Asian Journal of Urology (2015) 2, 70–78

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REVIEW

All about Peyronie's disease

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Received 21 November 2014; received in revised form 31 January 2015; accepted 10 February 2015
Available online 16 April 2015

KEYWORDS
Peyronie's disease;
Pharmacotherapy;
Surgical therapy

Abstract Peyronie's disease (PD) is an acquired connective tissue disorder of the tunica albuginea of the corpus cavernosum, characterized by excessive fibrosis and plaque formation. PD can result in significant physical and psychological morbidity; as it may prevent intercourse and cause adverse impacts on partner relationships. The exact etiology and pathophysiology remain unclear, and many misconceptions about the disease associations, course and treatment exist.

The disease has two distinct stages. The acute stage is characterized by pain, and disease may progress during this stage. Non-surgical managements at this stage aim to alleviate pain and stabilize the disease. Results for non-surgical treatment are often conflicting. The chronic stage occurs 6–12 months later, where pain disappears and the deformity stabilizes. Surgical treatment is reserved for significant deformity or with inability to penetrative intercourse. The choice of the surgical technique depends on the length of the penis, degree of deformity, erectile function, patients' expectations and surgeon's preference.

1. Etiology and pathophysiology

Peyronie's disease (PD) is an acquired connective tissue disease of the tunica albuginea of the corpus cavernosum, characterized by excessive fibrosis and plaque formation, which do not expand like the normal tunica albuginea causing penile deformities in the erect state including curvature, shortening, indentation and narrowing with a hinge effect [1,2]. PD can result in significant physical and psychological morbidity. Men may suffer from penile pain, deformities and erectile dysfunction (ED) that prevent sexual intercourse and reduce satisfaction, with adverse impacts on partner relationships [3].

Recent reports showed that the prevalence of PD may be up to 9%. However, the true prevalence may be underreported as some men may not seek medical advice due to embarrassment or as a result of the false belief that the condition is untreatable [4]. It typically affects males between 45 and 60 years [5]. However, 10% of patients who

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Peer review under responsibility of Chinese Urological Association and SMMU.

http://dx.doi.org/10.1016/j.ajur.2015.04.019

present with PD are younger than 40 years, including teenagers [6,7]. Younger patients are more likely to present earlier in the disease course, have pain, and more likely to progress [8]. It is more common in younger Caucasian men and after radical pelvic surgery, namely radical prostatectomy [9]. PD is commonly associated with some comorbid conditions and risk factors including diabetes, hypertension, hyperlipidemia, ED, smoking, and excessive consumption of alcohol [8,10,11]. PD occurs in 8% of type 2 diabetes mellitus patients [12], 16% of patients who had radical prostatectomy [9], and 20% of patients who have both diabetes and ED [13]. Men with PD usually suffer significant distress and nearly half of men with PD have mild or moderate depression [14,15]. Patients with PD are concerned about their sexual attractiveness, self-image, sexual functioning and performance. Anxiety, depression, low self-esteem and relationship disorders were reported in more than half of the patients [3,14–16]. The degree of distress does not necessarily correlate with the degree of penile curvature or deformity [15]. The natural history of PD varies; penile curvature worsens in 30%–50% of patients, stabilizes in 47%–67%, while spontaneous improvement may occur in 3%–13% of patients [8,16,17].

Misconceptions about PD are very common, especially among general practitioners, who are usually the initial encounters of PD cases [4]. Common misconceptions include the underestimation of PD, and the assumption that it is only a disease of the elderly. Many believe that it is not associated with ED and that no treatment is available, or it will resolve for sure with time [4]. These misconceptions represent obstacles to early treatment in the disease course. Studies showed that earlier age of presentation (40–50 years) and the presence of hypertension, diabetes mellitus and dyslipidemia pose a greater risk for early disease progression [8]. Studies suggest also that early detection and treatment may reduce psychological distress [4]. Therefore, greater awareness of the natural history and course of PD may promote early detection and prompt treatment of the disease, and improve physical and psychological outcomes in these men [4].

The exact etiology of PD is unknown. The most widely accepted theory is trauma or repeated microtrauma to the erect penis in genetically susceptible individuals. Repeated microvascular traumatic injury to the tunica albuginea causes inflammation, disruption of the elastic fibers and deposition on fibrin [18,19]. This theory is also supported by epidemiologic association of PD with some traumatic events [20]. Some studies suggested that vascular trauma leads to osteoid formation via osteoblast like cells originating from the vascular lumen [20]. More recent reports showed that upregulation of certain genes, namely, *osteoblast specific factor 1*, may be responsible for plaque calcification [21]. Another theory is cavernosal hypoxia, which induces collagen deposition and fibrosis. This may explain the penile morphological changes and the development of PD following radical prostatectomy [9].

Multiple pathways have been suggested although the exact pathophysiology of PD remains unclear. PD has two phases that may be distinguished by symptom presentation. It starts with an acute inflammatory process characterized by increased proliferation of the tunical fibroblasts, some of which differentiate into myofibroblasts, with excessive deposition of collagen. The transforming growth factor (TGF)-β1 may play an important role in induction of collagen production by fibroblasts/myofibroblasts in the development of PD plaques [19,22]. Animal studies have shown that TGF-β1 enhances collagen deposition and plaques formation, while on the other hand suppressors of TGF-β1 caused regression of the plaques [23,24]. Moreover, overexpression of TGF-β1 was found in tissue samples from human PD plaque [25]. The association of PD with Dupuytren's contracture (in 20%–40% of cases) suggests a common fibro-proliferative disorder [10,26]. The hallmark of this stage is pain, which may occur either in the flaccid state or as painful erections. It typically resolves after 12–18 months of the disease onset [17].

The second is the chronic or fibrotic phase. It usually begins approximately 12–18 months following disease onset. Pain typically disappears, and plaque and penile deformity stabilize. At this stage, penile curvature and deformity rarely improve [17]. One study found that PD deformity stabilization was more likely among older patients and those who presented in the first 6 months of symptoms, while improvement rates were higher among younger patients [27]. Prolonged inflammation causes formation of dense fibrotic plaques, which may progress to calcification or ossification. The exact mechanism by which tissue mineralization occurs remains uncertain [28]. Calcification may be considered dystrophic in nature and may result in penile curvature [19,29]. The incidence of calcification currently varies widely, and most reports correlated the presence of plaque calcification to disease stabilization and severity [30]. In this context, improvement of deformities can occur in the early stages of the disease prior to dense calcification of the plaques [31]. However, a recent study found that calcified plaques were detected as early as 6 weeks following the onset of symptoms, suggesting that it does not occur exclusively in the setting of chronic or severe PD [29].

Some reports showed that patients with calcified plaques are less responsive to non-surgical treatment modalities and are more likely to progress to surgery [30,32,33]. However, these studies stratified patients according to the presence of calcification or not rather than its extent. One interesting study stratified patients according to the maximum dimension of calcifications as they appear on penile ultrasound; grade 1 (punctate or $\leq$0.3 cm), grade 2 ($>$0.3 cm and $<$1.5 cm) and grade 3 ($\geq$1.5 cm or $\geq$2 plaques $>$1.0 cm) [29]. This study demonstrated that not all patients with calcified plaques will need surgery, while those with higher grades of calcification were more likely to have surgery. Hence, stratifying patients according to the extent of calcification may help prevent premature surgical intervention and may serve as a clinical tool to counsel patients on the odds of having surgery. This study also found that plaque calcification was associated with older age, penile deformity, and pain [29].

2. Diagnosis

History and physical examination usually are satisfactory for diagnosis. Symptoms usually differ according to the disease phase, which will impact the decision for medical