

Peyronie's Disease: Advances in Basic Science and Pathophysiology

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Peyronie's disease is an idiopathic, localized connective tissue disorder of the penis that involves the tunica albuginea of the corpus cavernosum and the adjacent areolar space. The tunica albuginea plays an important role in the mechanism of erection. Peyronie's disease is characterized by local changes in the collagen and elastic fiber composition of the tunica albuginea. The formation of fibrotic plaques alters penile anatomy and can cause different degrees of bending, narrowing, or shortening of the penis. Moreover, a significant number of men with Peyronie's disease develop erectile dysfunction. Penile blood flow studies in many patients with Peyronie's disease suggest a strong association with veno-occlusive dysfunction. Although long recognized as an important clinical entity of the male genitalia, the etiology of this disease has remained poorly understood. The following review focuses on recent research on the pathophysiology of Peyronie's disease.

Introduction

Peyronie's disease, or *induratio plastica*, is a penile condition named after Francois Gigot de la Peyronie, who first reported on a small clinical series of penile curvature in 1743. Despite its early recognition as a disease entity, the etiology and mechanism of this well-recognized symptom complex has remained an enigma. Peyronie's disease likely involves a sclerosing inflammatory process that invokes localized changes in the tunica albuginea of the penis. The end result is a fibrous plaque that contains an excessive amount of collagen, alterations in its elastin framework, and fibroblastic proliferation. The pathologic changes consequently alter penile anatomy and may dramatically affect erectile function. Approximately 10% of the men

suffering from erectile dysfunction have Peyronie's disease, whereas erectile dysfunction is known to occur in 20% to 40% of men with Peyronie's disease [1••,2,3].

Peyronie's disease usually affects males between the ages of 40 and 70, with a published 0.39% to 3.2% incidence; in a population-based study in Rochester, Minnesota, its prevalence was reported as 389 per 100,000 men [2,4,5]. The actual prevalence of this disease is likely to be higher due to patient embarrassment and limited reporting of this disorder by physicians. With increasing numbers of men being successfully treated for erectile dysfunction (ED), an increasing number of cases of Peyronie's disease are becoming manifest and presenting for clinical evaluation. Men with Peyronie's disease may report penile pain, penile angulation, palpable plaque, and decreased erectile function. The penile curvature is a result of scar tissue or plaque in the tunica albuginea of the corpus cavernosum of the penis (Fig. 1). The rigid plaque is found on the side of the corpus cavernosum to which the curvature is directed.

There are several proposed theories as to the origin of Peyronie's disease, including vitamin E deficiency; the use of beta-blocking agents; increased levels of serotonin, as in carcinoid syndrome; genetic disorders; and repetitive vascular trauma inciting a low-level autoimmune response with fibrosis and plaque formation [6-10]. Peyronie's patients may have a genetic predisposition, as witnessed by its association with Dupuytren's contracture and HLA-B7 antigens [11,12]. More current proposals suggest that fibrosis and collagen changes of the tunica albuginea are the result of an inflammatory process triggered by vascular trauma [1••,9]. Following trauma or injury to the penis, the release of cytokines theoretically activates fibroblast proliferation, resulting in collagen deposition and the formation of a Peyronie's plaque. Therefore, Peyronie's disease has been defined by some authorities as a wound-healing disorder, much like the dermatologic conditions of keloid formation, hypertrophic scarring, and Dupuytren's contracture [13]. Despite the myriad of etiologic theories, there has been until recently a limited number of advances in the basic scientific understanding of the pathophysiology of Peyronie's disease.

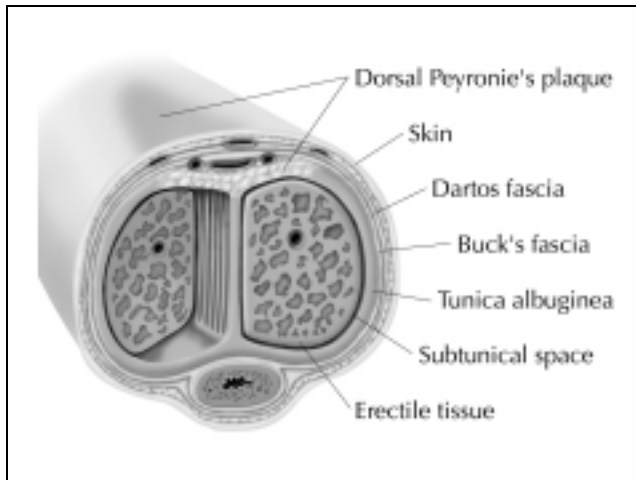


Figure 1. Cross section of a penis containing dorsal plaque of Peyronie's disease.

Pathophysiology

Peyronie's disease affects primarily the tunica albuginea of the penis. Elastic fibers located within the tunica albuginea of the penis form an irregular latticed framework upon which collagen rests. These elastic fibers are important in maintaining the structure of the collagen bundles. These two structural components are essential to penile erection because they permit both an increase in girth and length during tumescence [14,15]. Any defect of the tunical collagen or elastic fiber network may lead to significant alterations in the hemodynamics of erection. ED is a major quality-of-life issue, with estimates of 20 to 30 million men suffering from this condition in the United States alone [16,17]. There are estimates ranging from 20% to 40% of men with Peyronie's disease suffering from erectile dysfunction [1••,2,3]. Unfortunately, there is no proposed causal mechanism to explain why some patients with Peyronie's disease develop ED.

The histopathology of Peyronie's disease demonstrates an inflammatory process, characterized by chronic lymphocytic and plasmacytic infiltration of the tunica albuginea. The origin of the initial inflammatory process that causes changes in collagen and elastic fiber composition and leads to fibrosis, calcification, and plaque formation in the tunica albuginea is unknown. Devine *et al.* [18] have postulated that minor penile trauma can occur during sexual intercourse, whereby the corpora cavernosa bend and stretch, resulting in a delamination injury of the tunica albuginea predominantly at the dorsal, midline septum. Levine *et al.* [13,19••] have in turn hypothesized that following injury to the penis, an unregulated wound healing process occurs, with excessive fibroblast proliferation and extracellular matrix deposition. Peyronie's plaques typically form a loose areolar connective tissue sleeve that separates the corpus cavernosum from the tunica albuginea. In the early stages of this condition (usually less than 3 months), this sleeve contains a peri-

vascular lymphocytic and plasmacytic inflammatory cellular infiltrate. After this early inflammatory phase, progression to fibrosis occurs, leading to a thickened connective tissue plaque, with possible calcification. Electronmicrographic evaluation of these plaques confirms a vasculitis in the tunica albuginea associated with mast cells, further supporting the inciting role of inflammation [20].

The penile plaques of Peyronie's disease are mainly composed of collagen. Previous studies demonstrated this to be predominantly type I and type III collagen fibers. Somers *et al.* [21,22] quantitated the collagen content of Peyronie's plaques as a percentage of total protein in penile tissue and found that it increased from 47% in men without to 68% in patients with Peyronie's disease. Types I and III collagen expression are commonly present in penile scar tissue, whereas type III collagen is identified more abundantly in Peyronie's plaques. Moreover, the demonstration of increased type III collagen in the "normal" penile tissue adjacent to the plaque tissue suggests that this disease is not specific to the plaque but may be more generalized throughout the corporal tissues [22–25]. Of particular interest is the observation of increased type III collagen expression in patients with venogenic impotence [24]. In men who suffer from veno-occlusive dysfunction or who have Peyronie's disease and ED, type III collagen fibers are found in greater abundance in the tunica. This finding is rare in the tunica albuginea of potent men.

Elastic fiber concentrations in the tunica albuginea are also significantly decreased in Peyronie's patients. There is a significantly lower quantity of elastic fibers in impotent men with Peyronie's disease compared with Peyronie's patients who maintain potency. Antibodies to elastin are present in all individuals. However, Peyronie's patients exhibit increased levels of anti-tropoelastin (reflecting elastin synthesis) and anti- α -elastin (reflecting elastin destruction) [26], giving reason to believe that an autoimmune mechanism specifically affecting the elastin framework may be involved in the pathogenesis of Peyronie's disease.

New Advances in Research

Peyronie's disease research has intensified over the past decade. Previously, most basic research focused on in vitro models of cultured Peyronie's plaques, tunica albuginea, and cavernosal tissues. Unfortunately, these in vitro studies were not adequate to evaluate the in vivo physiology of the penis after induction of a Peyronie's-like condition. An exciting development has been the recent introduction of an animal model to study the mechanism of Peyronie's disease in vivo.

Historically, in the early 1980s, Somers *et al.* [27] developed a cell culture model of Peyronie's plaques to study the cell biology of Peyronie's disease. They demon-

strated that Peyronie's plaque cells grew to higher saturation densities with an enhanced proliferative capacity compared with normal cavernosal tissue found adjacent to the Peyronie's plaque. Transmission electron microscopy identified myofibroblast-like cells in the Peyronie's plaque cell line. More recently, Hirano *et al.* [28] have shown in vitro that cavernosal tissue adjacent to Peyronie's disease plaques exhibit ultrastructural changes in smooth muscle and endothelial cells. These authors concluded that the presence of Peyronie's disease affects more than the tunica albuginea tissue, with functional effects on corpora cavernosa tissue adjacent to Peyronie's plaques [28]. Nicholson *et al.* [29] have explored the concept that telomerases may play a role in the proliferation of tunical fibroblasts in cell culture and the pathophysiology of Peyronie's disease. They note that certain somatic cells, germ cells, and cancer cells possess telomerases, ensuring immortalization and proliferation of the involved cell line. However, they didn't detect any telomerase activity in tissue samples containing Peyronie's plaque and normal tunica albuginea [29]. This lack of telomerase activity may explain the self-limiting and benign course of this condition in the majority of affected men.

Oxidative reactions are often associated with fibrogenesis, and evidence in the literature supports the role of oxidative stress and the stimulation of reactive oxygen species in the pathogenesis of this type of disease [30]. One result of fibrogenesis is the increased synthesis of collagen. In 1993, Schellenberg *et al.* [31] postulated that free radicals were involved in the pathogenesis of Peyronie's disease. They reasoned that because early lesions involve perivascular infiltrates of lymphocytes, monocytes, and neutrophils, the mechanism of plaque fibrosis probably resulted from injury and an ensuing inflammatory process. Subsequently, Ahuja *et al.* [32] demonstrated that cavernosal cells subjected to the oxidizing reagent glyceraldehyde have an increased production of collagen types I and III fibers. These results demonstrate that oxygen free radicals can precipitate collagen formation in transformed fibroblasts from human cavernosal cells in culture.

Collagen synthesis in adult tissues is subject to regulation by a variety of endogenous and exogenous factors. Biologically active peptides, such as interleukin-1, tumor necrosis factor, epidermal growth factor, and transforming growth factor beta (TGF- β), have been implicated in normal collagen synthesis and fibrosis [33,34]. Among them, TGF- β has been shown to be involved in many chronic fibrotic conditions, in addition to being involved in numerous vital processes, such as inflammation, stimulation of extracellular matrix, and the normal healing process [33]. TGF- β is a vital cytokine to tissue repair; however, an excess may induce tissue damage and scarring as witnessed in a variety of connective tissue diseases (*eg*, pulmonary fibrosis, fibrotic liver disease, and systemic sclerosis [33]). Furthermore, TGF- β 1 is the isoform most

implicated in tissue fibrosis and is upregulated in response to tissue injury. Recently, El-Sakka *et al.* [35] demonstrated an upregulation of TGF- β in the tunica albuginea of Peyronie's disease patients compared with the tunical tissue of men without Peyronie's disease. The expression of TGF- β mRNA and protein in the tunica albuginea of the male penis as well as the induction of collagen synthesis in cell culture suggests a role for TGF- β in corpus cavernosum tissue synthesis [35,36].

A new animal model for Peyronie's disease has been proposed by El-Sakka *et al.* [37,38]. These authors have explored the role of TGF- β and surgical trauma in the induction of a Peyronie's-like condition in the rat. Their studies demonstrate histologic and ultrastructural alterations in the rat penis after a Peyronie's state was induced. Histologic changes observed in this animal model included chronic inflammatory infiltration; focal and diffuse elastosis; and thickening, disorganization, and clumping of the tunica albuginea [37,38]. The ultrastructural changes to the penis included dense collagen bundles and separation of neuronal fibers by clumps of packed collagen. Bivalacqua *et al.* [39] further characterized this rat model of Peyronie's disease by demonstrating a role for nuclear factor kappa B (NF- κ B), a transcription factor that regulates the expression of several genes that encode adhesion molecules. These authors demonstrated the immunohistochemical presence of NF- κ B in the initiation of a Peyronie's-like condition in the rat during the first 3 weeks after TGF- β injection and injury to the rat penis [39]. Also, with the use of immunohistochemistry techniques, an increase in collagen types I and III fibers has been observed in the TGF- β 1-injected rat tunica albuginea and cavernosal tissues [40]. This confirms that increases in collagen types I and III production contribute to the formation of Peyronie's disease. These rat penis studies demonstrate that TGF- β injection and surgical injury can induce symptoms similar to those found in humans with Peyronie's disease and that this animal model has the potential for further investigations into the mechanisms of Peyronie's disease.

In the penis, nitric oxide (NO) is released from nerve terminals and the endothelium lining of the cavernosal sinusoids and blood vessels, and subsequently diffuses into the smooth muscle cells where it binds to guanylate cyclase to increase intracellular levels of cGMP [41]. This process reduces intracellular calcium (Ca^{2+}), resulting in cavernosal smooth muscle relaxation and ultimately penile erection. NO is derived from its substrate, L-arginine, under the catalytic action of nitric oxide synthase (NOS) [41,42]. At least three distinct forms of NOS have been cloned and characterized. The constitutive forms of the enzyme, endothelial NOS (eNOS) and neuronal NOS (nNOS), are coupled to Ca^{2+} and calmodulin. The inducible form of NOS (iNOS) is independent of Ca^{2+} and calmodulin. It is primarily found in macrophages but is generally believed to be expressed after cytokine induction

and upregulated in pathophysiologic conditions and inflammatory states. The constitutive forms of NOS under the control of intracellular calcium are the principal mediators of cavernosal smooth muscle relaxation in the penis. In contrast, the activity of iNOS appears to be controlled at the transcriptional level through the activation of several transcriptional factors, including NF- κ B. The role of iNOS in the penis is less clear; however, it has been shown to exist in human corporal smooth muscle cells and in cavernosal tissue from Peyronie's disease and diabetic patients [43,44,45•]. Recently, Bivalacqua *et al.* [45•] showed that there is a significant decrease in erectile function as measured by cavernosal nerve stimulation and pharmacologic stimulation with the endothelium-dependent vasodilator acetylcholine in animals that have been injected with TGF- β 1 into the tunica albuginea or subjected to surgical trauma. At a time when erectile responses were reduced in the Peyronie's rats, there was an upregulation of inducible NOS and a downregulation of constitutive NOS protein expression [45•]. Together, these results unveil a homeostatic mechanism that may be important for the maintenance of vascular tone and document a possible mechanism by which some men with Peyronie's disease suffer from ED.

Conclusions

Peyronie's disease starts as a sclerosing inflammatory process and develops into a connective tissue disorder involving the tunica albuginea. A better understanding of the inflammatory response and the mechanisms by which fibrosis occurs in the tunica albuginea will undoubtedly offer new avenues for future medical intervention in Peyronie's disease. Agents that modify cytokine action, fibroblast function, and extracellular matrix deposition head the list in this area of therapeutic investigation.

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