

Review Article

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The Natural History of Peyronie's Disease

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Peyronie's disease (PD), a fibrotic disorder of the tunica albuginea fully described in 1793 by French physician Francois de la Peyronie, is characterized by pain, plaque formation, penile deformity, and ultimately sexual function decline. The epidemiological data on PD vary considerably across previous studies, with recent evidence reporting a prevalence of up to 9%. PD is generally divided into two different phases: active or acute and stable or chronic. Plaque formation generally occurs during the acute phase, while during chronic phase pain usually tends to complete resolution and penile deformity stabilizes. PD's pathophysiology is still subject of great discussion. Tunical mechanical stress and microvascular trauma are major contributory factors. However, better understanding of the molecular pathophysiology of this condition remains paramount towards an in-depth comprehension of the disorder and the development of newer and more effective disease-targeted interventions. In this review we provide a detailed overview of natural history of PD, specifically focusing on clinical manifestations and the underlying molecular regulation patterns.

Keywords: Natural history; Penile diseases; Penile erection; Penile induration

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INTRODUCTION

Peyronie's disease (PD) is a progressive fibrotic disorder affecting the tunica albuginea of the penis. The distinctive characteristic of the disease is the development of a fibrous scar at the level of the tunica albuginea ultimately leading to penile curvature and pain during erection. Erectile dysfunction (ED) is often an associated symptom secondary to pain discomfort during penetration, penile deformity and patient's emotional state [1].

Although first observed in 1561 by Fallopius and Vesalius, it was not until 1743 that the disease was fully described by Francois Gigot de la Peyronie, who

first depicted an induration of the penis resulting in penile curvature [2]. Ever since, it has been a disorder underestimated in both prevalence and impact. Actually, PD is assumed to affect 3% to 9% of the male population, with a higher prevalence among patients suffering from ED, diabetes and cardiovascular disease [3,4]. However, the true incidence is likely to be even higher due to underreporting from men not asking for treatment.

PD's pathophysiology is still subject of great discussion. It is widely believed there might be a disruption of the healing cascade at the level of the tunica albuginea, supposedly secondary to microtraumas during sexual intercourse, ultimately resulting in local inflam-

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mation and collagen deposition [5,6]. However, as the primary inflammation persists, the disturbance can worsen up to the formation of fibrous plaques, which cause the secondary penile abnormal curvature, shortening and narrowing [7]. In this light, PD is generally divided into two different phases: active or acute and stable or chronic. Plaque formation generally occurs during the acute phase [8,9]. Soon thereafter, during the chronic stage, penile pain will be reduced, and penile deformity stabilized.

In the last few years, we acknowledged a growing interest in basic and translational research on PD pathogenesis, including the developing of the first *in vitro* cell culture models [10,11]. Even though, little progresses have been made towards further elucidating the real etiology of the disease. Given the high prevalence of PD and its meaningful influence on affected men, a better understanding of PD course is pivotal. In this review, we aim to provide a detailed overview of what is currently known about natural history of PD. In particular, we focused on clinical manifestations and pathophysiology of PD, highlighting current limits of standardized definitions for both acute and chronic phase. Pathways and pro-fibrotic molecular regulators involved in PD are also discussed, with an emphasis on the importance of early intervention.

NATURAL HISTORY

The natural course of PD consists of two phases accompanied by different symptomatology. It is paramount to distinguish the two phases, since management can significantly differ depending on the different stages of the disturbance.

1. Towards a more accurate definition of acute phase

According to International Guidelines [12], acute phase is characterized by various and dynamic signs and symptoms. In addition, the hallmark of the active phase is the presence of inflammatory infiltrate within the tunica albuginea of the penis [13]. The duration of active phase has been demonstrated to differ considerably across previous studies and no significant correlation between disease duration and spontaneous healing in penile curvature was shown. It is usually assumed that active phase can last up to 12 to 18 months, even if several series do not include a temporal factor at all in the categorization of acute phase [14]. In our opinion, this might have contributed to further undermine the efforts towards a correct definition of acute phase.

2. Clinical manifestations during acute phase

As mentioned before, plaque formation generally occurs during the active phase. In the early phase of the disturbance, patient may present with penile pain, especially during erection and sexual intercourse, penile curvature, or simply penile deformation (shortening or narrowing) without clearly palpable plaque. It should be kept in mind that most patients present with a palpable plaque, but some are unaware of it [15]. In some cases, non-palpable isolated septal plaques without deformity of the penis may be present. In such condition, ultrasonographic evaluation may allow earlier identification and treatment of occult septal injuries or lesions and prevent subsequent fibrosis and its associated symptoms [16,17]. Location of the plaque considerably differs across previous studies, being dorsal location the most frequent at disease onset (Table 1) [18-21]. Similarly, deviation of erect penis is significantly changeable according to previous reports (Table 2) [18,20-23]. Clearly, there might be some patients who

Table 1. Location of plaque in the penis

Author (year)	Plaque detection	Plaque location			
		Dorsal	Lateral	Ventral	Septum
Byström and Rubio (1976) [19]	Physical examination	68%	15%	1%	16%
Levine et al (2003) [21]	Physical examination+US	-	81%	-	27%
Hinman (1980) [20]	Physical examination	67%	21%	6%	6%
Stewart et al (2015) [18]	Physical examination+US	45%	29.3%	8.8%	-

US: ultrasonography.

Table 2. Erect penis curvature

Author (year)	Evaluation	Type of curvature	Penile curvature					Atypical	Treatment
			Dorsal	Lateral	Both/complex	Ventral	Neither		
Levine et al (2003) [21] ^a	Pharmacological erection+modified Kelami classification	Primary	36.7%	73.3%	36.7%	13.3%	10%	Narrowing 33%	Verapamil injection (57%), observation (17%), collagenase injection (during a double-blind trial protocol) (3%), tunica albuginea plication (TAP) (10%), dermal grafting (7%), combination TAP/dermal grafting (7%) ^c
Hinman (1980) [20]	-	Primary	60%	21%	7%	6%	6%	-	Interferon- α 2b intralesional injection
Stewart et al (2015) [18] ^b	Goniometer measurement	Primary	84%	84%	-	16%	-	-	-
Margolin et al (2018) [22]	Pharmacological erection+goniometer measurement	Primary	41.4%	21.9%	10.9%	15.6%	10.2%	Indentations 39%; hourglass 23%; distal tapering 13%	-
Seveso et al (2018) [23]	History and/or patient's auto photography during erection	Primary	57%	23%	6%	14%	-	-	Surgical plication of albuginea

^aEleven patients had 2 different simultaneous curvature directions, thus making the cumulative curvature direction in excess of 100%. ^bDorsal and lateral curvature are grouped together. ^cThe above-mentioned results are referred to patient cohort younger than 40 years old.

traumatize their penis and, thus, develop a secondary curvature due to the inflammation process and loss of compliance. An association to trauma and position during sexual intercourse has been also suggested, based on the assumption that certain position of intercourse might be ultimately traumatic for the penis [12].

Active phase can manifest also with ED in a percentage of cases ranging from 22% to 54% [24]. Conversely, not all patients present with penile pain at disease onset. According to current available literature, its incidence ranges between 20% up to 70% of cases [24]. However, when penile pain is present, it generally tends to resolution within 12 to 18 months. On the contrary, when penile curvature is present, this tends to stabilize or even worsen during the natural course of the disorder [25].

As such, the watchful waiting approach of the acute phase could be dangerous for the patients due to the possible worsening of the curvature and penile shortening.

3. Molecular regulators during Peyronie's disease acute phase

As previously stated, it is hypothesized that repeated microtraumas might set off an inflammatory reaction in the tunica albuginea of the penis. In the last few years, a prominent role has been recognized in the extracellular matrix (ECM), as being both the main actor and part itself of the fibrotic process. More in detail, ECM is involved in pivotal functions to start and maintain the profibrotic cascade. The intricate milieu connecting ECM, fibroblasts and innate/adaptative immune system cells has been recently described in detail by Pakshir and Hinz [26]. In brief, in response to first mechanical insult and tissue damage, several damage-associated molecular patterns (DAMPs) are released either from stressed cells and the ECM itself. Binding between DAMPs and toll-like receptors (TLRs) displayed on the surface of macrophages/dendritic cells stimulates various inflammatory responses. Specifically, TLRs trigger necrosis factor- κ B release, which in turn is responsible for the production of a wide range of proinflammatory cytokines, such as interleukin 1b (IL-1b), IL-6, and tumor necrosis factor α and elicit release of chemotactic and T-cell activating factors (primarily CD80 and CD86). In addition, in this phase macrophages/dendritic cells are able to chemically communicate with fibroblasts to start a myofibroblast phe-

Table 3. Prevalence of Peyronie's disease from the literature in particular subgroups of population

Author (year)	Patient population	Prevalence (%)
Arafa et al (2007) [31]	Diabetic patients with erectile dysfunction	20.3
Akbal et al (2008) [35]	Retroperitoneal fibrosis	20
Mulhall et al (2004) [30]	Men screened for prostate cancer	8.9
El-Sakka (2006) [32]	Patients with erectile dysfunction	7.9
Rhoden et al (2001) [33]	Men older than 50 years undergoing prostate cancer screening	3.7
Shiraishi et al (2012) [34]	General population and men undergoing hemodialysis	0.6–9.2

notype transformation through release of transforming growth factor (TGF)- β 1, ultimately resulting in ECM production.

On the other hand, myofibroblasts start depositing collagen in response to TGF- β 1 and, thus, may play a significant role in plaque formation. Several animal models already confirmed that TGF- β 1 overexpression is able to stimulate collagen deposition by myofibroblasts, finally leading to plaque development. Conversely, inhibitors of the TGF- β 1 receptor kinase stimulate the involution of fibrotic plaques and, as a consequence, lead to a decrease in penile curvature [27]. In particular, IL-1b induces matrix metalloproteinase expression, while TGF- β strongly induces tissue inhibitors of matrix metalloproteinases (TIMP) expression, ultimately resulting in PD plaque progression. As such, the local increase of TIMPs together with decreased matrix metalloproteinase activity may represent, thus, the biochemical result of TGF- β overexpression [28].

A key role in PD pathogenesis is also attributed to reactive oxygen species (ROS). ROS are either released by damaged/stressed cells or through cytokine-mediated activation of nicotinamide adenine dinucleotide phosphate (reduced form) (NADPH)-oxidase. Indeed, several cells involved in innate and adaptive immune systems can participate to ROS production through NADPH-oxidase pathway. As further evidence, previous studies demonstrated that inducible nitric oxide synthase may play a role as a ROS-scavenging factor in PD, acting as an antifibrotic agent [29].

Proangiogenic factors are also considered to be pivotal for distribution of paracrine factors to surrounding endothelial cells to favour the myofibroblasts-induced fibrotic process. Neo-angiogenesis is stimulated by hypoxia, which elicits hypoxia-inducible factor 1 up-regulation and subsequent release of vascular endothelial growth factor, ultimately leading to a fibrogenic response.

In summary, there are few crucial triggers for maintenance of fibrotic disease (1) chronic tissue damage stimulating myofibroblasts activation and release of ROS; (2) persistent recruitment of innate and adaptive immune systems, establishing a pro-fibrogenic environment; (3) ineffective remodeling modulated by hypoxia and subsequent neo-angiogenesis.

4. Transition to chronic phase

The second phase of PD generally starts approximately 12 to 18 months after disease onset. Transition to the chronic phase is defined when penile deformity remains stable for at least 3 months from its onset [6]. In some cases, chronic phase may start even earlier, within 5 to 7 months from disease onset [30].

During chronic phase, pain usually tends to complete resolution since acute inflammation process attenuates, and penile plaque is typically palpable. However, in this stage some patients may experience “torque pain,” or pain with rigid erections due to forcible straightening of the penis. Penile plaque becomes firmer due to protracted fibrosis or hard when calcification takes place. Penile curvature may continue to worsen in some subjects, and it hardly ameliorates in this second phase of PD [24].

5. Patient characteristics and disease course

Although PD is thought to be a disease that primarily afflicts older men, evidence suggests that PD may occur also in younger men. The prevalence may differ further in certain sub-populations (Table 3) [30-35].

It has been shown that younger age at disease onset and the presence of baseline vascular comorbidities (i.e., diabetes and dyslipidemia) demand even more urgency for early recognition and prompt intervention because of a higher risk for disease progression [25,36]. Retrospective series have proven that patients younger than 40 years are more likely to ask for treatment sooner,

present with multiple palpable plaques and have at least one cardiovascular risk factors, as compared with older subjects. Moreover, in this subset of patients, PD might be more likely to progress rather than stabilize [37]. On the other hand, comorbid vascular diseases have been corroborated to significantly increase the risk for developing more severe PD, irrespective of age. In a study conducted by Kendirci et al [38], diabetes, was confirmed as a strong independent predictor of more severe penile curvature. More recently, also testosterone deficiency has been proposed to be involved in fibrotic process and wound healing, being correlated with more severe penile curvature [39,40]. However, literature regarding this topic is restricted by small studies with methodological flaws and caution is required in the interpretation of data. Larger, prospective studies are warranted to clarify the role of testosterone deficiency in the development, evaluation, and treatment of PD.

6. Psychological and psychosocial distress

Current available data suggest negative impact of PD also on psychological sphere. Needless to say, the psychosocial repercussions of penile curvature on the patient, as well as on his partner, represent a non-negligible aspect to consider, although often underestimated.

PD can have a significant unfavorable emotional influence on men, secondary leading to depression, anxiety and low self-esteem [41]. In some reports, nearly 80% of men with PD were also diagnosed with clinically meaningful depression, due to reduction of penile length and the incapacity to have satisfactory sexual intercourse. In addition, more than 50% of patients described relationship difficulties, confirming that the burden of the disease falls also on patients' partners [6].

Some series suggest that early recognition and management of PD may ameliorate also psychological symptoms. In particular, subjects promptly notified about the disorder and its treatment options might be more likely to experience less distress and better quality of life [42].

7. Genetic factors and gene expression in Peyronie's disease

In the last few years, meaningful progresses have been performed towards an in-depth comprehension of the genetic factors related to PD [43]. Bias et al [44] in

1982 first proposed there might be a genetic predisposition to PD by analyzing three families presenting with both PD and Dupuytren's disease.

As mentioned above, high levels of TGF- β 1 play a key role in PD pathogenesis. In some cases, TGF- β 1 overexpression could possibly be justified in part by the presence of heritable single nucleotide polymorphisms (SNPs). To date, only one SNP has been clearly associated with PD, namely the G915C SNP, determining the replacement of arginine with proline at position 25 in the TGF- β 1 protein [45].

Gene expression profile studies on both PD-associated lesions and healthy tunica albuginea have also been conducted [46]. The genes coding for pleiotrophin (a growth factor stimulating fibroblast recruitment and osteogenesis) and MCP-1 (a chemotactic factor for monocytes) were the ones showing the highest differential expressions. Conversely, the most important downregulated gene was the one coding for SMAD7, a part of the self-regulatory TGF- β 1 pathway, normally acting as an antifibrotic factor [47].

CONCLUSION

Several open questions about natural history of PD still remain unsolved. One of the main issues is still represented by lack of standardized definitions for the different stages of the disorder. Certainly, correct definition of acute and chronic phase has been hampered by a number of factors including lack of standardization of patient populations being studied and lack of a uniform definition of successful outcome in previous studies. To this regard, we identified future perspectives for a better comprehension of the natural history of PD and its underlying mechanisms: (1) further studies are required to better define the natural course of PD, specifically using objective, non-biased criteria and standardized definitions for categorize the different stages of the disorder; (2) future studies on this topic should also investigate risk factors related to PD progression; and (3) further prospective studies with a longer period of observation would be needed towards a better understanding of PD natural course. In this light, acknowledging that several papers reported low rate of spontaneous healing, we truly believe that PD represents a progressive chronic fibrotic process.

Conflict of Interest

The authors have nothing to disclose.

Author Contribution

Conceptualization: FDM, MC, AC. Data curation: LL, FV. Methodology: GC, AM. Project administration: AC. Supervision: GM, MC, AM, AC. Validation: GM, AM, MC, AC. Visualization: AM, AM. Writing – original draft: FDM, GC. Writing – review & editing: AC.

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