Peyronie's Disease: Epidemiology, Pathophysiology, Evaluation

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Key Points

1. Peyronie's Disease (PD) is a progressive condition resulting in fibrous plaque formation within the tunica albuginea (TA) of the penis which can lead to severe deformity and a palpable plaque (see **Figure 1**)
2. The etiology of PD is multifactorial, and a number of conditions and exposures have been associated with PD.
3. All men undergoing a work-up for PD warrant a detailed past medical, surgical, and sexual history, with a thorough history of disease presentation, progression and therapy, along with a complete physical and genitourinary exam. Understanding the goals of care or treatment for the patient is also of benefit.
4. A deformity assessment with in-office injection of the penis with erectogenic agent(s) to induce tumescence is recommended by the AUA Guidelines on PD prior to any invasive intervention for PD.

Keywords

Peyronie's, curved penis, bent penis, penile plaque, penile pain, curved erection

1. Introduction

Peyronie's disease (PD) is a progressive condition resulting in fibrous plaque formation within the tunica albuginea (TA) of the penis, in some cases leading to penile deformity such as shortening, narrowing, and/or curvature, pain with intercourse, and distress. [1] The incidence of PD is estimated to be 22.4 to 25.6 cases per 100,000 men. The condition most commonly presents in men 50 to 59 years old with an average age of presentation of 55 years.[2,3]

Despite the higher incidence in older men, men of all ages from adolescence to late adulthood may be affected.[4,5,6] The prevalence of PD ranges from 0.4% to 13%, although this is likely an underestimation due to underreporting bias among men reluctant to discuss the condition.[7]

Based on the current data, Caucasian men are most commonly affected, however, this may be due to a lack of data evaluating and addressing racial differences and PD. In a small study evaluating 159 patients who were undergoing treatment for PD, 8.2% were African American. [8] In another study evaluating 1,731 Brazilian men presenting for prostate cancer screening, the prevalence of PD was found in 0.9% of Brazilian men.[9] A Japanese study evaluating a total of 1,090 men receiving a routine health check as well as 130 patients undergoing maintenance hemodialysis, found the prevalence of PD to be 0.6% and 9.2% respectively. [10]

2. Etiology and Risk Factors

The etiology of PD is multifactorial and our understanding of its pathophysiology continues to evolve. A number of conditions and exposures have been associated with PD but causality remains unclear in most cases. Additional work is needed to confirm these relationships and understand the common mechanisms which drive them.

Penile trauma, including both acute traumatic events and chronic repetitive microtrauma (including during sex) is considered the leading etiology.[11] PD has been associated with infectious conditions such as nongonococcal urethritis as well as iatrogenic trauma during cystoscopy, urethral catheterization, transurethral resection of the prostate, and radical prostatectomy(RP).[6,12]

Tal et al found the incidence of PD after RP to be roughly 15% with a mean time to develop PD after RP, being 13.9 +/- 0.7 months. They found younger men and men of white race to be at increased risk for PD in their study[13]

Smoking and alcohol are associated with PD, although the risks associated with alcohol are more controversial; a separate, larger study failed to reproduce an initial association.[11,12,14] Diabetes mellitus is also a possible PD risk factor. Arafata et al. found that a high proportion (20.3%) of diabetic men also had PD.[15]

Moreno and Morgentaler found that the prevalence of hypogonadism, defined as total testosterone (TT) values less than 300ng/dL and or free testosterone (FT) less than 1.5ng/dL, among men with PD was high (74.4%). Among men with PD, those with lower FT are reported to have more significant penile curvature (37.5 vs. 55.9 degrees, respectively, P = 0.003). Severity of penile curvature correlated significantly with FT (r = −0.314, P = 0.016).[16]

Mulhall et al reported a prevalence of ED of up to 32% in patients with PD.[17] However, it remains unclear whether PD results in ED, vice versa, or whether both conditions occur simultaneously, but independently.

Dupuytren's disease (DD), a superficial fibrotic condition affecting the palmar fascia, resulting in hand contracture, has also been associated with PD.9 One study observed a 21% incidence of DD in a cohort of 134 PD patients compared to a 0% incidence in a control group. Another study reported that 26% (95% confidence interval 17-35%) of men with confirmed DD reported penile shape changes; it is unclear whether these changes represented actual PD.[18]

In addition, while many possible long-term sequelae of Coronavirus disease 2019 (COVID-19) remain unidentified, Ramasamy's group found that after COVID-19 infection, a man developed PD confirmed by ultrasound, as well as endothelial dysfunction demonstrated by low endothelial progenitor cell colony-forming units and low brachial artery flow-mediated vasodilation.[19]

3. Pathophysiology

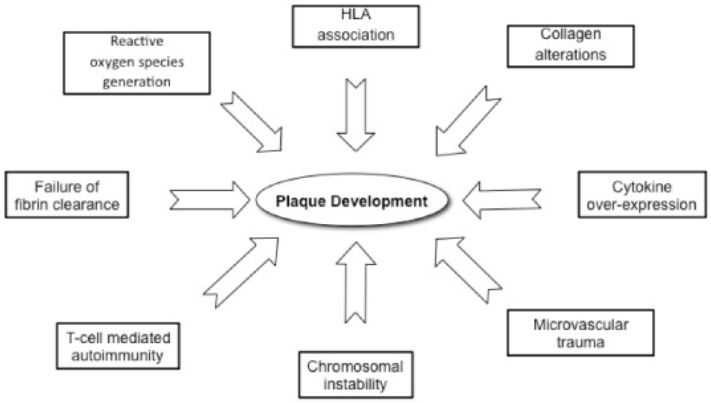

Figure 1: Factors affecting plaque development

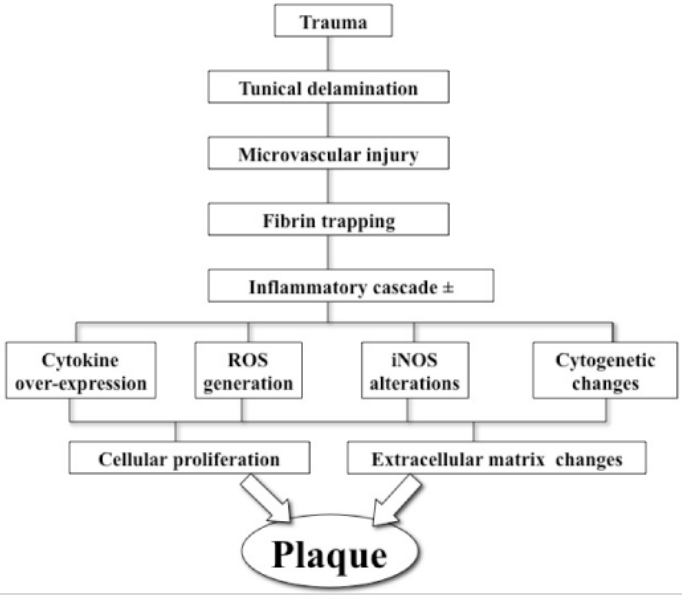

Figure 2: Plaque Development Process

PD plaque represents fibrosis that forms within the TA, typically commencing at the convergence of septal fibers with the inner layer of the tunica, dorsally or ventrally. A number of factors appear to contribute to plaque development (**Figure 1**). The plaque itself is composed of an altered and increased ratio of disorganized collagen I and III fibers combined with a reduction in the density of elastin fibers. [20,21]

It is hypothesized that PD is the result of accumulated microvascular trauma to the penis secondary to sexual activity in genetically predisposed men. The TA is bilaminar dorsally and monolaminar ventrally; buckling trauma may cause delamination of the tunica at the junction of the septum and circular fibers. Extravasation of blood at the site of injury is proposed as a triggering factor in an inflammatory cascade that begins with the pathological deposition of fibrin. Collagen undergoes a transition from predominately type I to type III, leading to the inelasticity of the plaque. This effect is amplified by degradation/disorganization of elastin fibers due to elastase release from macrophages. [20,22] Failure to clear fibrin from the relatively avascular TA may result in release of pro-fibrotic molecules, such as transforming growth factor ß (TGF- ß), and anti-fibrinolysis molecules, such as plasminogen activator inhibitor type 1 (PAI-1) (**Figure 2**).[23,24,25,26]

Other factors that have been proposed as contributors to the development of plaque in the TA include: chromosomal instability of PD plaque-derived fibroblasts, aberrations in the inducible nitric oxide pathway, patient HLA sub-type, and the presence of cytomegalovirus within the tunica.[21,27,28,29]

Studies with fibroblast cell culture models have documented individual chromosomal abnormalities associated with PD. Somers et al,[30] found detectable karyotype abnormalities in PD plaque-derived fibroblasts in 7/12 patients with PD. Interestingly, these chromosomal abnormalities were not present in cell cultures derived from adjacent TA, dermis, or lymphocytes in men with PD. This would argue against the presence of a heritable mutations in these men, but support single genomic alterations in affected cells in PD. Experimental data has shown that TGF-β1 has an important role in the pathology of PD. Hauck et al, found an increased frequency of a homozygous nucleotide polymorphism in the coding region of the TGF-β1 gene in patients with PD compared to healthy controls.[31]

It is hypothesized that increased expression of TGF-β1 is due in part to the presence of heritable single-nucleotide polymorphisms (SNPs) that could affect gene expression. To evaluate whether SNPs were present in men with PD, Dolmans et al., assessed allele frequencies for the SNPs in 111 men with PD and 490 unaffected controls. [32] They found a significant association observed at the WNT2 locus on chromosome 7, implicating a common set of genetic factors for PD and Dupuytrens disease.

PD family history has previously been observed to co-aggregate in 1.9% - 4% of first-degree relative pairs (e.g., father-son).[12,33] This low number may partly be explained by the sensitive nature of the topic and reluctance of men to

discuss this with their family members. In another study of 307 individuals with PD including their 1st through 5th degree relatives, 0.12% of the population had PD, and 1.3% of PD probands had a diagnosis of DD as well. Seventy-five percent of identified PD probands belonged to pedigrees with a statistical excess of PD, providing evidence supporting a genetic contribution of PD cases. [34] Perhaps one of the strongest studies evaluating a genetic link came from Ziegelbaum, et al, in which twins brothers underwent HLA immunotyping. Their father, both twin brothers and 1 of their children all exhibited a positive B7 cross-reactive antigen; all of those with the B7 positivity were found to also have penile deformities consistent with PD. [35] Animal models using the injection of TGF-beta type molecules (cytomodulin) and fibrin in the rat penis have been developed. Unfortunately, it remains unclear whether these models are representative of human PD or of a more generalized condition of penile fibrosis.[28,36,37]

Further research is necessary to provide a more extensive understanding of the genetic factors associated with PD.

4. Clinical Presentation

While PD most commonly affects men in the sixth decade of life, patients as young as 15 years old have been identified.[6] The distinguishing characteristic of PD compared to congenital penile curvature (CPC) or a normal anatomical variant, is that PD is an acquired penile curvature often with a palpable plaque. (**Table 1**) Some young men may present believing they have PD, but on exam have no palpable plaque and actually have CPC. Differentiating the two is usually not difficult as CPC presents as a lifelong (not acquired) curvature and the deformity is usually a bowing of the penis without sharp angulation and no palpable plaque. Further, in patients with CPC, ventral curvature tends to predominate. Men with preexisting CPC may have an increased risk of future development of PD, and therefore notating this during the history and physical exam is important. For patients with true PD, curvature can occur in any direction, although dorsal curvature predominates in the majority of cases. [17] The deformity commonly presents during erection although may be obvious even during the flaccid phase. When the penis is flaccid, the formation of plaques may result in the loss of stretched penile length. Other associated deformities include tunical indentations, hourglass deformity with erection, a bottle-neck appearance, wide-base appearance and penile instability or buckling with axial loading despite maximal erection.[17] In the setting of PD, penile plaques and curvature are commonly uniplanar but can be multiplanar in complex cases. Just as the direction of penile curvature is variable, PD plaque location is similarly variable with one study finding 72% of plaques in the dorsal midline, 17% ventrally, and 11% on the lateral aspect of the penis.[17]

The natural history of PD consists of an acute phase followed by a chronic phase.[1] During the acute phase, which typically lasts 6 to 18 months, progressive penile deformity occurs which may be associated with pain in both the flaccid and erect states.[17] Eventually, transition into the chronic phase of PD occurs; this phase is marked by cessation of plaque progression, decrease in prevalence of pain with erections, and overall stability of the deformity.[38,39]

Severe penile curvature and/or reduced penile rigidity secondary to plaque formation may make sexual intercourse challenging and, in some cases, impossible. ED resulting from deformity, performance anxiety, and vaso-occlusion due to plaque formation can significantly affect patients' quality of life and lead them to present to the clinic.[1]

Table 1. Differentiating Congenital Penile Curvature from Peyronie's Disease		
Characteristics	Congenital Penile Curvature	Peyronie's Disease
Palpable Plaque	No	Frequently
Direction of curvature	Generally Ventral	Any
Duration of Curvature	Lifelong	Acquired/New onset

5. Impact of PD

It is important for clinicians to appreciate the psychological and psychosocial sequelae for patient and partner. Men with PD report embarrassment and shame, and may avoid sexual relationships, which can take a tremendous toll on their quality of life.[40] Nelson et al found that 47% of men with PD reported clinically meaningful depression.[41] Smith et al reported that 81% of PD patients have emotional difficulties and 54% suffer relationship distress as a result of PD.[42] On multivariate analysis, the presence of relationship problems and loss of penile length were independent predictors of emotional problems due to PD.

Rosen et al conducted focus groups composed of men with PD and controls.[40] A total of sixty-four US men (twenty-eight with PD, thirty-six without) underwent structured discussions and identified six main areas of concern among men with PD: physical appearance, sexual self-image, loss of sexual self-confidence and attractiveness, sexual function and performance, performance anxiety, and social stigmatization. Many of the men with PD expressed a sense of social stigmatization and isolation, and found it difficult to communicate with healthcare professionals or sexual partners. Salter et al found that while the psychosocial impact of PD is significant in all men, it appears to be even greater in gay men. [43]

Farrell et al, compared PD characteristics, treatment and psychosocial factors among men who have sex with men (MSM) to a control group of non-MSM patients and showed there were few differences in the clinical presentation and treatments used between MSM and non-MSM PD patients. Their study showed evidence of emotional distress in both groups and that more MSM presented with a primary complaint of penile deformity. [44]

It is important to appreciate that degree of deformity or clinical severity of PD does not correlate with psychological distress; men with “mild” PD are just as apt to have serious psychological distress as those with severe “PD”. Partners of men with PD have also been shown to have decreased sexual function, sexual satisfaction, and mood, compared to population-based norms.[45]

6. Patient Evaluation

6.1 History

All men undergoing a work-up for PD warrant a detailed past medical, surgical, and sexual history, as well as a thorough history of disease presentation, progression and therapy. [18,1] Particular attention should be paid to the nature and magnitude of the deformity, duration of symptoms, presence of pain with and without erection, change in deformity over time, and whether ED is present. There is a potential increased risk of development of PD in men with preexisting CPC, and therefore, notating this during the history and physical exam may be worthwhile. Characteristics of ED such as degree of rigidity, ability to sustain an erection, presence of nocturnal erections, and the timing of the onset of the ED (pre or post PD development) will aid in assigning an etiology to the ED. Men often report good erectile rigidity but complain of loss of rigidity only distal to the plaque and point of maximum curvature and/or indentation. It is critical to establish the degree of bother for patient and partner as this will aid the clinician in the long-term management of the patient. Clinicians should determine if the patient’s bother is related to functional and/or psychological impairment. At initial presentation, defining the duration of the condition is paramount for defining a treatment plan. The approach to the acute phase patient, will differ in its urgency and in treatments offered compared to the patient with stable disease.

6.2 Physical Examination

In addition to a complete physical and genitourinary exam, the patient’s hands should be examined for any evidence of DD.[1] The penis should be examined in the stretched flaccid state, with careful palpation of the shaft, from pubic bone to coronal sulcus, to elucidate a plaque or any firmness or induration. The patient may have more than one plaque present and may have counter-balancing plaques on the dorsum and ventrum. Palpation, applying side-to-side and dorso-ventral pressure, is the optimal means of outlining plaque and septal anatomy. Side-to-side compression beginning at the 3 and 9 o’clock position on the shaft and rolling firmly upwards (for dorsal plaque) and downwards (for ventral) plaque should be conducted meticulously along the entire shaft. The plaque location, morphology and size should be documented, and measurement of the stretched flaccid length is advisable (pubic bone to coronal sulcus). [1]

6.3 Deformity Assessment

An accurate appraisal of the deformity is a critical step in the management of the PD patient. It is imperative to document characteristics such as direction of the curvature, and if the curvature is simple (uniplanar) or biplanar. Associated deformities such as indentation, hourglass deformity, bottle-neck deformity or penile rotation/torsion should also be recorded.[1] Deformity assessments should be performed prior to invasive treatments for PD.

Options for deformity measurement include patient self-assessment, at-home photography (AHP), application of in-office vacuum erection device (VED), and intracavernosal injection (ICI)-assisted erection. The degree of penile deformity is greatest at maximum erectile rigidity; hence, maximal erectile rigidity is preferred for a true accurate assessment.

Patient self-assessment is generally inaccurate. Bacal et al compared patient self-estimate of curvature to ICI-assisted erection measurement and found that the majority of men either overestimated (54%) or underestimated (26%) their curvature. Only 20% of men were accurate within 5°. The most reliable means of assessing deformity and accomplishing all three goals of assessment is the use of intracavernosal injections. AHP and VED are also notorious for inaccurately defining the nature and degree of deformity. Photographs are generally unreliable, as they are often taken with less than full rigidity, and at counterproductive angles, thereby underestimating the degree of curvature.

In office injection of the penis with erectogenic agents to induce tumescence is recommended by the AUA Guidelines on PD prior to any invasive intervention.[1] This testing serves the dual purpose of permitting examination of the penis in the erect state and verifying that the patient is able to achieve an erection sufficient for penetrative sexual activity. Injection may be combined with Doppler ultrasound (when available) to provide additional information regarding vascular integrity and/or the presence of penile plaques/calcification.[1] Additional suggestions on how to properly perform the penile Duplex Doppler ultrasound (PDUS) may be found under the AUA core curriculum, Erectile Dysfunction: Patient Evaluation, Investigations.[46] The second part of the assessment is focused on the magnitude of the deformity. For curvature, it is most often recorded in number of degrees, preferably using a goniometer. Less than 10° curvature is difficult for the patient to discern. On curvature assessment at presentation, the average curvature magnitude is typically around 45°, although patients with magnitudes of greater than 90° may also be seen. For patients with biplanar curvature, each respective magnitude should be recorded. Primary curvature is the curvature with the greater magnitude, while additional deformities are secondary or tertiary. Indentation assessment is more complicated, and less standardized.[1] It is important to remember that most cases of CPC consist of ventral curvature rather than dorsal, biplanar or other deformities.

A third essential part of the assessment is to evaluate for the presence and severity of penile instability. Many patients have degrees of curvature that do not preclude penetrative sexual relations. However, associated indentation(s) or the position of the curvature (especially a retrocoronal location) may render the penis unstable and prone to buckling during attempted penetration. As with indentation measurement, there is no standardized means of recording instability, but documenting its presence, and the amount of force required to induce buckling, is worthwhile.[1]

Characterization of a patient's deformity is essential, so that baseline and post-treatment deformity assessments can be accurately compared. When comparing pre- and post-therapy deformity, it is vital that the erectile rigidity for both assessments be comparable, since there is a correlation between rigidity and degree of deformity. Accurate knowledge of the degree of deformity is also a critically important factor in defining the course of management and prognosis for the individual patient. For example, treatment may not be necessary in a man with 10° of uniplanar, simple curvature. On the other hand, a patient with a biplanar deformity of greater than 45 degrees in both dimensions and gross instability may be confidently told that irrespective of what medical therapy is undertaken, it is likely that surgical correction will be required.

6.4 Laboratory Assessment

There is no mandate to obtain laboratory testing in PD patients. Because there is minimal evidence that hypogonadism is related to the development or severity of PD, acquiring a baseline T level is not necessary unless indicated as per the AUA Guidelines on **Low Testosterone** and/or **Erectile Dysfunction**.

6.5 Imaging & Adjunctive Testing

No imaging study is mandatory for a complete PD workup. Under select circumstances, additional evaluation with imaging may be very useful.[1]

Penile Duplex Doppler ultrasound (PDUS) is a tool that can provide valuable objective data in the PD patient. Penile ultrasonography is both cost effective and amenable to bedside use with minimal risk to the patient.[47] The AUA Guidelines on PD state that clinicians should perform in-office ICI test with or without PDUS prior to invasive intervention.[1] However, the procedure is nuanced and should be performed by practitioners with sufficient training and/or experience to conduct the procedure appropriately and correctly interpret the results.

PDUS has the potential to locate plaques not easily palpated, identify calcification in a plaque, and define erectile hemodynamics in men with concomitant ED prior to undergoing surgical reconstruction for PD.[1,48,49,50]

A subset of patients with PD will not have palpable plaques, and instead have isolated septal scarring (ISS) and punctate scarring (PS). PS appears as small isolated calcifications >3mm, while ISS appears as tunical thickening on the medial aspect of the corporal body.[47,51] Punjani et al, found 30% of patients had ISS and 27% had PS solely detected by penile ultrasonography only, with 33% and 75% respectively having no abnormalities noted on physical examination. [51]

Calcified plaques often respond poorly to medical treatment and are unlikely to resolve spontaneously, and thus ultrasonography is a reliable tool for detecting plaque calcifications with reportedly 100% sensitivity. [52]

PDUS can further define erectile hemodynamics and help identify concomitant ED in patients with PD, thus guiding treatment. In a natural erection, relaxation of cavernosal arteries occurs with filling of venous sinusoid spaces within the corporal bodies and subsequent constriction of the subtunical venous plexus system.[53] Specific measurements during the PDUS can reflect these changes. Peak systolic velocity (PSV) is the cavernosal blood velocity at the start of systole while end diastolic velocity (EDV) is the blood velocity at the end of diastole, immediately prior to systole. These values should be serially measured after penile injection. Normal hemodynamics of erectile function on PDUS show a PSV of greater than 30mL/s and an EDV of less than 5 mL/s.

A PSV of <25-30 mL/s, is considered evidence of arterial insufficiency, whereas an EDV of >5mL/s indicates venous leak, or poor venous occlusion during erection.[54] Failure to dose titrate penile injections during PDUS and severe patient anxiety can lead to false positives during PDUS. Additional information on how to perform PDUS may be found under the AUA core curriculum, Erectile Dysfunction: Patient Evaluation, Investigations.[46]

Sonoelastography and vibroelastography are advances in ultrasound technology that may play a future role in evaluating patients with PD and ED, but further studies are needed.

Thin section, high-resolution T2 Magnetic Resonance Imaging (MRI) without fat suppression, has been shown to be an excellent imaging modality for penile pathology, including PD. [55,56,57] Plaques appear as low-signal-intensity areas of thickened TA, and calcifications are poorly appreciated.[57] MRI provides excellent penile soft tissue characterization, and subtle deformities such as corporal narrowing are better demonstrated on MRI compared to ultrasound. Expense and lack of widespread availability make the utility of MRI in routine PD unclear.

7. Educational Material

PD Fact-Sheet

Presentations

PEYRONIE'S DISEASE EPIDEMIOLOGY, PATHOPHYSIOLOGY, EVALUATION Presentation 1

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