesized to act via the same mechanism as traction, current evidence is limited. These devices are anticipated to be further integrated into the guideline recommendations as additional evidence accumulates.

5.3 | Topical therapy

Topical treatments come in several flavors and include medications, shockwave therapy, and laser treatment. Overall these have weak evidence for use, with some limited indications. Medications can be administered in gel formulation or via iontophoresis, also known as electromotive drug administration. This latter technique involves transfer of drug particles across the skin via induction of a voltage gradient. This technique has been used to treat patients since the 18th century[71]. Verapamil can be administered both as a gel or iontophoresis; studies have shown that while levels of the medication cannot be detected in the tunica albuginea after gel administration, it can be found in the penile tissues after iontophoresis[72]. Nevertheless, randomized data shows conflicting results in terms of improvements in angulation, pain, and erectile function. Though not recommended in guidelines, topical verapamil remains commonly prescribed. Other medications including superoxide dismutase and a formulation known as H100 (emu oil, nicardipine, and superoxide dismutase) have been assessed with promising, if limited, results in terms of curvature improvements[73].

5.4 | Shockwave and laser therapy

ESWT is thought to traumatize the plaque architecture and induce remodeling, increase vascularity locally, and result in plaque resorption. However, available studies have not been able to repeatedly confirm curvature improvements or plaque size reduction. Two randomized trials did report a reduction in pain, and therefore use of this therapy is permitted by the AUA guidelines (and discussed in the European Association of Urology and ISSM guidelines) for that specific purpose[74,75]. Low-intensity laser treatment has been theorized to reduce collagen levels. When used in conjunction with verapamil, some studies have shown nondurable curvature improvement as well as pain reduction and erectile function improvement[76].

5.5 | Radiotherapy

Low-dose radiotherapy has been used to treat many benign inflammatory conditions and has been reported in various case series with some evidence of success in reduction of pain, curvature, plaque volume, and improved sexual function[77]. The hypothesized mechanism is induction of anti-inflammatory effect via the induction of nitric oxide synthase and modulation of the adhesion of white blood cells. However, radiation in penile tissue has deleterious effects including fibrosis and erectile dysfunction, via ionizing injury to endothelial cells and smooth muscle collagenization. In addition, the risk of secondary malignancy has not been quantified, making it difficult to advocate for this therapy and limiting widespread use at this time.

5.6 | Intralesional therapy

Intralesional injections show the most promise of all nonsurgical treatments, though indications remain somewhat narrow. Various medications have been used including collagenase CCH (also known as Xiaflex), interferon alpha-2b, the calcium channel blockers verapamil and nicardipine, hyaluronic acid, thiocolchicine, steroids, and platelet-rich plasma (PRP). Of these, only CCH and interferon alpha-2b have strong evidence of beneficial outcomes. CCH was evaluated in the IMPRESS I and II randomized trials and was found to have double the curvature improvement of the placebo group in patients with stable curvatures between 30° and 90°[78,79]. Small case series have also suggested improvements for active phase disease[80–82]. Adverse events include injection site pain, penile swelling, hematoma, and penile fracture. Of note, there was some thought that the action of administration itself supplied some benefit, via disruption of the plaque from needle trauma itself. This may be responsible for the benefit seen with other injectable medications. The utility of CCH injections in men with atypical diseases such as ventral curvature or complex deformity is yet unknown due to trial exclusion. A systematic review of injection therapies showed that CCH and interferon alpha-2b showed the best outcome in terms of curvature, while hyaluronic acid improved erectile function the most[83]. While CCH, interferon, and verapamil are each discussed in the guidelines, steroids are specifically contraindicated given potential side effects. Injections overall remain an option for men with stable disease, particularly for those who prefer to avoid surgery. Nevertheless, they remain limited in their indications

and may be less effective in comparison to the existing surgical options.

6 | THERAPY—SURGICAL

Surgical management of PD is indicated once the plaque has progressed to the stable phase, as the aim of surgical correction is to allow for a functional erection[84]. Surgical intervention is not recommended in the acute phase as the plaque is evolving. As the plaque changes, the extent of the lesion is not yet clear and may resolve or improve. As well, the final degree of curvature or deformity may also not be sufficiently bothersome to preclude sexual function. One exception to this general clinical principle is for patients with severe erectile dysfunction in the acute phase, who may benefit from inflatable penile prosthesis placement for length preservation[85].

Various options to achieve a functional erection exist, with the major branch points in management dependent on the severity or complexity of curvature and the presence of sufficient erectile function. Surgical practice has therefore changed little from the algorithm originally proposed by Levine and Lenting in 1997, which is based on these principles[86]. In brief, tunical shortening, aimed at correction of curvature, is employed for curvature under 60° without complex deformity. Tunical lengthening, aimed at addressing the lesion directly, is used for complex or bidimensional curvature, curvature of >60°, or the presence of an hourglass deformity or hinge effect. For men with both erectile dysfunction and PD, penile prosthesis is recommended and will be discussed separately.

For those with good penile rigidity, which will be ascertained during the initial workup, the surgical philosophy advises one of two branches[87]. First, there is an address of curvature, the source of bother specifically. Second, there is an address of the disease focus, the plaque. In the first camp, various plication techniques with or without tunical incision or excision have been proposed, while in the second, various plaque incision or excisional techniques, with associated grafting, have been developed. The major benefit of the tunical shortening, or plication-based procedures, tends to be minimal effect on erectile function compared to tunical lengthening, though penile size/length is by definition reduced. Conversely, tunical lengthening procedures, typically reserved for complex deformities with high degrees of curvature or significant functional impairment, do not typically preserve, or may worsen erectile dysfunction. This occurs via tunical fibrosis with suboptimal emissary vein compression, damage to the cavernosal arteries or tissue, or even damage to the neurovascular bundle[88]. Nevertheless, these options will preserve or potentially improve length.

6.1 | Tunical shortening

The first use of a tunical shortening technique was described by Nesbit in 1965 for the correction of congenital curvature (i.e., penile curvature without a lesional component)[89]. The technique relied on excision of a portion of tunica albuginea opposite the site of maximal curvature, with subsequent transverse closure causing plication and straightening. The technique was then applied to PD[90]. Subsequent modifications to this technique, including longitudinal incision with Heineke–Mikulicz fashion (Yachia) and partial rather than full-thickness excisions have been proposed[91,92]. Nonincisional/excisional techniques utilizing plication alone were first reported by Gholami and Lue, including the famous 16-dot technique[93]. These procedures are generally offered for mild curvatures which are bothersome or functionally limiting. For one, the length loss sustained with progressively greater curvature will become prohibitive, while multiplanar deformities that will not be corrected with one-directional plication will require the address of the lesion itself. In these cases, tunical lengthening procedures are preferred[94].

6.2 | Tunical lengthening

Tunical lengthening procedures, in which the offending plaque is either incised or excised, with subsequent patching of the defect(s) in the tunica albuginea, were initially described in 1950 with the report of plaque excision and fat grafting to the defect[95]. In 1974, a dermal graft was used instead for its greater tensile strength and ability to maintain erection[96]. Since then, numerous materials have been employed for grafting purposes[97]. Grafts fall into four classifications, three of which are still used. Autografts, made of tissue taken from the patient, include dermis, vein, temporalis fascia, tunica vaginalis, and buccal mucosa. Allografts, made of human tissue but from a donor cadaver, include the pericardium (Tutoplast), fascia lata, and dura mater. Xenografts come from animal tissues, and include bovine pericardium, porcine small intestine submucosa, porcine dermis, and equine collagen matrix (Tachosil). Finally, synthetic grafts include Dacron and Gore-Tex, although these have been abandoned in PD surgery due to increased reaction and fibrosis, infection, and poor functional outcomes[98]. No particular graft type has been concretely demonstrated to be superior[99].

Surgical techniques which focus on penile length preservation include incisional, excisional, and extratunical grafting, and may be used with or without a penile prosthesis. We will first discuss those techniques which are used without prostheses. With any incisional or excisional technique, the risk of erectile dysfunction increases from damage to the underlying cavernosal tissue. Therefore, plaque incision or partial excision is

used when able, with full excision reserved for plaques that cause significant destabilizing deformities. The first incisional technique, known as the Lue procedure, was reported by El-Sakka and colleagues and involves making linear, H-shaped, or I-shaped tunical incisions performed at the point of maximum curvature on the concave side of the curvature (opposite from the area of incision/excision in the Nesbit-style procedures). Outcomes did show that while the majority of patients had preserved penile length, a significant number had, or progressed to, reduced length[100]. The Egydio technique was later described, which involved the use of geometric principles to make a circumferential relaxing incision forked at either end, designed to maximize length based on the tethering neurovascular bundle[101]. While length does increase with this technique, the rate of erectile dysfunction is higher compared to the Lue technique[102]. Partial excisional techniques include the sealing technique, in which a partial plaque excision is performed and the resulting tunical defect is closed with a self-adhesive collagen fleece that does not require suture fixation[103].

Extratunical grafting is a third option for special cases in which indent or hourglass deformity creates a space that can be filled by a graft. This technique involves exposure of the tunical layer without any incision into it and does not require mobilization of the neurovascular bundle or urethra[104]. This procedure can correct the indention but will not fix any curvature associated with the deformity.

6.3 | Penile prosthesis implantation and adjunctive procedures

A significant proportion of men with PD do suffer from concomitant erectile dysfunction, with a range of severity. For men with mild erectile dysfunction who are able to sustain good rigidity with medications, the aforementioned tunical shortening or lengthening procedures may still represent good surgical options. Of note, intracavernosal erectile dysfunction treatments are not recommended for these patients as plaques may interfere with appropriate administration[105]. However, for those men with significant erectile dysfunction or those who do not wish to utilize medication, the use of a prosthesis with or without additional adjunctive procedures or techniques is recommended[12].

While the placement of an inflatable prosthesis may in and of itself resolve bothersome curvature, residual curvature may necessitate additional techniques[106]. For those with curvature less than 30°, no additional intervention is needed. For curvature greater than this, manual modeling may be employed. Modeling involves prosthesis inflation followed by forcible bending in the direction opposite the plaque. While it has been shown to have excellent success in resolving residual curvature, surgeons should be aware of about 4% risk of urethral injury[107]. If curvature persists greater than 30°, then a relaxing incision or plication can be employed. If a large (> 2 cm) defect is required, then grafting should be undertaken. Various strategies for grafting include sliding, modified sliding, and multiple slice techniques, in which multiple tunical defects are created and reinforced by a prosthesis, with either grafting or closure of Buck's fascia over the defects[108]. One recently described incisional technique, slices around the point of maximal curvature (SAPOC), attempts to minimize the need for a large graft by making small incisions around, instead of at, the point of maximal curve, with the initial cohort study of 27 patients undergoing this technique as part of IPP implantation showing statistically significant increases in penile length, a functionally straight phallus in all cases, and high patient satisfaction[109]. While fifteen cases did require a graft, this represents a significant decrease as these patients would otherwise have necessitated grafting material due to their severe cases. Minimal complications were reported included one case each of device malfunction requiring revision, infection requiring explant, and intractable pain requiring explant. Comparing SAPOC against grafting in a controlled design will shed further light on acceptable complication rates.

Other techniques that help minimize the need for adjuvant procedures, reduce the risk of urethral injury with modeling, or facilitate prosthesis placement in complex deformity involving address of the lesions prior to implantation. One technique involves passing a cystoscope through a corporotomy and making an incision into the plaque through this instrument[110]. A similar strategy is the “scratch” technique in which a pair of scissors or a scalpel is passed via the corporotomy to abrade the plaque internally[111]. This technique was initially reported as a surgical technique but has been evaluated as part of a combined protocol including postoperative vacuum therapy for a cohort of heterogenous patients with combined erectile dysfunction and PD[112]. The cohort study found improvement in curvature regardless of plaque location as well as high satisfaction low complication rate. The use of a bone saw to incise calcified plaques resistant to other instruments has also been described[113].

7 | FUTURE DIRECTIONS

Despite the significant body of work investigating the etiology, diagnosis, and management for PD, many questions remain unanswered. While surgical options are available for diseases ranging from simple curvature to severe complex deformity, medical options are either ineffective, cost-prohibitive, or limited in their indication. The limited treatment options may expand or find effective roles as the etiology is better understood and

diagnosis of more specific disease subtypes becomes possible.

7.1 | Etiology

As the etiology of Peyronie's is better understood, opportunities for precision therapy may become available. Bioinformatics-based research has shown to be a promising avenue for further work into genetic etiology, leading to further advances in the identification of potential biological mechanisms. For example, one group, building on prior work that identified candidate genes, performed functional enrichment analysis and showed various biological processes including glucose metabolism, carbon metabolism, and inflammatory processes such as cytokine-cytokine receptor interactions and the JAK-STAT signaling pathway may have a modulatory role in the development of PD[114,115]. Additional biological processes have been implicated in PD, along with various molecular agents, and are summarized in Figure 2[116]. These agents, ranging from inflammatory proteins to growth factors that regulate gene expression, have been implicated and may represent opportunities for targeted medical therapy. For instance, inhibition of transforming growth factor-β, which is an action of both tamoxifen and pentoxifylline, may be a viable treatment strategy for the appropriate disease chronicity, despite current evidence showing a lack of benefit to these medications[117].

7.2 | Diagnosis

The ability to more accurately categorize or describe PD, as well as more rigorously determine the disease phase, may improve the effectiveness of existing and developing therapies. One group developed a "PTNM" staging system to better describe disease subtypes, basing disease characteristics on Peyronie's disease component (P: Ca-calcifying, Cl—classical, P—progressive, R—relapsing/remitting, U—undifferentiated), trauma component (T: 0—absent, 1—present), non-PD component (N: C—congenital, M—maturational, U—undifferentiated), and mode (M: 0—stable, 1—active)[118]. Additional, non-PD categorizations included congenital (lifelong), maturational (developed around puberty), and trauma induced. The ability to better

FIGURE 2 Biological pathways and targets for precision therapy. Dark blue figures refer to general biological processes while red figures refer to molecular actors or signaling pathways. FGF, fibroblast growth factor; HIF, hypoxia-inducible factor; IGF, insulin-like growth factor; JAK, Janus kinase; MMP, matrix metalloproteinase; NF-κB, nuclear factor κ-light-chain-enhancer of activated B cells; PDGF, platelet-derived growth factor; ROCK, Rho kinase; STAT, signal transducer and activator of transcription; TGF, transforming growth factor; TIMP, tissue inhibitor of metalloproteinase.

specify disease characteristics may lead to improved outcomes. For example, oral medical therapy has historically been variably effective in the literature, which may be due to significant disease heterogeneity. Certain treatments might be shown to be effective once patients are stratified by disease characteristics.

In a similar vein, imaging represents another opportunity to revolutionize PD diagnosis and classification, assist with treatment planning, and improve the evaluation of posttreatment complications[119]. While currently the use of cross-sectional imaging is not recommended routinely as detection of calcification typically does not offer actionable information above what is garnered on ultrasound, detection of inflammation might assist in the determination of active versus stable disease. Contrast-enhanced magnetic resonance imaging and nuclear scintigraphy have been studied in this context, though the correlation between clinical signs (penile pain) and inflammation on imaging was questionable in various studies[120–123]. More recently, PD was incidentally reported on positron-emission tomography/computed tomography performed for prostate cancer evaluation, consistent with the clinical mechanism of inflammatory uptake of radiotracer[124]. This suggests improvements in imaging protocols across various modalities may facilitate more precise detection of clinically relevant inflammation and therefore improve diagnostic capability.

7.3 | Regenerative therapy

Regenerative treatment options represent a burgeoning field which may allow for a revolution in Peyronie's management. As an inflammatory and fibrotic disease, even surgery does not fully restore the penis to its previous functional capacity. Treatments such as stem cells and PRP are thought to promote wound healing, angiogenesis, and connective tissue repair. The major presumed benefit of these treatments in Peyronie's disease is simultaneous address of both fibrosis as well as erectile function. Stem cells have primarily been studied in animal models, where they have been shown to limit fibrosis as well as improve erectile function[125,126]. Only one study has reported on the use of stem cells in humans, with investigators finding a decrease in curvature[127]. On the other hand, PRP has been extensively utilized already in the fields of orthopedics and dermatology. Studies of PRP in men with PD are inconclusive, though promising; while several studies with participants ranging from 1 (case report) up to 90 patients (prospective cohort trial) are available with generally positive outcomes, the body of evidence is limited by lack of peer review (several unpublished), variations in protocol, lack of randomization or comparison groups, and limited follow up[128].

7.4 | Clinical trials

As of the time of writing, ongoing clinical trials for PD treatments include investigations into new oral agents; regenerative therapies including stem cells, PRP, and nanofat; and combination treatments utilizing shockwave, traction, and injections to maximize the effectiveness of each individual therapy. These are summarized in Table 1. Perhaps these treatments will one day slow, arrest, or reverse disease progression in the acute phase, or enhance recovery after surgery. Novel surgical techniques utilizing combinations of existing operations and procedures continue to be proposed, and new grafting materials and devices continue to undergo experimentation. One surgeon reported on the use of autologous pericapsular tissue for grafting, while another group demonstrated the Rigicon implant used in tandem with collagen fleece penile sealing technique to be quite promising[129,130]. One technique has even been reported for penile girth enhancement via use of the Himplant device[131]. Surgical planning, especially for complex deformities, will benefit from three-dimensional reconstruction technology, which has already proven useful in various fields of surgical reconstruction[132–135].

8 | CONCLUSION

PD is a devastating condition affecting a significant number of men worldwide. Accurate diagnosis relies on the history and physical examination. Current management paradigms rely on symptomatic control in the acute phase, with definitive therapy reserved for stable disease. Many treatment options besides surgery have been evaluated, though few have shown significant effectiveness apart from intralesional treatments. The future direction of PD treatment relies on advances in diagnosis, etiology, and precision therapies. As diagnostic capabilities improve, treatment can be tailored toward active or stable phases. As etiology is better understood, previously used therapies which showed little or no benefit may be applied in a more targeted fashion. As well, genetic or precision treatments will likely emerge, as the various signaling pathways and their derangements or pathologic alterations are more concretely described. Surgical techniques and outcomes will continue to improve, though may one day prove unnecessary as the secret of PD is fully unlocked.

AUTHOR CONTRIBUTIONS

Skyler Howell and Kareim Khalafalla participated in the study conceptualization and methodology. Skyler Howell participated in the investigation and original draft preparation. Skyler Howell, Travis Green, and Kareim Khalafalla participated in review and editing and visualization. Kareim Khalafalla provided supervision and

TABLE 1 Active clinical trials in Peyronie's disease.

Title	ClinicalTrials.gov ID	Intervention	Status	Phase	Enrollment group	Outcome measure	Location
A randomized, double-blind, placebo-controlled, crossover trial on the safety and efficacy of autologous PRP for the treatment of Peyronie's disease	NCT04512287	Intralesional PRP	Recruiting	II	Active, stable	Curvature, bother, adverse events	United States
Comparison of CCH to Surgery for the management of Peyronie's disease: A randomized trial	NCT04786106	CCH (Xiaflex), plication, I&G, RestoreX	Not yet recruiting	IV	Any	Satisfaction, bother, erectile function, curvature, length, adverse events	United States
Concurrent LiSWT on clinical outcomes with CCH in Peyronie's disease: A randomized controlled trial	NCT06065436	CCH (Xiaflex) with/without LiSWT	Recruiting	N/A	Stable	Bother, erectile function, rate of surgical straightening	United States
Efficacy of a novel CCH protocol for Peyronie's disease among prior nonresponders: A randomized, controlled, single-blinded study	NCT05108558	CCH (Xiaflex)	Recruiting	IV	Prior CCH nonresponders	Curvature, bother, erectile function scores	United States
Efficacy of a step-wise protocol in optimizing CCH outcomes in men with Peyronie's disease	NCT06649539	CCH (Xiaflex), sildenafil (Viagra), RestoreX	Recruiting	IV	Prior CCH nonresponders	Curvature, length, adverse events, satisfaction	United States
Intralesional injection of hyaluronic acid compared with verapamil in Peyronie's disease: A prospective randomized clinical trial	NCT05855070	Intralesional hyaluronic acid, intralesional verapamil	Not yet recruiting	N/A	Active	Curvature, plaque size	Egypt
Nonablative radiofrequency and LiSWT in fibrotic plaque in men with Peyronie's disease: Case series	NCT06303661	Monopolar nonablative radiofrequency electromagnetic LiSWT	Recruiting	N/A	Active, stable	Erectile function, pain, mental health	Brazil
Pilot study to evaluate the safety and efficacy of 3.2% high (HHA) and low (LHA) molecular weight hyaluronic acid sodium salt [32 mg (HHA) + 32 mg (LHA)/2 mL] for intralesional penile injection in Peyronie's disease	NCT05871177	Intralesional hyaluronic acid	Not yet recruiting	N/A	Active	Adverse events, subjective improvement, curvature, length	Italy
Safety and efficacy of CCH after prior intralesional PRP for Peyronie's disease	NCT05777031	CCH (Xiaflex)	Recruiting	IV	Stable	Safety, adverse events	United States
Safety of cultured allogeneic adult umbilical cord-derived mesenchymal stem cells for the treatment of Peyronie's disease, erectile dysfunction, and interstitial cystitis	NCT05147779	Intralesional treatment with stem cells (AlloRx)	Recruiting	I	Any	Safety, adverse events	Antigua and Barbuda

Note: When determining enrollment groups, "acute" and "active" disease are considered equivalent terms, along with "chronic" and "stable." The requirement for the presence of pain similarly was interpreted as active disease.

Abbreviations: CCH, collagenase *Clostridium histolyticum*; I&G, incision and grafting; LiSWT, low-intensity shockwave therapy; PRP, platelet-rich plasma.

project administration. All authors have read and agreed to the published version of the manuscript.

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CONFLICT OF INTEREST STATEMENT

Kareim Khalafalla is one of Editorial Board Members of *UroPrecison*. He was excluded from the peer-review process and all editorial decisions related to the acceptance and publication of this article. Peer-review was handled independently by the other editors to minimize bias. The remaining authors declare no conflict of interest.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author, Kareim Khalafalla, upon reasonable request.

ETHICS STATEMENT

Neither ethics approval nor patient consent was required for this narrative review using publically available records.

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