

# Mini-reviews

There is a wide variety of topics covered in this section. The epidemiology, aetiology and clinical evaluation of the deformity in Peyronie's disease is described, followed by a discussion of recent advances in the biology of diabetes-associated bladder complications. Bladder cancer and its molecular prognostic factors are presented, and the section ends with an in-depth presentation of an evidence-based approach to the understanding of the pharmacological class effect in the management of prostatic diseases.

## Peyronie's disease: the epidemiology, aetiology and clinical evaluation of deformity

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### DEFINITION

Peyronie's disease (PD) is a localized connective tissue disorder that affects the tunica albuginea of the penis. Fibrous scar tissue, which replaces the normally elastic fibres, causes a characteristic penile deformity that is most evident during erection. This pathological process can manifest as increased curvature, indentation, shortening or an 'hourglass' irregularity of the penis. The diagnosis of PD is often preceded by painful erections, and can be associated with erectile dysfunction and palpable areas of induration (plaques).

### EPIDEMIOLOGY

While PD was once considered to be relatively uncommon, studies now suggest that its prevalence is similar to that of diabetes or urolithiasis [1]. A recent epidemiological study reported an overall prevalence of the condition of 3.2% [2], much higher than once thought, highlighting the potential physical and psychosocial impact of the disease on society. Compounding these effects on the community are the changing demographics of the population, which are predicted to increase age-related conditions.

Of concern is the belief by some that even the most recent data underestimate the true prevalence of PD. Men might be reluctant to report a condition that they consider embarrassing, and older men might often accept their symptoms as insignificant consequences of ageing. Many physicians agree that the true prevalence of PD has become more apparent since the advent of oral sildenafil, which has seen a marked improvement in community awareness of erectile dysfunction [1].

Unfortunately, the quality of epidemiological data on PD remains erratic, with one contributing factor being the various criteria used by researchers to define the condition. The most accepted objective measures include the number, size and location of plaques, as well as induration and curvature. Nevertheless, epidemiological data have been used to propose risk factors associated with PD. Hypertension, smoking, diabetes and hyperlipidaemia have all been suggested as risk factors, but these are more likely to be related to erectile dysfunction in general, and current research has shown no substantial relationship between these factors and the severity of penile curvature [3].

### AETIOLOGY AND PATHOPHYSIOLOGY

Although the exact causes of PD remain enigmatic, recent developments in animal

(*in vivo*) and cell culture (*in vitro*) models have provided an invaluable medical platform to analyse the pathophysiology of PD. El-Sakka *et al.* [4] used rats as an experimental model in a causal *in vivo* investigation of PD. Injections of cytomodulin (a synthetic heptapeptide with a similar action to TGF- $\beta$ ) into the penile tissue of rats consistently produced an intense fibrotic reaction in the tunica albuginea. The study provided evidence of the pathogenetic function of TGF- $\beta$  in PD, and promoted the use of *in vivo* analysis as an effective tool in the search for therapeutic solutions.

Mulhall *et al.* [5] cultured cells from plaque-derived tissue; this *in vitro* analysis showed reliable phenotypic, genotypic and functional alterations in pathological tissue compared to normal tunica-derived or neonatal foreskin-derived fibroblasts. While this model was not able to flawlessly replicate the *in vivo* environment, it allowed an investigation of factors upstream of TGF- $\beta$  that influence the pathogenetic pathway. Other advantages of the cell-culture model include cost and time efficiency, reproducibility, and the identification of tissue cell variance between patients.

Many of the theories that seek to explain the pathogenesis of PD have been derived from either animal or cell-culture research. While trauma is considered to be the provocative stimulus, other theories include: failure of fibrin clearance; collagen alterations; genetic predisposition; autoimmune factors; free radical production; and cytogenetic aberrations. In 2003 Mulhall [6] described a paradigm that encompassed these different theories to explain plaque developmental pathogenesis in PD; an adapted version follows:

- Penile trauma in genetically susceptible males, leading to;
- endogenous and/or exogenous factors (localized autoimmune response), leading to;
- loss of suppressor genes and activation of promoter genes, leading to;
- cell-cycle regulator dysfunction, leading to;
- biological transformation of constituent cells within tunica/plaque, leading to;
- cytokine over-expression, free radical production and cytogenetic changes, leading to;
- unregulated extracellular matrix deposition (fibrin and collagen), leading to;
- plaque formation.

## TRAUMA

Trauma is reported to be the important initiating factor, and the ensuing inflammatory response is considered to be heightened through confinement in the densely packed layers of the tunica albuginea. It is proposed that the trauma originates from excessive physical forces inflicted on the penis during penetrative sex, which result in tunical delamination and microhaemorrhaging into the subtunical spaces [6]. The subsequent formation of scar tissue in the tunica albuginea occurs where the strands of the septum are attached to the dorsal and ventral aspects of the penis; these are the points under maximum stress when the elastic tissue of the penis is stretched to its capacity [7].

The fibrin deposited initially as a consequence of repetitive microvascular injury is a normal component of wound healing, but pathological scar tissue forms when repetitive trauma leads to inadequate resolution of the lesion [7]. Recent research has shown that the additional accumulation of collagen in the tunica albuginea is disorganized, and there is a diminished and chaotic dissemination of elastin fibres [8]. Despite these findings, more information is needed on the cause of the fibrin deposition and subsequent failure of degradation.

## GENETIC PREDISPOSITION AND AUTOIMMUNE FACTORS

Genetic predisposition has been suggested as a causal factor, because of the familial clustering of the condition, and studies assessing human leukocyte antigen linkage have shown that PD is strongly associated with both Dupuytren's contractures and human leukocyte antigen B27 [6]. Patients with PD have various degrees of autoimmunity, supporting the theory that an autoimmune reaction after trauma might be the cause of the additional fibrosis and scarring [9]. Diverse markers of immune incompetence were reported in affected patients, but the proposed autoimmune susceptibility is believed to be localized to the tunica albuginea.

## CYTOGENETIC ALTERATIONS

Chromosomal instability has been shown in fibroblasts from pathological plaques in PD, and similar cytogenetic abnormalities have been found in samples from patients with

Dupuytren's contracture. This raises the possibility of a common pathway leading to fibrosis. Genotypic analyses have shown that chromosomal instability is significant in plaque-derived cells with fibroblasts from either foreskin or normal tunica [5].

Profibrotic or fibrogenic cytokines increase fibroblast collagen production and proliferation rates. While there are many families of fibrogenic cytokines, it has been established that TGF- $\beta$ 1 is up-regulated in PD [10]. TGF- $\beta$ 1 also stimulates the expression of the profibrotic cytokines, including monocyte chemoattractant protein 1 and connective tissue growth factor. Further contributing to this fibrogenic effect, increased levels of basic fibroblast growth factor in plaque-derived cell cultures cause an overproduction of extracellular matrix by fibroblasts [11].

Cellular over-proliferation in PD is associated with aberrant p53 function that allows damaged cells to pass through the cell cycle and proliferate. This abnormal pathway has been shown in plaque-derived fibroblasts and indicates an absence of cell-cycle checkpoints in these cells [12]. While a significant presence of p53 protein has been recognized in pathological plaque fibroblasts, relatively low levels were found in normal control samples [13].

## FREE RADICAL FORMATION

Cellular antioxidants are reported to have a role in preventing plaque growth in PD; their ability to combat the effects of free radicals, including reactive oxygen species and reactive nitrogen intermediates, appears to be an important component in minimizing the proposed damage caused by oxidative stress [14]. However, therapeutic antioxidants (vitamin E and superoxide dismutase) have been used with mixed success, and given that many signalling pathways are poorly understood, further research is needed to determine the function of free radicals in calcification and plaque formation.

Smooth muscle cells and macrophages, among other cell types, produce inducible nitric oxide synthase when stimulated. When this enzyme is up-regulated, high levels of nitric oxide generate potent free radicals, which lead to oxidative stress and poor vasorelaxation. Although this process is thought to exist in PD, some studies suggest that nitric oxide might limit tunical scarring

TABLE 1 A summary of the clinical evaluation of penile deformity in PD

Measures Subjective	Objective
Questionnaire or clinical history:	Penile length:
Presenting symptoms	Measure dorsally from base to meatus
Duration of disease	Ensure penis is at full stretch
Previous penile injury	
Risk factors for erectile dysfunction	Plaque characteristics:
Medical and sexual history	Callipers or rulers most reliable
Level of satisfaction	Ultrasonography or MRI
Psychological distress	
	Erectile capacity:
Patient observations:	Penile duplex ultrasonography after
Curvature direction and degree of severity	a vasoactive penile injection
Girth-related changes	
	Penile curvature:
Physical examination:	Protractor most reliable, recorded at point of
Genitourinary assessment	maximum erection
Hands and feet for systemic fibromatosis	
'Eyeball' curvature, length, and erection capacity	

and contraction by restricting myoblast proliferation [15].

#### OTHER CAUSES

PD is also associated with invasive procedures on the penis, e.g. radical retropubic prostatectomy, cystoscopy and urethral catheterization; genital or peritoneal trauma; urethritis; uric acidemia; and lipoma [16]. Atherosclerosis has been mentioned as a specific area of interest, as its pathological mechanism is similar to that of PD [5], as atherosclerosis is also subject to cellular over-proliferation leading to fibrotic plaque formation.

#### CLINICAL EVALUATION OF THE DEFORMITY

The accurate clinical evaluation of penile deformity secondary to PD requires both subjective and objective measures (Table 1).

#### SUBJECTIVE MEASURES

The initial component of a subjective evaluation is often achieved using a questionnaire or clinical history to estimate the degree of deformity and its effects on the patient's quality of life. There are many established questionnaires to assess sexual function, including the International Index of Erectile Function, the Derogatis Interview for

Sexual Functioning, and the Social Desirability Scale. The Peyronie's Disease Index, first introduced by Shabsigh *et al.* [17], is a questionnaire specifically designed to address issues most pertinent to patients with PD.

The aim of the initial evaluation is to provide information on the duration of disease, recalled injury and presenting symptoms (curvature, length, rigidity, softening, erection pain, coitus, girth and hinge). Ideally, information on psychological distress and level of satisfaction should be obtained, as well as potential risk factors for erectile dysfunction. Strategies to elicit the patient's assessment of curvature direction and degree of severity might include the use of visual analogue scales.

The next component of subjective evaluation involves a physical evaluation. Levine and Greenfield [18] recommend that the examination should start with a routine genitourinary assessment, which is then extended to involve an assessment of hands and feet for indications of systemic fibromatosis (e.g. Dupuytren's contracture). Other subjective information sometimes noted on physical examination includes 'eyeball' evaluations of penile curvature, penile length change and differences in erection capacity. Girth-related changes are most commonly reported by the patients, despite the recommended use of string or flexible rulers to measure it directly.

#### OBJECTIVE MEASURES

The objective evaluation of penile deformity in PD includes measurements of length, plaque characteristics (size and location), erectile capacity and curvature. There is currently no standardized approach for assessing penile length, but it is recommended to measure it dorsally from the base to the meatus while the penis is at full stretch [18]. It is hoped that this will minimize the potential effect of proximal penile fat and skin variability. Unfortunately, measurements of length obtained in the erect state are difficult to reproduce.

While a reduction in plaque size has not been shown to correlate with improvements in other functional deformities, it is often reported as a target for treating PD [18]. Measuring the plaque size is difficult because of extensions through the septum and variability in thickness, with the use of callipers or rulers thought to offer the most practical solution. Ultrasonographic techniques are useful to verify the presence of any arterial or mixed vascular abnormalities, and can be used to identify distinguishing plaque features including size, hypo/hyperechogenicity, calcification and tunical albuginea thickening [19]. MRI might provide additional information about local inflammation if required [20].

Erectile capacity or rigidity is often measured subjectively in standardized questionnaires, and this is important in assessing patient satisfaction and quality of life. However, objective measurements can also be obtained using penile duplex ultrasonography after administering a vasoactive penile injection. Other objective measurement options include nocturnal penile tumescence and rigidity monitoring, and cavernosometry, but these are poor predictors of sexually induced erections [18].

Penile curvature is recorded at the point of maximum erection, and measurement by protractor is reported to be the most reliable technique. However, assessing penile angulation is often inaccurate because of variability in penile rigidity at the time of evaluation. Vacuum-induced erection in the clinic contributes to this variability, as the erection obtained is often not representative of the patient's normal erection. Measurement of angulation from photographs has also been suggested to be inaccurate because of several inconsistencies [18].

## CONCLUSION

The prevalence of PD is much greater than previously thought, with the condition now reported to affect 3.2% of the male population. This confirms fears that it is becoming a major public health issue for ageing men, with action now required to minimize the impact on society. The development of extensive screening programmes would offer a means for evaluating associated comorbidities, and would provide a better understanding of the risk factors for PD. The need for medical practitioners to adopt a standardized approach to the clinical evaluation of penile deformity will also be greater as the condition becomes more common.

Much debate remains over the pathophysiological mechanisms leading to excessive scarring and fibrosis. Recent refinements of cell culture and animal models have enhanced understanding of what is thought to be a multifactorial process. While it appears that penile trauma is the major inciting factor in the causes of PD, it is unlikely to be solely responsible, as only some men are susceptible, despite having similar sexual experiences to the rest of the population. With further research into the pathological cascade of cellular and molecular events, and an increase in community awareness of the disease, the development of effective therapeutic and prophylactic measures will become a realistic objective.

## CONFLICT OF INTEREST

None declared.

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**Abbreviations:** PD, Peyronie's disease.