Current aspects of the medical and surgical management of Peyronie’s disease

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Abstract
Peyronie’s disease is characterized by an alteration in the scarring process of the tunica albuginea that conditions deformity, curvature, and narrowing and shortening of the penis, along with significant sexual dysfunction. Numerous non-surgical treatments have been studied and suggested, but none of them has shown a real and effective correction of penile deformity. Therefore surgery continues to be the criterion standard for the correction of curvature and deformity caused by Peyronie’s disease. This article describes important aspects to be considered in the diagnosis and medical and surgical management of Peyronie’s disease.

PALABRAS CLAVE
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Resumen
La enfermedad de Peyronie es una enfermedad que se caracteriza por una alteración en el proceso de cicatrización de la túnica albugínea que condiciona deformidad peneana, curvatura, estrechamiento y acortamiento del pene, y compromete la función sexual de manera importante. Aunque se han estudiado y sugerido múltiples tratamientos no quirúrgicos, ninguno de estos ha demostrado de manera real y efectiva la corrección de la deformidad peneana. Por dicha razón, la cirugía continúa siendo el estándar de oro para la corrección de la curvatura y deformidad generada por la enfermedad de Peyronie. En este artículo mencionamos aspectos importantes a considerar en el diagnóstico y manejo médico-quirúrgico de la enfermedad de Peyronie.

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**Introduction**

For many men the form, size, and function of the penis are the scale by which they measure their health and masculinity. The appearance of any disease that conditions dysfunction or deformity in the penis causes great concern. Penile deformities are more frequent than what is generally thought. They cause severe sexual function alteration sometimes resulting in serious problems for the couple, given that penetration can be impossible and also painful. This conditions great frustration and depression that leads to psychosexual dysfunction, which in turn causes erectile dysfunction. Peyronie's disease is one of the acquired penile deformities. It was first described by Francois Gigot de la Peyronie in 1743 and is a condition that presents deformity of the penis characterized by a fibrous plaque in the penile tunica albuginea. 

Erectile dysfunction and pain are a frequent manifestation of this disease. Its etiology and the mechanism by which it is produced are not fully understood. Microtrauma and the alteration of scarring mechanisms are accepted as the main cause.

Medical treatment advances have been made, but there is still no effective medication. Surgical management continues to be the criterion standard once the formation of plaque has stabilized.

**Epidemiology**

The epidemiologic data of Peyronie's disease has varied widely since it was first reported. In 1928 Polkey reported 550 cases worldwide and an Italian report published in 1966 described 3,600 affected patients. In 1968 Ludvik established a rate of 0.3%-0.7% in patients seen in urologic private practice. In 1991 Lindsey postulated a prevalence of 388.6 cases of Peyronie's disease per 100,000 patients in Rochester, Minnesota. At the Devine Center, close to 1% of the medical population between the ages of 30 and 65 years has Peyronie's disease. Peyronie's disease diagnosis has been established much more frequently in autopsies. Smith observed a mild form of Peyronie's disease in 23 of 100 postmortem examinations. In 2002 in a study conducted by the Urology Department of the University Hospital of Cologne, Germany in which 4,432 patients were surveyed, Schwarzer et al. reported a prevalence of 3.2%. In the last few years the reported prevalence has been between 3% and 9% in the adult male population.

Peyronie's disease prevalence may be greater, given that patients are reluctant to report this pathology.

**Pathophysiology**

Peyronie's disease mainly affects the tunica albuginea of the penis. Elastic fibers are found there that maintain the structure of collagen bridges. However, this disease has functional effects on the tissue of the corpora cavernosa adjacent to the plaque, exhibiting ultrastructural changes in vitro in the smooth muscle and endothelial cells.

The plaque in Peyronie's disease is due to the replacement normal structural elements of the tunica albuginea with disorganized and excessive collagen, fragmented elastic fibers, and their eventual calcification. Histologically, it is a process of inflammation characterized by chronic infiltration of the tunica albuginea by lymphocytes and plasma cells.

The origin of this inflammatory process is unknown, but microtrauma and an unregulated wound healing process with excessive proliferation of fibroblasts and extracellular matrix deposition is the most accepted cause.

Fibrin deposit seems to be an early event in the pathophysiology of plaque formation.

After an initial period, the plaque present in Peyronie's disease progresses to fibrosis. This plaque is composed mainly of type I and type III collagen, the latter being the most abundant.

An overexpression of the transforming growth factor beta 1 (TGF-ß1) has been demonstrated in patients with Peyronie's disease and the relation between this factor and fibrosis has been described. The transcription of genes that control the synthesis and deposit of collagen and proteoglycans is increased and protease secretion is decreased, resulting in the synthesis of proteins that inhibit protease activity, reducing the synthesis of nitric oxide (NO) by transcriptional inhibition of inducible nitric oxide synthase (iNOS), while reactive oxygen species (ROS) are simultaneously created. These changes have been replicated in animal models injected with cyt moodulin, a TGF-ß1 analog.

Fibrin has been directly applied to the tunica albuginea in animal models, producing plaque similar to that in Peyronie's disease, sooner than in those injected with TGF-ß1, but TGF-ß1 levels were found to be significantly higher in the lesions.

Establishing fibrin as the initiator of the pathophysiology of Peyronie's disease has been limited because the samples are obtained during surgical correction, when there is no immature plaque.

Additionally, the overexpression of monocyte chemoattractant protein-1 (MCP-1) has been associated with fibrosis in organs such as the liver, kidney, lung, and skin and it has been tested as a potential target of directed therapy in Peyronie's disease.

Platelet-derived growth factors (PDGF-A, PDGF-B) can exacerbate fibroblast proliferation; their receptors have been found to be strongly expressed in cells similar to fibroblasts in the tunica of samples from men with Peyronie's disease.

Myofibroblasts (differentiated fibroblasts that have acquired an intermediate phenotype between the progenitor cell and the smooth muscle cells) are replicated and activated to produce collagen, cytokines, TGF-ß1, and other inflammatory mediators, NO and ROS; in addition they have receptors for TGF-ß1, PDGF, and fibroblast growth factor.

The potential role of chromosomal instability in the pathophysiology of Peyronie's disease has been studied in cell cultures derived from plaque. They have been shown to have random chromosomal changes, suggesting karyotypic instability, whereas cell cultures derived from adjacent tissue have been normal. Aneusomies have been demonstrated in chromosomes 7, 8, 17, 18, and X; and recurrent Y chromosome deletions.
The ROS are reduced by the antioxidant effect of NO, which is not fibrogenic, but can be pro-apoptotic in high concentrations. The balance between NO and ROS determines the balance between fibrosis and normal wound healing.

Gene therapy has been used for administering iNOS in the fibrotic plaque created with fibrin in animal models, resulting in significant plaque reduction, highlighting a new treatment option for Peyronie's disease. 20

**Diagnosis**

An internationally accepted evaluation standard has not yet been established for Peyronie’s disease. A form of standardized evaluation has been suggested that includes the medical history, physical examination, diagnostic imaging, and not-yet-validated questionnaires. 21

The anamnesis should contain the time of onset, the initial symptoms and how they presented, including pain, deformity, and palpable plaque. The patient should be asked about any event of trauma preceding symptom onset in the previous months and whether there is a family history of Peyronie’s disease or other disorders such as Dupuytren’s disease. He should be asked about previous treatments he may have received, the grade of erection on a scale of 0-10 before and after disease onset, and also asked to estimate the grade and direction of penile curvature. 22

The physical examination should include measuring the length of the penis; the technique described by Wessells can be used in which the patient is in the supine position, the penis is stretched at a 90º angle, and with a rigid ruler pressing the fat up the pubic bone, is measured dorsally up to the corona of the glans penis or the meatus 23 (fig. 1).

The hands and feet should be examined for evidence of Dupuytren’s contractures and Ledderhose nodules. Penile deformities should be measured and photographed in erection. Duplex ultrasound can be used in the initial evaluation for determining fibrosis of the body and calcification of the plaque, as well as the vascular integrity of the penis in erection and the erectile response to vasoactive agents. Recent articles suggest that a resistance index below 0.8 in the Doppler ultrasound is predictive of postoperative erectile dysfunction and should be regarded as a parameter for placing a prosthesis vs. graft corporoplasty. 24 Curvature should be measured with a goniometer, measuring the width at the base, subcoronal area, and stretching zones.

**Treatment**

The appropriate therapy is chosen based on the erectile status of the patient, presence of pain, time of onset, and psychological state. In the initial stages, conservative management is usually recommended. Indications include men that are in an early disease phase (<12 months) manifested by progressive and unstable deformity, painful erections, and patients that do not wish to undergo surgical management. 22,26

Oral therapy includes various medications such as: vitamin E, colchicine, potassium aminobenzoate (Potaba), tamoxifen citrate, carnitine, pentoxifylline, and 5-phosphodiesterase inhibitors. These medicines have not proved to be completely effective and larger studies are needed in order to recommend them as treatment. 22,25,27

Intralesimal therapy has used corticosteroids, calcium channel blockers, and different types of interferon with widely varying results. However, their possible benefits are that they stabilize the disease, prevent its progression, and in a very low percentage of patients, prevent disease recurrence. 27-29

Currently, special attention has been paid to collagenase *Clostridium histolyticum*, a biological agent classified as a specific matrix metalloproteinase -1, -8, and -13, which is applied intralesionally in a maximum of 4 cycles at doses of 0.58 mg (2 injections per cycle separated by 48 to 72 hours) followed by penile stretching or penile remodeling 3 times for 30 seconds. Each cycle is applied at 6-week intervals. This collagenase specifically degrades the collagen type I and type III found in the plaque of Peyronie’s disease. 30 The results of 2 large phase 3 randomized double-blind studies have recently been published that evaluated the
effectiveness, safety, and tolerability of collagenase applied by intralesional injection in 417 patients in one study and 415 patients in the other. The studies were begun in September 2010 and ended March 2012 and showed a 34\% reduction in curvature compared with 18.2\% in the placebo group, supporting its clinical efficacy for treating Peyronie’s disease. 31

The benefit of mechanical treatments that include iontophoresis, shock wave therapy, penile traction apparatuses, and radiation has not been demonstrated.32-34

Surgical treatment is indicated in patients presenting with stable disease (more than one year since onset with no change in deformity for at least 6 months) that have no pain in the penis, are unable to maintain sexual activity due to the deformity or inadequate rigidity, in whom conservative treatment has failed, and who present with plaque calcification.20,24 The possibility of persistence of residual curvature of 20 degrees or less, curvature recurrence in 6\%-10\% of the patients, reduced penile length and rigidity in at least 5\%, and diminished sexual sensitivity in about 20\% of the patients should be discussed prior to surgical management. 35

Tunica albuginea plication techniques are recommended for patients with simple curvature of less than 60 to 70 degrees, no hinge or hourglass effect, and in whom a loss of less than 20\% of the length of the penis is anticipated. A way of predicting the length of the shortening is by measuring the longitudinal axis of the penis in erection ventrally and dorsally from the base to the tip of the glans penis. The difference between the 2 measurements is the estimated loss of penile length in centimeters after plication.

Numerous plication techniques have been described. The
Nesbit procedure involves the excision of the tunica on the side contralateral to the curvature and permanent suture closure. Its variants in the Yachia technique use the Heineke Mikulicz technique (vertical incision and transverse closure), the 16-dot procedure in which no incision is made and the tunica albuginea is only folded with non-absorbable Lembert sutures. Another variant is the Duckett-Baskin modification of tunica albuginea plication, in which parallel transverse incisions are made on the side contralateral to the greatest point of curvature and closed with non-absorbable sutures (figs. 2-8).

All plication procedures reduce the length of the penis. They are not useful for hinge or hourglass deformities and can exacerbate these conditions producing instability. In addition, there may be pain associated with the sutures. No plication technique has been shown to be superior to another, and therefore the ideal technique is the one the surgeon is most familiar with.

Incision or partial excision techniques and graft are recommended for patients with complex curvature above 60 degrees that present with the hinge or hourglass effect or short penis. The patient should have adequate preoperative erections given that there is a high risk for postoperative erectile dysfunction, the predictors of which are age (>55 years), evidence of veno-occlusive dysfunction in the Doppler ultrasound study, ventral curvature, and the severity of the curvature. 22,27,40

Graft techniques include plaque incision or partial plaque excision. There is a high risk for erectile dysfunction with total plaque excision and therefore today a relaxing H or double-Y incision in the area of maximum curvature is preferred. This allows the tunica to expand at this site, correcting the curvature, after which these areas are covered with grafts. Partial plaque excision at the site of greatest deformity can be useful in patients with severe indentation or important calcification of plaque. The geometric principle has been used in an effort to obtain the exact graft size and correct the curvature more precisely, without compromising the length of the penis (figs. 9-16).

Multiple grafts have been used that include the tunica vaginalis, dura mater, temporalis fascia, fascia lata, saphenous vein, and buccal mucosa; however, they need a second incision and increase the surgery duration. Synthetic grafts such as Dacron® and polytetrafluoroethylene (PTFE) have fallen into disuse due to the risk for infection, inflammation, and fibrosis that they provoke. Allografts and xenografts that include bovine and human pericardium and porcine intestinal submucosa are the 2 most commonly used types. Examples of these are Tutoplast®, a thin, strong graft processed from thin human and bovine pericardium that does not contract and Surgisis® ES, a graft from intestinal submucosa that has properties similar to the pericardium but has 25% contraction and therefore is associated with cases of recurrence. 43

![Figure 7](image1.png) Freeing of the medial suspensory ligament for increasing the length of the penis after plication.

![Figure 8](image2.png) Measuring of length after surgery.

![Figure 9](image3.png) Erection induction to evaluate curvature.
Penile prostheses have been suggested for patients with Peyronie’s disease that present with erectile dysfunction that does not respond to medication, but clear criteria for its indication have yet to be described. A prosthesis simultaneously corrects the deformity and treats the erectile dysfunction. Penile prosthesis placement can be done without additional correction maneuvers if the patient has minimum curvature or an unstable penis; manual remodeling is recommended in patients with considerable curvature. If residual curvature is above 30 degrees, the tunica albuginea is incised and covered with a graft in incisions that condition a defect greater than 2 cm so that herniation of the prosthesis and scar contracture are prevented. 35

New therapeutic options still under research using inhibitors of activin receptor-like kinase 5 (ALK5), a type 1 receptor of TGF-β, have demonstrated promising results. Significant plaque regression has been shown in studies on rats. The molecule currently referred to is IN-1130, but there are other similar molecules being studied that have displayed antifibrotic and anticancer activity. 44,45

**Conclusions**

Peyronie’s disease is a pathology that has a tremendous psychosocial impact on the adult and therefore the urologist should be thoroughly familiar with the disease and its integral approach. There are numerous treatment modalities, but up to the present, surgical correction of Peyronie’s disease, with or without the placement of a prosthesis, is regarded as the criterion standard for
correcting the deformity. These patients should be evaluated as carefully and judiciously as possible in order to offer them the most adequate treatment.

Oral or intralesional medical treatment can be used in an early phase of the disease for the purpose of stabilizing or attempting to prevent its progression, with widely varying results. It is very important to wait until the disease has stabilized (>6 months) before performing any surgical procedure. Surgical correction should be exhaustively explained in relation to each patient's particular situation. The technique to be carried out (plication, graft corporoplasty, prosthesis placement) will depend on the clinical situation, type of deformity, shaft length, erectile function, plaque characteristics and location, and the experience of the surgeon. Informed consent for a surgical procedure is of the utmost importance, given that a patient can have false hopes and not be aware of the behavior of a disease. This consent should warn the patient of the possible complications of curvature persistence or recurrence after surgery, shaft shortening even in graft application procedures, diminished rigidity or erectile dysfunction, and a decrease in penile sexual sensation. Nevertheless, the selection of the adequate treatment for each individual case will provide successful results and patient satisfaction. The main treatment aim in Peyronie’s disease is based on incorporating the patients into a normal sexual life.

Conflict of interest

The authors declare that there is no conflict of interest.

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