

A narrative review of pathophysiology and therapeutic concepts in Peyronie's disease

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Peyronie's disease (PD) is an acquired connective tissue disorder characterized by fibrotic plaque formation within the tunica albuginea that can significantly impair sexual function and quality of life. Despite being described over 280 years ago, its pathophysiology remains incompletely understood, contributing to variable and often limited efficacy of nonsurgical therapies. PD is a multifactorial condition resulting from the interaction of mechanical injury, metabolic comorbidities, and individual susceptibility, with genetic contributions supported by familial clustering, associations with fibroproliferative disorders, and emerging cytogenetic and epigenetic data. At the molecular level, PD reflects dysregulated wound healing characterized by persistent myofibroblast activation, impaired

extracellular matrix turnover, and sustained transforming growth factor- β -mediated profibrotic signaling. These insights support a phase-based clinical framework, with active-phase focused on pain control, penile traction, and intralesional injections, and surgical intervention reserved for stable-phase disease with functionally significant deformity. Among nonsurgical options, collagenase clostridium histolyticum has the strongest evidence for curvature reduction, while other emerging therapies remain investigational. Surgery remains the most reliable option for severe PD, with evolving techniques aimed at correcting complex deformities while preserving penile length and girth. The purpose of this narrative review is to provide a unified framework for PD assessment and treatment by integrating current evidence on pathophysiology, contemporary non-surgical and surgical management, and patient selection strategies.

Key Words: Peyronie's disease, pathophysiology, collagenase, intralesional therapy, surgical innovations

Introduction

Peyronie's disease (PD) is an acquired, progressive condition characterized by aberrant fibrotic plaque formation within the tunica albuginea.¹ Unlike normal wound healing, where fibrosis sustained after injury undergoes appropriate remodeling, PD plaques fail to remodel, resulting in a persistent, inelastic scar.² This abnormal fibrosis impairs normal penile expansion during erections and may lead to penile pain, curvature, shortening, loss of girth, and erectile dysfunction (ED).¹ Although PD was first described over 280 years ago, the pathophysiology of PD remains incompletely understood, reflected in the paucity of effective non-surgical therapies.^{3,4}

The prevalence of PD is approximately 9% in the general population, with reported rates approaching 20% among men with both diabetes and ED.⁴⁻⁷ However, the true prevalence of PD is likely underestimated, as affected men may avoid seeking medical attention due to stigma and embarrassment.⁵ Spontaneous improvement of PD is uncommon, and up to 48% of men experience worsening penile deformity and curvature within 6 to 18 months of symptom onset.^{8,9} Although PD is not associated with life-threatening sequelae, its impact on sexual function, body image, and intimate relationships can impair quality of life.^{10,11} The objective of this narrative review is to synthesize current evidence on PD pathophysiology, integrate these insights into a critical evaluation of contemporary nonsurgical and surgical treatment strategies, and provide a clinical framework that supports individualized, patient-centered care.

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Data Sources and Search Strategies

This narrative review provides an overview of PD, focusing on molecular mechanisms of fibrosis and contemporary non-surgical and surgical management strategies. A literature search was conducted using PubMed to identify English-language, peer-reviewed studies published through January 2026. Search terms included "Peyronie's disease," "pathophysiology," "TGF- β ," "myofibroblasts," "epigenetics," "collagenase," "intralesional therapy," "traction therapy," "extracorporeal shock wave therapy," "erectile dysfunction," "penile curvature," "plication," "plaque incision/excision and grafting," "penile prosthesis," and "surgical innovation."

Eligible studies included adult men (>18 years) with clinically diagnosed PD. Animal studies were included to inform pathophysiologic insights, while studies involving congenital penile curvature or pediatric populations were excluded. Case reports, editorials, and letters to editors were also excluded. Prospective studies and randomized controlled trials (RCTs) were prioritized; however, given the limited high-level evidence pertaining to PD, retrospective series were also included. Approximately 60% of cited references were published within the past five years to reflect current evidence, and foundational studies were incorporated where appropriate. Three authors contributed to the study selection process, including two senior reviewers (RB and PB).

Data evaluated from clinical studies included study design, PD phase (active vs. stable), intervention type, and clinical outcomes, specifically penile curvature, pain, sexual function, and treatment-related adverse events. Given the heterogeneity across studies, findings were synthesized narratively. The organizational framework of this review was informed by guidelines from the American Urological Association (AUA), Canadian Urological Association (CUA), and European Association of Urology (EAU).

Findings

Risk factors

Environmental exposures and genetic predisposition contribute to PD development, making it difficult to predict who will be affected and with what degree of disease severity. PD commonly affects men in their fifth decade of life, though cases in younger men have also been reported.¹² The age-associated increase in PD prevalence is likely multifactorial and may reflect

the higher burden of metabolic and vascular comorbidities seen with advancing age. Among these, the association between PD and diabetes has been frequently examined, with reported diabetes prevalence among men with PD ranges from 13%–50%.¹³ Men with long-standing diabetes appear to be at increased risk for PD, with those having diabetes for more than 10 years up to six times more likely to develop PD than those with shorter diabetes duration.^{6,13} Chronic hyperglycemia has been proposed to contribute to PD-associated fibrosis by reducing tunical elasticity and impairing normal wound healing.¹³

Diabetes is also a risk factor for ED, which can coexist with PD. While 20% of men report ED preceding PD onset, 15% report ED developing after PD diagnosis. In one cohort, 44% of men with PD had concurrent ED.^{14,15} These findings support a bidirectional relationship: impaired erections may increase susceptibility to mechanical penile shaft injury during sexual activity, while fibrotic plaque formation may limit uniform tunical expansion, leading to inadequate subtunical venous compression and contributing to venogenic ED.^{14,16}

Penile trauma is associated with PD, with repetitive microtrauma during sexual activity commonly considered a key precipitating factor.^{12,17,18} Acute penile trauma, such as penile fracture, has also been implicated, although earlier studies showed no clear association.^{19,20} More recent data suggest that men >45 years were more likely to develop PD within five years of penile fracture, whereas prompt surgical restoration of tunical integrity may mitigate PD risk.²¹ These findings suggest that genetic susceptibility may modulate response to injury, potentially explaining why some develop PD after minor repetitive trauma while others do not despite more severe injury.

Radical prostatectomy has also been proposed as a risk factor, with PD reported in up to 15.9% of men within three years following prostatectomy.²² However, the mechanism underlying this association remains unclear. Reduced penile oxygenation with associated fibrotic and calcific changes has been described at six months post-prostatectomy, supporting a hypothesized role for hypoxia-associated fibrosis; however, penile curvature was not reported.²³ Larger studies with longer follow-up are needed to determine whether early post-prostatectomy fibrotic changes progress to clinically significant PD and to clarify the relationship between penile oxygenation and plaque formation.

Smoking has been associated with PD, with higher prevalence observed with longer smoking duration and greater daily cigarette consumption.^{24–26} The proposed underlying mechanism may include

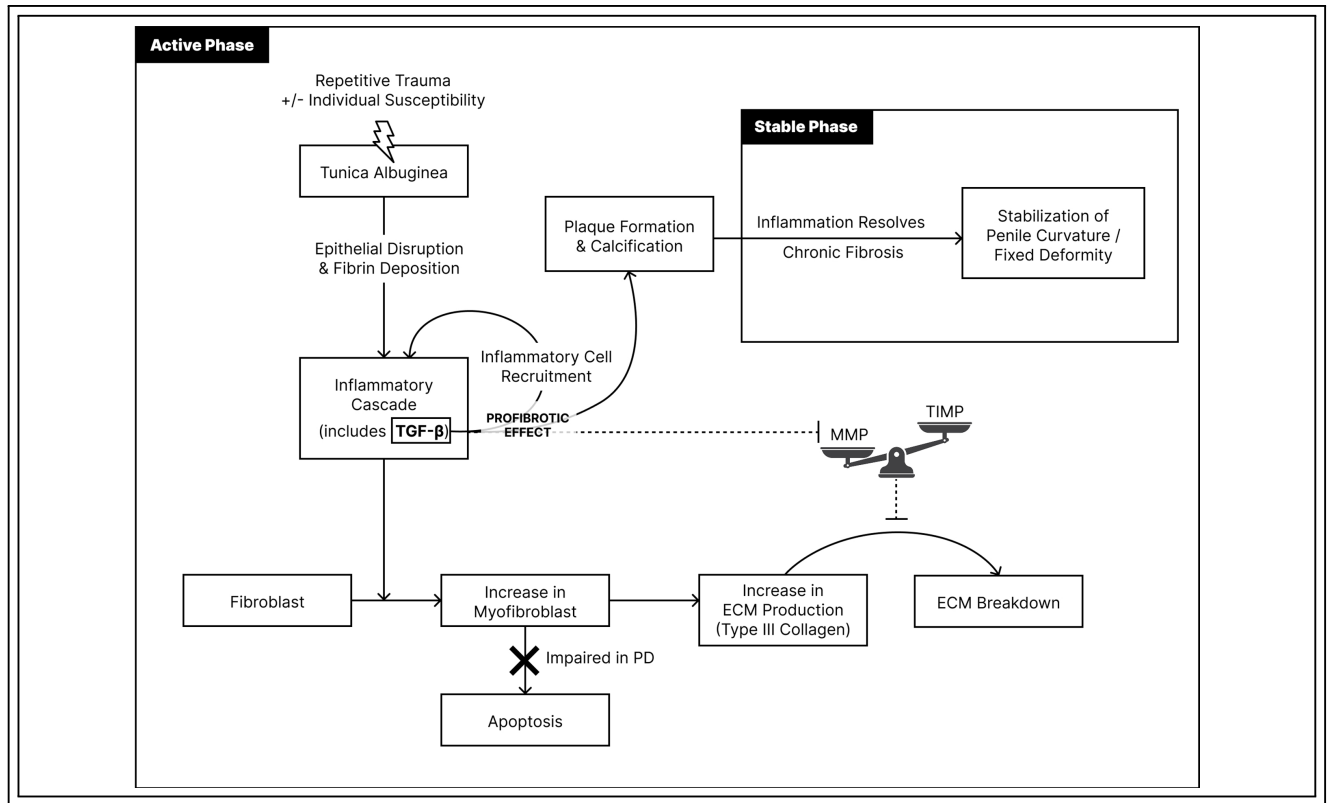


FIGURE 1. A simplified schematic of the pathophysiology of Peyronie's disease (PD). **TGF-β:** Transforming Growth Factor-Beta; **ECM:** Extracellular Matrix; **MMP:** Matrix Metalloproteinase; **TIMP:** Tissue Inhibitor of Metalloproteinases

smoking-related epigenetic changes and increased oxidative stress promoting profibrotic signaling.²⁷ Hypogonadism and alcohol consumption have also been proposed as risk factors, though supporting evidence remains limited.²⁸ Overall, these observations highlight the multifactorial nature of PD, arising from the interplay of comorbid conditions, mechanical injury, and individual susceptibility.

Pathogenesis

Mechanical injury to the erect penis has been proposed to cause delamination of the tunica albuginea, triggering a localized inflammatory cascade characterized by fibrin deposition, cytokine upregulation, and altered collagen accumulation.^{1,29,30} However, growing evidence, as discussed in the following section, suggests that PD does not result from one mechanism, but rather reflect the convergence of multiple molecular pathways involved in inflammation, fibrosis, and extracellular matrix (ECM) remodeling, influenced by genetic susceptibility.^{2,31} A schematic of the pathophysiology is shown in Figure 1.

Genetic susceptibility

Multiple studies support a heritable component contributing to PD susceptibility. Frequent co-occurrence with fibroproliferative disorders, such as Dupuytren's disease (DD), provides some of the earliest support for a genetic contribution to PD. In 1982, Bias et al.³² conducted a pedigree analysis of three families affected by both PD and DD, identifying an autosomal dominant inheritance pattern with incomplete penetrance for PD. Subsequent studies further reinforced the association between PD and DD.³³ In a cohort of 415 men with PD, approximately 22% had concomitant DD and 6.7% reported a family history of DD.³⁴ Notably, reported rates of family history of PD range from 1.4% to 4%, though these likely underestimate true prevalence due to underreporting.^{34,35} DD has also been reported to occur bilaterally more frequently in PD patients than in those without PD (86% vs. 51%), supporting a shared systemic predisposition to fibrotic disease and potentially overlapping genetic pathways.^{33,34,36}

Additional support for genetic predisposition comes from a population-based study in Utah that demonstrated significant familial clustering of PD. Elevated relative risks were observed among first-degree relatives and among more distant relatives, a finding not previously reported.³⁷ Nearly 75% of men with PD belonged to pedigrees with a statistically significant excess of PD, indicating that most affected individuals came from families in which PD occurred more frequently than expected by chance alone.³⁷ Although relative risks for DD were increased among PD probands, they were not elevated among their relatives, suggesting that while PD and DD share overlapping features, their patterns of familial aggregation may differ.³⁷

Large genome-wide association studies (GWAS) specific to PD remain limited.³⁸ A commonly cited study by Dolmans et al.³⁹ examined whether previously identified GWAS susceptibility loci for DD were also associated with PD. Of the nine DD-associated loci evaluated, only WNT2 on chromosome 7 showed an association with PD.³⁹ In a separate study, whole-genome sequencing (WGS) in three nonfamilial men with PD and DD identified a ALMS1 mutation, a gene involved in TGF- β signaling and fibrotic pathways.⁴⁰ Using WGS, Li et al.⁴¹ further identified a 43% overlap in deleterious genetic variants between familial and sporadic PD, and observed PD-associated variants in lipid metabolism pathways, highlighting possible therapeutic targets. Collectively, this suggests that genetic susceptibility to PD may involve multiple pathways that partially overlap with those implicated in DD and lipid metabolism.^{38–41}

Cytogenetic studies have reported chromosomal abnormalities involving chromosomes 7, 8, 17, 18, X, and Y in affected individuals.⁴² Notably, aneuploidies involving one or more chromosomes have also been identified in non-plaque tunica albuginea cells following serial cell culture passage, suggesting chromosomal instability and a potential “field effect” extending beyond visibly diseased tissue.⁴² Studies examining plaque and non-plaque tissue from the same individuals have demonstrated upregulation of profibrotic pathways and downregulation of antifibrotic pathways.⁴³ Although no direct gene sequencing was performed, the use of tissue derived from the same individuals makes fixed germline differences less likely, suggesting instead altered gene expression within specific cell populations.⁴³

Epigenetic regulation has also emerged as a plausible contributor to PD susceptibility.⁴⁴ A pilot study comparing non-plaque tunica tissue from men with ED alone to those with ED and PD identified 26 differentially methylated regions in the group with

PD. This suggests that epigenetic alterations extend beyond the plaque, supporting a more diffuse predisposition rather than a purely localized process.⁴⁴

Collectively, these findings support a model in which inherited genetic variants and epigenetic regulation interact to influence individual susceptibility to PD. No identified genetic variant has reached clinical actionability, and routine genetic testing is not currently warranted. The association of WNT2 and the recurrent implication of TGF- β signaling across multiple genetic models suggest these pathways merit further investigation as potential therapeutic targets, though considerable work remains before such strategies could be considered for clinical application. Epigenetic observations suggest that molecular changes extend beyond the visible plaque, with potential implications for biomarker development. Incomplete genetic overlap with DD and distinct familial patterns further support that PD is likely biologically heterogeneous. Whether clinically meaningful subtypes exist and carry therapeutic relevance remains uncertain, but their validation could enable more precise, individualized treatment strategies guided by disease phase, severity, and molecular profile.

Molecular pathogenesis

Under normal conditions, tissue injury initiates a tightly regulated wound-healing response characterized by transient activation of an inflammatory cascade. Central to this process is transforming growth factor- β (TGF- β), which promotes fibroblasts differentiation into myofibroblasts responsible for ECM production and wound contraction.⁴⁵ Effective tissue repair requires timely resolution of myofibroblast activity through coordinated deactivation, apoptosis, cellular reprogramming, and immune-mediated clearance.⁴⁵

Following wound healing, connective tissue homeostasis is maintained through dynamic ECM turnover regulated by a balance between matrix metalloproteinases (MMPs), which degrade ECM components, and tissue inhibitors of metalloproteinases (TIMPs), which restrain excessive matrix breakdown.³¹ This balance allows appropriate restoration of normal tissue architecture.³¹ However, in fibrotic disease, myofibroblast activation becomes sustained through persistent growth-factor signaling and metabolic reprogramming.^{31,45} Concomitantly, an increase in TIMP further reduces ECM degradation, resulting in progressive accumulation of matrix proteins.^{31,45}

In PD, myofibroblast persistence appears to be driven by impaired apoptosis, excessive proliferation, and heightened responsiveness to profibrotic mediators.² Repetitive trauma to the tunica albuginea is thought to result in endothelial disruption and fibrin deposition that is inadequately cleared, promoting sustained fibroblast activation, inflammatory cell recruitment, and progressive fibrosis characterized by excessive collagen accumulation, with a relative predominance of type III collagen.^{1,30}

TGF- β has emerged as a key regulator linking inflammation, myofibroblast persistence, and pathologic ECM remodeling. Sustained TGF- β signaling contributes to a fibrotic response that fails to appropriately resolve, with evidence suggesting that activation beyond approximately 36 h may induce irreversible fibroblast-to-myofibroblast differentiation and drive persistent transcriptional reprogramming through altered MAPK-Hedgehog pathways.^{31,46,47} Elevated TGF- β expression within PD plaques further supports its role in disease pathogenesis.³¹ Through canonical SMAD-dependent and non-canonical pathways, TGF- β promotes profibrotic gene expression and inflammatory cell recruitment.^{2,31} TGF- β also disrupts ECM turnover by suppressing fibrinolysis and inhibiting MMP activity, shifting the balance toward collagen accumulation.² Consistent with this, animal models and human plaque samples demonstrate a pattern favoring increased TIMP expression.³¹

Repeated administration of recombinant TGF- β 1 via adenoviral vectors in animal models produced inflammatory cell trapping, fibrotic scarring, penile curvature, and plaque calcification. Control adenoviral-LacZ vectors confirmed these changes were TGF- β -specific.^{2,48} These findings suggest that PD is driven less by initial injury and more by failure to appropriately terminate TGF- β -mediated profibrotic signaling.

Several additional inflammatory mediators have also been examined in PD, though findings are generally less consistent. Interleukin-6 (IL-6) has been implicated in fibrogenesis by regulating fibroblast proliferation and promoting ECM protein production.³¹ However, reported IL-6 levels in PD are inconsistent across studies, likely reflecting differences in disease phase at time of sampling.^{31,49,50} IL-1, released by macrophages at sites of injury, promotes fibroblasts recruitment and may suppress MMP production, though direct clinical correlations with PD severity remain limited.^{2,31}

Tumor necrosis factor- α (TNF- α) has been linked to myofibroblast proliferation and collagen production.² Anti-TNF therapies in early DD reduced nodule

hardness and size, albeit without clear functional benefit.⁵¹ In PD, plaque tissue studies of TNF- α yielded mixed results, likely influenced by inclusion of both active- and stable-phase disease.^{31,50} Growth factors also modulate fibrotic responses. Platelet-derived growth factor (PDGF) promotes fibroblast proliferation, chemotaxis, collagen production, and TIMP expression, with increased expression reported in PD tissue.^{2,31} In contrast, fibroblast growth factor (FGF) appears to exert pro- or antifibrotic effects depending on tissue type, with an unclear role in PD.³¹

Hypoxia-inducible factor (HIF) signaling has also been proposed as a contributor.³¹ Local injury may reduce perfusion, activating hypoxia-responsive tissue repair pathways, that, when sustained, may promote profibrotic remodeling.⁵² Consistent with this, increased hypoxia-associated gene expression has been observed in PD tissue, and HIF-1 α has been reported to regulate TIMP transcription, possibly linking hypoxia to altered ECM turnover.^{31,52} Clinical observations of early fibrotic changes following radical prostatectomy further support a potential role for hypoxia-associated fibrosis in PD pathogenesis.²³

Finally, the Wnt/ β -catenin pathway, implicated broadly in fibrotic disease, has also been investigated, with some analyses reporting increased Wnt4 expression and β -catenin accumulation in PD plaque tissue. However, its functional role remains incompletely defined.^{31,39,53}

These pathways highlight the close relationship between inflammatory and fibrotic mechanisms in PD. Clinically, PD progresses from an active-phase (typically 6–18 months) marked by penile pain, evolving plaque, and curvature changes to a stable-phase defined by plaque maturation and >6 months of curvature stability, with spontaneous improvement occurring in a minority of patients.^{1,29} Pain with erection alone should not define disease activity, as it may reflect torque-related pain from mechanical strain rather than disease progression. This phase-based framework has therapeutic implication, as anti-inflammatory strategies alone are less likely to be effective once fibrosis is established, limiting opportunities for biologic modulation to early disease.^{46,47} Although targeting TGF- β signaling, including selective estrogen receptor modulators, has demonstrated antifibrotic effects in preclinical models and underscore the importance of disease timing, these findings have not translated into consistent clinical benefit and are not recommended as disease-modifying therapies.^{1,31,46} Delayed patient presentation further constrains the feasibility and effectiveness of early intervention.

Non-surgical treatment

An improved understanding of the molecular and phase-dependent biology of PD has informed current management strategies and the development of targeted therapies. Management is individualized according to deformity severity, erectile function (EF), and patient goals, with shared decision-making vital for setting realistic expectations. Patients should be reassured that, in the absence of pain or difficulty with penetrative intercourse, treatment is often unnecessary, as PD is not life-threatening. This section reviews non-surgical treatment options (see Table 1).

Oral therapy

The use of oral therapies without strong supporting evidence may delay initiation of more effective interventions. Penile pain is a hallmark feature of active-phase PD and should be managed initially with nonsteroidal anti-inflammatory drugs (NSAIDs) for symptomatic relief—a guideline-supported recommendation across American Urologic Association (AUA), Canadian Urological Association (CUA), and European Association of Urology (EAU).^{1,29,54}

Phosphodiesterase-5 inhibitors (PDE5i) have been evaluated for a potential antifibrotic role in early PD. Sustained nitric oxide and cyclic guanosine monophosphate (cGMP) signaling may attenuate profibrotic mediator expression, including TGF- β 1, inhibit fibroblast-to-myofibroblast differentiation, and promote myofibroblast apoptosis.^{46,55} In one observational retrospective study, daily tadalafil 5 mg during the active-phase was associated with reduced rates of curvature progression and improved symptoms.⁵⁵ These effects appear to be time-dependent, with PDE5i potentially preventing but not reversing myofibroblast transformation, supporting their use primarily in early disease.⁴⁶ The EAU includes PDE5i as an option for pain control during the active-phase; however, the AUA and CUA do not formally recommend their routine use, reflecting the absence of high-quality randomized evidence.^{1,29,54}

Pentoxifylline has been proposed as an oral antifibrotic agent based on its ability to inhibit TGF- β -mediated inflammation, reduce collagen deposition, and act as a nonselective phosphodiesterase inhibitor.⁵⁶ However, clinical data supporting its efficacy remain inconsistent, and further high-quality studies are needed to clarify its therapeutic role.^{56,57} Evidence supporting potassium para-aminobenzoate, colchicine, and coenzyme Q10, is similarly limited.⁵⁶ While the CUA suggests these agents may be considered selectively, the AUA makes no recommendation due to insufficient evidence, and the EAU advises against their use.^{1,29,54}

Finally, the AUA, CUA, and EAU agree that evidence is insufficient to support tamoxifen, vitamin E, procarbazine, and omega-3 fatty acids.^{1,29,54} The limited evidence base reflects both the complex biology of PD and methodological limitations of existing studies, including small sample sizes, lack of randomization, inconsistent disease-phase definitions, and heterogeneity in treatment protocols and outcome measures.^{56,58}

Topical therapy

Current guidelines cite insufficient evidence to support topical therapies for PD, and these approaches remain investigational.^{1,29,54,56} One agent is H-100 gel, a topical formulation combining nicardipine and superoxide dismutase in an emu oil base. Nicardipine may inhibit collagen production, superoxide dismutase reduces reactive oxygen species associated with inflammation, and emu oil may enhance transdermal delivery.⁵⁹ An industry-sponsored pilot study with a very small sample size ($n = 3$) demonstrated tunical penetration of nicardipine in both active- and stable-phase PD, providing very preliminary evidence that topical H-100 gel might reach target tissue.⁵⁹ While these results are of interest, the evidence base is currently insufficient to support clinical use outside of a trial setting, and larger studies establishing optimal dosing and clinical efficacy are required.

Low-intensity extracorporeal shock wave therapy (Li-ESWT)

Li-ESWT is a guideline-endorsed option for penile pain during the active-phase.^{1,29,54} However, evidence for curvature improvement remains limited and not a supported indication. In a 10-year retrospective study of men with active-phase PD—one of the largest long-term follow-up cohorts available for this modality—Li-ESWT was associated with pain improvement as early as three months, suggesting accelerated pain resolution relative to the natural history of PD.⁶⁰ However, curvature did not improve and progressed at three and twelve months.⁶⁰ Patient satisfaction remained high, likely reflecting improvements in pain-related quality of life.⁶⁰

Mechanical therapies

Penile traction therapy (PTT) has been evaluated as noninvasive monotherapy or adjunctive treatment for PD. Prolonged mechanical tension is thought to promote collagen remodeling, supported by *in vitro* data demonstrating upregulation of MMPs involved in collagen degradation.⁶¹ Benefits are supported by two RCTs, representing among the higher-quality of evidence available.

Moncada et al.⁶² reported that use of the Penimaster PRO for 3–8 h daily in men with stable, unidirectional curvature $\geq 45^\circ$ was associated with increased SPL (+1.8 cm) and curvature reduction (-31.2°), demonstrating a dose-dependent effect. Adverse effects were mild and transient, including local discomfort, glans numbness or edema, and pain.⁶² Ziegelmann et al.⁶³ evaluated the RestoreX device in men with PD across all disease phases and deformity types, and found that 30–90 min of daily use over three months resulted in significant improvements in SPL (+1.5 cm) and curvature (-11.7°), with similar tolerability.⁶³ Continued therapy for an additional three months led to further SPL gains of 0.6–0.8 cm without additional curvature improvement, while control patients who crossed over to traction achieved comparable benefits to those observed in the initial 0–3-month treatment period.⁶⁴ These RCT-level findings support PTT as a noninvasive option that may improve penile length and reduce curvature.

Intralesional therapies

Collagenase clostridium histolyticum

Intralesional injection therapy is an option for patients with persistent symptoms despite conservative management who wish to avoid or are not candidates for surgery. Collagenase clostridium histolyticum (CCH), approved by the U.S. Food and Drug Administration in 2013, is among the most well-studied nonsurgical interventions for PD, with efficacy established in phase III RCTs (IMPRESS trials). CCH degrades plaque collagen and, in stable-phase PD without significant plaque calcification or ventral curvature, was associated with greater curvature improvement than placebo ($\sim 17^\circ$ vs. 9°) and reduced symptom bother.^{5,65} Common adverse effects included bruising or hematoma, pain, and swelling, with rare corporal rupture reported.⁶⁵

Subsequent studies, largely prospective cohorts, has focused on refining patient selection for CCH to optimize outcomes. Greater baseline curvature, hourglass or indentation deformity, concurrent PTT, higher patient motivation, and clinical signs of plaque disruption during treatment (e.g., popping sensation, rapid detumescence) have been associated with greater curvature improvement.⁶⁶ Non-lateral curvatures demonstrated greater response, and adjunctive PTT was associated with the largest improvements, highlighting the importance of patient engagement in maximizing CCH efficacy.⁶⁶ In a separate prospective study of men with stable dorsal or lateral curvature undergoing self-penile modeling, PDE5i with CCH was associated with greater curvature reduction

compared with CCH alone; however, these findings require further validation given the small sample size and nonrandomized design.⁶⁷

Post-IMPRESS studies have also expanded evidence regarding CCH use in ventral curvatures. Comparable efficacy and safety between ventral and nonventral deformities has been reported, with greater relative curvature reduction in ventral deformities (44.7% vs. 33.6%) and no urethral injuries.⁶⁸ Additional data suggest that patients with limited initial response to CCH may still benefit from completing all four treatment cycles, with incremental curvature improvement observed across successive cycles.⁶⁹ Emerging retrospective data from a multicenter study also suggests that CCH may provide comparable curvature reduction in active- and stable-phase PD, although further validation is needed.⁷⁰

Cost and access remain key limitations. From a healthcare system standpoint, CCH is among the most expensive PD treatments, with estimated costs of \$6000–9000 per cycle and up to \$15,000–20,000 for a full treatment, compared with approximately \$2000–5000 for surgery.⁷¹ Patient out-of-pocket costs are generally comparable across modalities, ranging from \$300–800 for CCH and \$140–500 for surgery.⁷¹ Access is also limited in some regions, including Europe and Canada, where CCH has been withdrawn largely for economic reasons.^{29,54}

Calcium channel blockers

Intralesional calcium channel blockers, including verapamil and nifedipine, have been investigated based on proposed anti-fibroblast and procollagenase activity.⁵⁶ However, clinical efficacy data are inconsistent. Randomized studies have generally not demonstrated meaningful curvature improvements, although one nifedipine study reported plaque size reduction.⁷² Reflecting this limited evidence, guideline recommendations vary. The CUA considers intralesional verapamil an option in selected patients. The AUA states it may be offered, citing weak efficacy data but a favorable safety profile, with adverse effects typically limited to dizziness and local bruising and pain.^{1,54} The EAU recommends against its use due to lack of demonstrated clinical benefit.²⁹ Overall, further high-quality studies are needed to clarify their role in PD management.

Hyaluronic acid

Intralesional hyaluronic acid (HA) remains investigational and is not recommended outside of clinical trials by current guidelines.^{1,29,54} Its anti-inflammatory and antioxidative effects may be relevant in active-phase PD.^{54,72,73} In a prospective comparative study of men with active-phase PD, weekly intralesional

HA injections were associated with greater improvements in curvature, EF, and pain compared with verapamil.⁷³ While these finds are of interest, ventral curvatures and complex deformities were excluded, and the current evidence base is insufficient to support routine use. Further studies are needed to define its role.

Platelet-rich plasma

Platelet-rich plasma (PRP) has generated interest as a minimally invasive treatment option for PD but remains investigational with no guideline support for routine clinical use. Proposed mechanisms include immunomodulatory reduction of proinflammatory cytokine signaling, angiogenesis that supports nutrient delivery, serotonin-mediated pathways that may contribute to analgesia, and PDGF-mediated tissue homeostasis.⁷⁴

Clinical data remains limited. A randomized crossover study found that at six months, two 0.5-mL PRP injections were associated with a statistically significant curvature reduction in men initially treated with PRP, whereas improvement after crossover from placebo did not reach statis-

tical significance.⁷⁵ Results should be interpreted cautiously given the small, heterogenous cohort that included both active- and stable-phase PD. A separate uncontrolled study treated men with stable PD using a higher-dose PRP regimen consisting of three 6-mL PRP injections combined with vacuum-assisted penile remodeling between injections.⁷⁶ Improvements in curvature, plaque size, and symptom bother were observed without any reported adverse events.⁷⁶ Trimodal therapy incorporating PRP, daily PDE5i, and vacuum-assisted penile stretching have also shown modest short-term curvature improvement. Interpretation of both studies is limited by the absence of controls, short follow up, and heterogenous treatment protocols.⁷⁷ Before routine clinical adoption, larger randomized studies are needed to further establish the durability and efficacy of PRP.^{76,77}

Potential reasons for limited disease modification with nonsurgical therapies

The limited disease-modifying efficacy of nonsurgical therapies in PD likely reflects several intersecting

TABLE 1. Summary of non-surgical treatment options

Therapy	Mechanism	Indication	Advantages	Limitations
Oral therapies				
NSAIDs	Anti-inflammatory, analgesic	Active-phase with penile pain ^{1,29,54}	Symptomatic pain relief; widely available	No effect on curvature or plaque ^{1,29,54}
PDE5i	↓ TGF-β1; inhibit myofibroblast differentiation; ↑ myofibroblast apoptosis ^{46,55}	Active-phase; possible prevention of curvature progression ^{29,55}	Familiar safety profile; possible benefit in early disease ⁴⁶	Timing-dependent; no reversal of established fibrosis ⁴⁶
Pentoxifylline	Inhibits TGF-β-mediated inflammation; ↓ collagen deposition ⁵⁶	Investigational use in early PD; currently, not recommended ^{1,29}	Oral; antifibrotic rationale ⁵⁶	Inconsistent efficacy; limited high-quality trials ^{56,57}
Topical therapies				
H-100 gel	Antifibrotic and antioxidant effects via transdermal delivery ⁵⁹	Investigational use ^{1,29,54}	Preliminary evidence of tunical delivery of nicardipine in both active- and stable-phase ⁵⁹	Limited data; efficacy and optimal dosing not established ^{1,29,54,59}
Energy and mechanical based therapies				
Li-ESWT	Delivery of low-intensity acoustic energy	Active-phase PD with penile pain ^{1,29,54}	Improves penile pain; high patient satisfaction ⁶⁰	Does not improve or prevent curvature progression ⁶⁰
PTT	Mechanical tension promotes collagen remodeling and upregulation MMP ⁶¹	Active- and stable-phase PD monotherapy or adjunct therapy ⁶³	Noninvasive; SPL and curvature improvements ^{62,63}	Requires adherence; mild, transient adverse effects ^{62,63}
Intralesional therapies				
CCH	Enzymatic degradation of collagen within plaque ⁶⁵	Stable PD with palpable plaque; curvature 30°–90° ^{1,29,54}	Greater curvature improvement; reduces symptom bother; can consider PDE5i addition ^{65,67}	Rare corporal rupture; multiple treatment cycles; limited evidence in active-phase ⁶⁵

(Continued)

TABLE 1. Continued

Therapy	Mechanism	Indication	Advantages	Limitations
Calcium channel blockers	Anti-fibroblast and pro-collagenase activity ⁵⁶	May be considered in selected patients with no alternative options ¹	Favorable safety profile ^{1,54}	Inconsistent efficacy; variable guideline support ^{1,29,54}
Hyaluronic acid	Anti-inflammatory, antioxidative ^{54,72,73}	Investigational in active-phase PD ^{29,73}	Favorable safety profile; pain, curvature, EF improvement ⁷³	Limited data; not recommended by guidelines ^{1,29,54}
PRP	Proposed immunomodulatory and pro-angiogenic effects ⁷⁴	Investigational; clinical trials	Minimally invasive; no reported adverse events ⁷⁶	Limited evidence; inconsistent efficacy ^{76,77}

Note. **NSAIDs**: Nonsteroidal anti-inflammatory drugs; **PDE5i**: Phosphodiesterase type 5 inhibitors; **TGF-β**: Transforming growth factor beta; **PD**: Peyronie’s disease; **EAU**: European Association of Urology; **Li-ESWT**: Low-intensity extracorporeal shock wave therapy; **PTT**: Penile traction therapy; **MMP**: Matrix metalloproteinase; **SPL**: Stretched penile length; **CCH**: Collagenase clostridium histolyticum; **PRP**: Platelet-rich plasma; ↑: increase; ↓: decrease.

biological and clinical factors. As plaques mature, particularly with calcification, the collagen-dense scar becomes less clinically responsive to pharmacologic remodeling with currently approved agents such as CCH, and is associated with higher rates of surgical intervention compared with non-calcified plaques.⁷⁸ Additionally, nonsurgical therapies that target inflammatory mediators make early active-phase disease the period most amenable to modification; however, this window can be missed in up to one-third of men with PD.^{47,79,80} Phenotypic heterogeneity further complicates non-surgical treatment standardization, as patients vary considerably in curvature severity, EF, plaque composition, and deformity pattern. Furthermore, there are currently no validated clinical biomarkers to reliably predict response to non-surgical therapy, limiting effective patient selection.⁸¹ Meaningful progress will likely depend on earlier recognition of active-phase disease, improved biologic characterization at presentation, and combination strategies targeting multiple components of the fibrotic cascade simultaneously.

Surgical treatment

Although many patients prefer to avoid surgery, it remains the most definitive treatment for men with severe PD causing functional impairment or for those who have failed nonsurgical therapy. Surgical intervention provides rapid and reliable deformity correction, with procedure selection guided by baseline EF, deformity severity, and patient goals.

Thorough preoperative evaluation is necessary to optimize outcomes.

In-office deformity assessment, with or without penile duplex Doppler ultrasound, facilitates accurate characterization of curvature, rigidity, girth loss, deformity, instability, and plaque calcification, and is generally more reliable than patient-submitted photographs. Given the risks inherent to surgical intervention, understanding patient-specific factors that influence interest in surgery is important for shared decision-making and setting realistic expectations. Younger age, depression or anxiety history, perceived penile shortening, and greater curvature have been associated with an increased likelihood of considering surgery prior to consultation.⁸² However, further studies are needed to assess how these factors change after comprehensive counseling regarding natural history of PD and available treatment options.

Interpersonal factors may also influence a patient’s decision regarding surgical treatment, making involvement of the sexual partner during counseling valuable. Although men with stable-phase PD and their partners report similar rates of intercourse difficulty and reduced intercourse frequency, men report significantly greater distress related to penile appearance as well as to the difficulty with and frequency of intercourse.⁸³ This suggests that perceived partner dissatisfaction may exceed actual partner concern. Partner engagement may therefore help align treatment decisions with patient priorities, reduce anxiety-driven pursuit of surgery, and improve psychosocial outcomes.

Guidelines recommend surgery during the stable phase of PD.^{1,29,54} Surgical options can be categorized into tunical shortening procedures, tunical lengthening procedures, and penile prosthesis implantation (see Table 2). A phase-based clinical algorithm is shown in Figure 2.

Tunical shortening procedures

Tunical shortening procedures correct penile curvature by shortening the convex side opposite the deformity. Optimal candidates have adequate baseline penile length, preserved EF with or without oral therapy, and curvature $<60^\circ$ without complex deformities, such as hourglass narrowing.⁸⁴ These procedures are favored for their technical simplicity and relative shorter operative times, with reported curvature correction rates of 42%–100% and patient satisfaction of 68%–100%; however, procedure selection is largely guided by surgeon experience in the absence of randomized comparative trials.^{84,85}

The primary limitation of these procedures is their inherent risk of additional penile length loss, which is more pronounced with greater curvature severity and ventral deformities.⁸⁶ Reported shortening may reach up to 3 cm, with 22%–69% of men experiencing a 1–1.5 cm reduction.^{29,84} Although objective penile length loss can be modest, patient-perceived shortening may be greater, underscoring the importance of preoperative counseling and patient selection.⁸⁵ Predictive models for estimating postoperative length loss have been proposed but should be viewed as general guides rather than definitive predictors.⁸⁴ Other complications include palpable suture knot discomfort in one-third of patients, curvature recurrence ($<11\%$), *de novo* ED ($<23\%$), penile narrowing ($<17\%$), and sensory changes ($<21\%$).^{84,86}

While traditionally reserved for curvatures $<60^\circ$, limited data suggest tunical shortening procedures may be considered in selected patients with more severe deformity who have adequate penile length and EF.⁸⁵ Following plication for curvature correction, adjunctive techniques such as extra-tunical grafting (ETG) have been explored to address residual indentation deformities.⁸⁵ ETG does not add structural stability but may potentially reduce postoperative ED risk, especially relative to PEG.⁸⁵ Roadman et al.⁸⁷ reported that approximately 90% of men without axial instability who underwent ETG maintained durable correction at two years, with graft palpability limited to the flaccid state. Further studies are needed to better define its role in managing complex deformities.

Tunical lengthening procedures

Tunical lengthening procedures, including plaque incision and grafting (PIG) and partial plaque excision with grafting (PEG), may be considered in men with severe ($>60^\circ$) and/or multiplanar curvature, complex deformities, extensive calcification, or shorter penile length where tunical shortening techniques would result in bothersome length loss.^{29,54,85} These procedures are least likely to cause additional length loss and may partially restore PD-related shortening; however, careful patient selection is essential, as reported rates of postoperative ED ranges from 0%–63% and may be higher with ventral graft placement.^{29,86,88} Tunical lengthening procedures should therefore be reserved for men with excellent baseline erectile rigidity, while those with borderline EF or elevated ED risk should be counseled toward prosthesis implantation.

Reported outcomes for PIG and PEG vary, with curvature correction rates of 57%–96% and patient satisfaction rates of 35%–100%.^{85,86} Variability in satisfaction may reflect postoperative EF, transient penile hypoesthesia (3%–18%), and penile shortening ($<25\%$).^{85,86} However, appropriate patient selection, thorough preoperative counseling, and setting realistic expectations continue to be key determinants of patient satisfaction. Direct comparative data between PIG and PEG are limited; therefore, procedure selection is guided by deformity characteristics, surgeon experience, and patient preference.⁵⁴

Contemporary PIG techniques evolved from earlier plaque excision approaches, which were associated with unacceptably high ED rates.⁸⁸ By employing limited incisions at the point of maximal curvature, PIG allows localized tunical expansion to correct the deformity.^{88,89} Efforts to reduce postoperative ED have focused on preserving veno-occlusive function. Leveraging the bilaminar structure of the tunica albuginea, Hegarty et al.⁹⁰ compared partial-thickness plaque incisions without grafting to full-thickness incisions with collagen fleece grafting. Both approaches improved penile shape and length without apparent compromise of EF; however, interpretation is limited by the nonrandomized design and absence of controls.⁹⁰

Despite higher postoperative ED risk with larger tunical defects, PEG may remain an option in carefully selected patients with severe indentation deformities to improve narrowing, instability, and girth.⁸⁶ Langbo et al.⁹¹ reported lower rates of successful intercourse and higher rates of subsequent penile prosthesis placement among men who elected PEG over recommended prosthesis implantation,

underscoring the importance of thorough preoperative counseling.

Graft selection is central to tunical lengthening procedures. Options include autologous grafts (e.g., buccal mucosa), allografts (e.g., human pericardium), xenografts (e.g., bovine/porcine materials), and synthetic grafts.²⁹ Synthetic grafts are discouraged due to higher risks of infection, inflammation, contracture, and fibrosis.^{29,54} An ideal graft would minimize these complications while remaining inexpensive and easy to handle. No graft material has demonstrated clear superiority, as most evidence derives from single-arm series.⁸⁶ Autologous grafts may increase operative time and donor-site morbidity, whereas collagen fleece grafts avoid graft harvest and allow sutureless application.⁹² Long-term outcomes are needed to better define their roles.

Penile prosthesis implantation

Penile prosthesis implantation is the preferred treatment for men with PD and ED refractory to medical therapy, and for those who have failed prior surgical correction. Deformity correction rates range from 84%–100%, with patient satisfaction rates exceeding 90%.^{54,85} The AUA and CUA recommend inflatable penile prostheses, whereas the EAU reports comparable satisfaction with both inflatable and malleable devices.^{1,29,54}

Prosthesis implantation alone may correct mild curvatures (<30°); however, the need for adjunctive maneuvers increases with deformity severity,

reaching approximately 12% for curvatures of 31°–45°, 75% for 45°–60°, and nearly 100% for curvatures >60°. ⁸⁵ Adjunctive techniques include manual modeling, tunical plication, and plaque-releasing incisions with or without grafting.⁸⁶ Grafting is recommended when tunical defects exceed 2 cm to reduce the risk of prosthesis herniation.⁵⁴ Collagen fleece grafts are increasingly favored for shortened operative times and reduced risk of prosthesis damage, as there is no need for suturing near the implant.⁸⁶ Notably, a multicenter retrospective study found that grafting, though used least frequently, was associated with greater median curvature correction than modeling or plication.⁹³

Penile prosthesis implantation carries meaningful risk, highlighting the importance of careful patient selection. Glans ischemia, though uncommon and typically associated with complex reconstructions requiring neurovascular bundle mobilization, is a serious complication that can progress to glans necrosis and tissue loss if not promptly recognized. Risk factors include underlying vasculopathy, smoking, prior radiation therapy, and compromised penile perfusion related to postoperative compression (e.g., penile wrapping, intracorporal cylinder inflation, prolonged catheter-related urethral pressure).⁹⁴ Thus, preoperative counseling regarding these risks is critical.

Emerging tunica-preserving strategies, including auxetic tunical expansion and the tunical expansion procedure (TEP), aim to correct complex penile deformity while minimizing incision to reduce the

TABLE 2. Summary of surgical treatment options

Therapy	Mechanism	Indication	Advantages	Limitations
Surgical therapies				
Plication/corporoplasty	Tunical shortening of convex side	Stable PD with adequate length, EF, and <60° curvature without complex deformities ⁸⁴	Good success and satisfaction rate; shorter operative time ^{84,85}	Penile shortening; recurrence; <i>de novo</i> ED; sensory changes ^{29,84,86}
Surgical therapies				
Plication/corporoplasty	Tunical shortening of convex side	Stable PD with adequate length, EF, and <60° curvature without complex deformities ⁸⁴	Good success and satisfaction rate; shorter operative time ^{84,85}	Penile shortening; recurrence; <i>de novo</i> ED; sensory changes ^{29,84,86}
Extra-tunical grafting	Placement of graft outside of tunica albuginea without tunical violation	Residual indentation deformity after plication ⁸⁵	May reduce risk of postop ED relative to PEG; durable correction ⁸⁵	Graft palpable when flaccid; does not address instability; limited data available ⁸⁷
PIG/PEG	Limited tunical incision/excision with graft to allow localized expansion	Severe and/or multiplanar curvature; complex deformity; preserved EF ^{29,54,85,86}	Corrects severe curvature, complex deformity ^{29,54,85}	Higher ED risk; variable satisfaction ^{29,85,86,88}

(Continued)

TABLE 2. (Continued)

Therapy	Mechanism	Indication	Advantages	Limitations
Penile Prosthesis Implantation (±straightening maneuvers)	Cylinders restore rigidity; adjunctive modeling, plication or grafting may correct residual curvature	PD with refractory ED; failed prior interventions ^{1,29,54}	High satisfaction; definitive ED treatment ^{54,85}	Risk of device infection, malfunction, herniation, or glans necrosis ⁹⁴

Note. **PD**: Peyronie's disease; **EF**: Erectile function; **ED**: Erectile dysfunction; **PIG**: Plaque incision and grafting; **PEG**: Partial plaque excision with grafting.

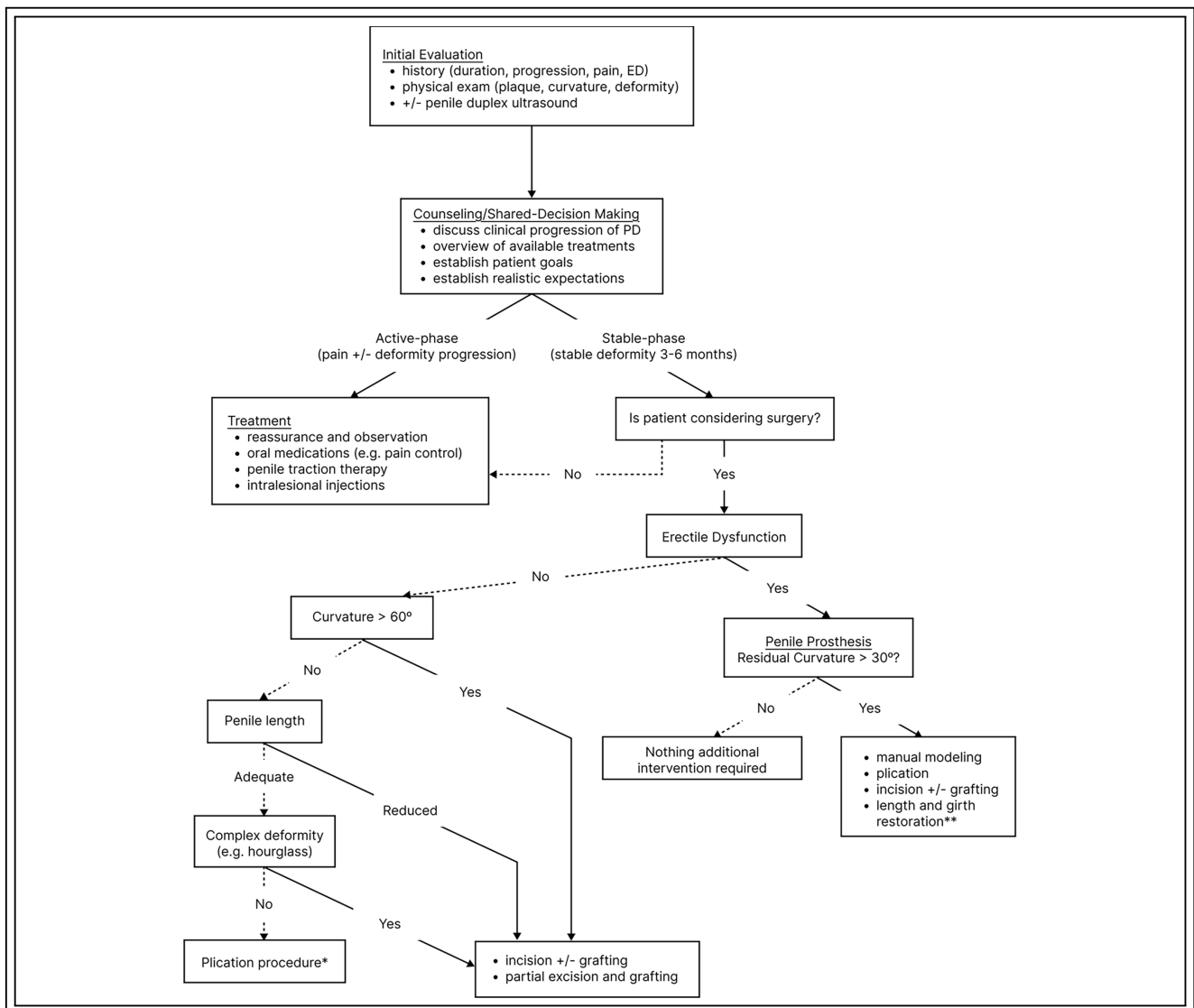


FIGURE 2. Phase-based treatment algorithm of Peyronie's disease. **ED**: erectile dysfunction; **PD**: Peyronie's disease; *If residual indentation post plication, consider extra-tunical grafting; **These are investigational techniques appropriate for experienced surgeons and patients willing to accept associated risks

likelihood of cylinder herniation through the graft site. Early results are encouraging, but larger studies are needed to establish feasibility and long-term durability of these approaches.^{95,96} Detailed technical considerations of modern tunica-preserving surgical techniques are reviewed separately in this special issue.

Limitations

This review has limitations inherent to its narrative design. Contribution to the study selection was performed by three authors, including two senior reviewers with subspecialty expertise in PD; however, some degree of selection bias cannot be excluded. Although a pre-registered protocol was not used, as is consistent with the narrative review format, this approach allowed for the integration of foundational, translational, and contemporary clinical evidence across a broad scope of topics.

The underlying evidence base represents an additional limitation. High-quality randomized data are available for a minority of nonsurgical therapies, with most studies consisting of small prospective cohorts, retrospective series, or uncontrolled study designs with inconsistent disease-phase definitions and outcomes measures, limiting cross-study comparability. Similarly, surgical outcomes data are largely derived from studies without direct comparators, and treatment selection is therefore often guided by expert consensus rather than comparative trial.

Molecular and genetic insights are primarily from preclinical models and early translation studies; while they provide a mechanistic framework for ongoing investigation, their clinical applicability remains uncertain. Finally, restriction to English-language publications may have excluded relevant data published in other languages.

Conclusions

PD can adversely affect sexual function, psychological well-being, and quality of life. While many patients favor nonsurgical management, treatment efficacy is variable, reflecting the complex and phase-dependent biology of PD. Surgery remains an important option for appropriately selected patients with functionally limiting deformity. Continued advances in translational research are refining disease understanding and informing emerging therapies, with careful patient selection, realistic expectations,

and shared decision-making remaining essential to optimizing outcomes.

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Availability of Data and Materials

Not applicable.

Ethics Approval

Not applicable.

Conflicts of Interest

The authors declare no conflicts of interest.

Abbreviations

The following abbreviations are used in this manuscript:

AUA	American Urological Association
CCH	Collagenase clostridium histolyticum
cGMP	Cyclic guanosine monophosphate
CUA	Canadian Urological Association
DD	Dupuytren’s disease

EAU	European Association of Urology
ECM	Extracellular matrix
ED	Erectile dysfunction
EF	Erectile function
ETG	Extra-tunical grafting
FGF	Fibroblast growth factor
GWAS	Genome-wide association studies
HA	Hyaluronic acid
HIF	Hypoxia-inducible factor
IL-1	Interleukin-1
IL-6	Interleukin-6
Li-ESWT	Low-intensity extracorporeal shock wave therapy
MMP	Matrix metalloproteinase
NSAIDs	Nonsteroidal anti-inflammatory drugs
PD	Peyronie's disease
PDGF	Platelet-derived growth factor
PDE5i	Phosphodiesterase-5 inhibitors
PEG	Partial plaque excision with grafting
PIG	Plaque incision and grafting
PRP	Platelet-rich plasma
PTT	Penile traction therapy
RCT	Randomized controlled trials
SPL	Stretched penile length
TEP	Tunical expansion procedure
TGF- β	Transforming growth factor-beta
TIMP	Tissue inhibitor of metalloproteinase
TNF- α	Tumor necrosis factor-alpha
WGS	Whole-genome sequencing

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