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Peyronie's Disease: Lights and Shadows

Abstract

Peyronie's disease (PD) is characterized by the onset of fibrous plaque inside the tunica albuginea of the penile corpora cavernosa that can cause pain and bending during the erection, making intercourse difficult or impossible. Evidence of the literature supports the autoimmune etiology of PD and suggests genetic and familial conditions, penile traumas, and a history of genital tract diseases as risk factors, but no definitive conclusions arise about the pathogenesis of the disease. Few randomized trials demonstrated that medical therapies, such as vitamin E, colchicine, potassium aminobenzoate, tamoxifen, and injection therapy with verapamil, can stabilize the acute phase of the disease. Extracorporeal shock wave therapy and iontophoresis cannot be considered first-line or gold standard therapies. Satisfactory results have been published with the Nesbit operation in large series with low-stage disease, whereas plication procedures have shown significant relapse rates. A high incidence of long-term penile retractions has been reported in high-stage disease treated with plaque incision and simple graft insertion. Malleable, soft, or inflatable prostheses combined with graft implantation have given the best results in terms of penile straightening and lengthening and patient satisfaction. In conclusion, the etiopathogenesis of PD is not yet clearly understood, no medical therapy is fully effective, and surgery remains the gold standard in patients with severe deformity and/or erectile dysfunction.

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Introduction

Peyronie's disease (PD) is characterized by fibrous plaque arising within the tunica albuginea of the penile corpora cavernosa that can cause pain and bending during the erection, making intercourse difficult or impossible.

Recent epidemiological studies [1, 2] reported an overall prevalence of 3–5%. An autopsy study of 100 men [3] demonstrated that 22% of the patients had asymptomatic fibrotic lesions of the tunica albuginea. About two thirds of the patients are aged 40–60 years, with the youngest reported being 18 years and the oldest 80 years [4]. PD has been associated with an increased incidence of Dupuytren's contractures, plantar fascial contractures (Ledderhose's disease), tympanosclerosis, trauma, transurethral procedures, diabetes, gout, Paget's disease, and even beta blocker use [5]. Three main factors seem to increase the risk of developing PD: penile traumatism, genetic and familial conditions, and a history of diseases of the genital tract [5, 6]. The relationship between some histocompatibility antigens such as HLA-A1, HLA-B8, HLA-Cw7, HLA-DR3, HLA-DQw2, and HLA-B7 and the occurrence of PD strongly supports the hypothesis of a genetic predisposition to the disease [7–9].

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Fig. 1. Severe penile bending and corporal stenosis due to PD.

Etiology

The etiology of PD is unknown, and the pathogenesis is still unclear. A case-control study based on 66 patients [10] suggested the hypothesis of autoimmune etiology and investigated the immune response patterns of the disease. Skin test (Multi-Test®) and in vitro lymphocyte transformation test had been performed, and serum immunoglobulins, anti-DNA, antinuclear, and anti-smooth muscle cell antibodies, C3 and C4 complement fractions, and antistreptolysin and anti-C-reactive titers have been evaluated in all patients. The majority (75.8%) of the patients exhibited at least one abnormal immunological test in comparison with only 10% among the controls. Alterations of cell-mediated immunity (lymphocyte transformation test; Multi-Test) were observed in 48.5% of the patients, whereas failure of the humoral immunity (immunoglobulin) and alterations of markers of autoimmune disorders were found in 31.8 and 37.9%, respectively.

The traumatic hypothesis suggests that stretch and bend traumas, which may occur during sexual intercourse, can result in delamination of the tunica albuginea, resulting in microvascular injury and hematoma formation. The process starts predominantly along the dorsal cavernous surface, where the midline septum inserts [11].

Neutrophils, macrophages, and mast cells secrete cytokines and vasoactive factors which then become involved in fibrosis development [12–14]. Platelets have an

important part in plaque formation, as they release serotonin, platelet-derived growth factors, transforming growth factors, and fibrin which are incorporated into the scar [15, 16].

Clinical Presentation and Diagnosis

During the early phase of the disease, frequent symptoms are the presence of penile nodules or plaque, painful erection, and penile curvature or deformity during the erection. Symptoms of the late phase are harder plaque, stable penis deformity, erectile dysfunction (ED), and penile retraction (fig. 1). Differential diagnoses to be excluded are congenital curvature with or without chordee, dorsal vein thrombosis, infiltrative cancer, posttraumatic lesions, fibrosis cavernosa after prostaglandin E₁ injection, or a sexually transmitted disease. The initial evaluation of patients with PD is finalized to obtain information about presenting symptoms (degree and location of the curvature, penile length, girth-related changes, erection pain, presence of ED, sexual performance, duration of disease, risk factors and associated pathologies, psychological distress, and level of patient satisfaction) [4]. Specific standardized questionnaires, such as Peyronie's Disease Index [17], have been proposed to complete harvesting information from the patients.

PD and ED

The reported incidence of ED among PD patients is partly due to the plethora of ED-related comorbidities found within this age group. Although some authors consider ED as a late-developing feature, the overall risk for PD-specific ED at any age is 30% [9].

A physician should always consider the possibility of PD in older patients presenting with ED only [18, 19]. An impaired erectile capacity may be caused by concomitant vascular disease that occurs in 30% of the patients with PD [20]. Lopez and Jarow [21] studied 76 patients with PD and found veno-occlusive dysfunction in 59% of them. The remaining 41% of these patients had arterial disease. Arterial insufficiency is more frequent in patients with an hourglass abnormality, because the large volume of plaque leads to compression of the arterial system [22]. Veno-occlusive dysfunction is an important mechanism involved in the pathophysiology of EDs: PD associated and more prevalent in patients with ventral curvature. Venous leakage is caused by reduced tunical compliance, so that an emissary vein, passing through

this rigid segment of the tunica towards dorsal veins of the penis, cannot be compressed between by tunical layers, resulting in a segmental venous leak and detumescence [23].

Dynamic Doppler ultrasonography provides information about plaque size, hypo-/hyperechogenicity, calcification, and tunica albuginea thickness [24]. Simultaneous intracavernous injection of vasoactive drugs allows to assess the preoperative baseline of ED and the degree of penile bending [25, 26]. Magnetic resonance imaging provides more accurate information on plaque formation at the penile basis. Calcification can only be proven by ultrasound [27].

Treatment

Medical Therapy

Many medical treatments have been described, but few prospective controlled trials have been carried out. Vitamin E (200 mg three times daily) is a popular treatment modality, for its low cost and excellent tolerability. In 1948, Scardino and Scott first introduced the use of vitamin E in the treatment of PD. In 1993, Devine and Snow reported a 99% reduction in pain in 105 men taking vitamin E, but 70% of them had no reduction in curvature [see 28].

Colchicine (500 mg three times daily) has the property of binding tubulin, a structural cytoplasmic protein, inhibiting leukocyte adhesion and motility, cellular mitosis, and proliferation of both fibroblasts and inflammatory cells. Colchicine activates collagen formation and inhibits inflammation by blocking the lipooxygenase pathway of the arachidonic acid metabolism [29]. In an uncontrolled study including 24 patients followed up for 3–5 months, it was reported [30] that 11% of the patients had a slight and 26% a marked decrease of the curvature, whereas 50% noted a decrease of the plaque size after colchicine treatment.

Potassium para-aminobenzoate (Potaba®; 12 g once daily for 3 months) decreases fibrogenesis through the inhibition of abnormal fibroblast proliferation and the increase of tissue use of oxygen, likely as a result of an increase of the monoamine oxidase activity and a local reduction of the serotonin levels. Weidner et al. [31] indicated a significant plaque-related effect of Potaba, with a decrease of plaque size on average from 259 to 142 mm², while there was no significant improvement of the preexisting penile deviation. These authors also reported that patients not treated with Potaba had an increase in plaque

size and degree of curvature. Considering these results, Potaba appears to be useful to stabilize the disorder and to prevent progression of the penile curvature, although it is quite expensive, and negative gastrointestinal side effects have been reported [31].

Tamoxifen inhibits the inflammatory response by modulating the transforming growth factor alpha secretion from human fibroblasts. Gulino et al. [32] designed a pilot study with 36 men treated with tamoxifen (20 mg three times daily). An improvement in 20 patients (55%) was reported in terms of pain relief and decrease of the curvature.

Levine in 1994 was the first to suggest the use of the calcium channel blocker verapamil in the treatment of PD. Verapamil decreases fibroblast activity and induces collagenase activity. An uncontrolled study about verapamil, recruiting a small number of patients (12 patients completed the study), demonstrated that 100% of the men with severe deformity have some improvement: 91% had reduced pain, 42% a subjective reduced curvature, and 58% had an improved sexual function [33]. Follow-up studies suggested that the best results have been found in men with small (<4 cm) noncalcified plaques and penile bending <30 degrees [34].

Serious adverse events, like local tissue atrophy and tissue fibrosis, have been reported with intralesional injection of dexamethasone and long-acting triamcinolone in men with small plaques [35]. The recent success in treating orthopedic contracture disorders, such as Dupuytren's disease, suggested the use of collagenases. Walsh treated 31 men with collagenase injections directly into the plaque [36, 37]; 65% of the patients reported a reduced curvature, with the best results obtained in those with small-size plaques.

Interferon injection into Peyronie's plaque reduced the rate of fibroblast proliferation and the production of extracellular collagen and increased the production of collagenases. Several clinical studies demonstrated that the mean objective improvement in plaque size has been 20 degrees, and the best results were achieved in plaques <4 cm [9]. Usually interferon caused adverse events such as sinusitis and arthralgia.

Energy Transfer

This treatment modality includes extracorporeal shock wave therapy (ESWT), laser and ultrasound therapy, and orthovoltage radiation. Several studies have reported that ESWT was able to reduce both penile curvature and pain, improving the sexual function of PD patients [38]. An exploratory meta-analysis of clinical trials

Fig. 2. Final result of a Nesbit operation with satisfactory penile straightening.

about the use of ESWT for PD did not reveal a clear effect on penile curvature, plaque size, and, most importantly, intercourse satisfaction. ESWT is effective in pain reduction; it seems to resolve faster than during the natural course of the disease [39]. In conclusion, ESWT does not appear as a gold standard nor as first-line treatment for PD.

Topical Treatment

Fitch and Easterling [40] assessed the effectiveness of verapamil by topical administration in a randomized study over 3 months and demonstrated that, when compared to placebo, patients receiving topical verapamil had significant improvements in curvature and erectile quality as well as a decreased plaque size.

Iontophoresis is the electrokinetic transdermal transport of electrically charged molecules into affected tissue. The use of this technology in PD has been extrapolated from successful applications for the treatment of arthritis and other soft-tissue diseases. In 1995 Montorsi et al. [41] reported the use of iontophoresis carrying dexametasone and verapamil in PD treatment, with satisfactory results. A relatively recent study [42] exposed 100 men to iontophoresis carrying dexamethasone, lidocaine, and verapamil. In this study 96% of the men reported less pain, 37% described a subjective improvement in curvature, and 53% experienced a reduction in plaque size; 15% of the patients had recurrence of their disease after 5.5 months.

Surgical Treatment

The main surgical procedures used to treat PD are: (1) penile straightening, (2) penile lengthening, and (3) penile prostheses.

Penile Straightening

Penile straightening procedures are advised in those patients with not severe bending, with slight retraction, without ED. These procedures yield excellent results, but can cause a variable degree of penile shortening, depending on the original deformity. The Nesbit technique was first described in 1965 to correct a congenital curvature and was first used to treat PD in 1975. It consists of excision of ellipsoidal sections from the convex portion of the tunica albuginea, the gaps being closed horizontally, so that the longer side of the tunica albuginea is made equal in length to the shorter side [43] (fig. 2). According to a study done by Ralph et al. [44], based on 359 patients, 295 (82%) patients operated on reported satisfactory results and were able to have intercourse. The main complications of the Nesbit procedure are penile shortening, persisted curvature, and impaired erection [45]. Recurrence of deformity may appear immediately after surgery, as a consequence of a surgical error or suture cutting out or, after some weeks (8–10), probably caused by suture failure. Recurrence of deformity can derive from reactivation of disease at the original site, and it is often associated with pain. Shortening <2 cm is considered a satisfactory result.

A study performed by Savoca et al. [46], based on 279 patients with PD treated by the Nesbit procedure, showed that 83.5% of the patients were completely satisfied by the results of surgery after a median follow-up period of 89 months. Complete correction of the penis was obtained in 86.3% of the patients. Shortening of the penis (ranging from 1.5 to >3 cm) occurred in 17.4%, but only in 2.3% interfered with the ability to have intercourse.

In 1990, Yachia [47] introduced an original technique to straighten the penile curvature which provides the same results as the Nesbit procedure, with a lower surgical risk. An artificial erection is achieved by taking bites from the most convex portion of the corpus with Allis clamps. Then a longitudinal incision is made between the marks left by the Allis clamp jaws. The edges of incision are pulled from the middle with a pair of hooks, and finally the horizontal incision is closed. No large series evaluating long-term results of the Yachia technique have been reported. A study based on this technique done in 12 patients with penile curvature reported that penile straightening was achieved in all patients, while 67% of

them reported penile shortening (1–2.5 cm), although the decreased length did not cause interference with sexual activity. No surgery-related complication, such as pain or loss of sensitivity, was reported, and 83% of the patients reported full satisfaction [48].

In 1985, Essed and Schroeder [49] described a surgical technique, derived from the Nesbit procedure, for the correction of congenital and acquired penile curvatures. Four or six plication sutures are applied to the point of maximum curvature in order to completely straighten the penis. The most common complications of this procedure are penile shortening, depending on bending degree and penile geometry, recurrent curvature, and suture knot related symptoms. Several studies, using non-absorbable sutures, showed a curvature recurrence rate of 23–27% at long-term follow-up [50–53].

In 1992 Donatucci and Lue described a simplified technique of plication, later modified by Gholami and Lue [54], consisting of multiple parallel plications of the tunica albuginea below the neurovascular bundle. At 6 months of follow-up, 93% of 132 patients had straight erection, 41% presented penile shortening (0.5–1.5 cm), 12% had symptoms from suture knots, 11% had a painful erection, and 6% had a decrease in penile sensation [54].

Tunical shaving and plication technique is a modification of the Nesbit plication, with partial thickness shaving instead of conventional excision of the tunica albuginea. This technique reduces intraoperative bleeding and cavernous tissue injury, improving adhesion of pliated tunical layers. Of 26 patients undergoing tunical shaving and plication procedure for penile curvature due to PD, 78% reported favorable outcomes [55]. Corporeal herniation through the site of plication is a possible complication of this procedure. This eventuality has to be considered a consequence of excessive shaving of the tunica albuginea rather than depending on the type of suture used [56].

The Ebbehøj-Metz technique consists of plication of the penile tunica albuginea using introflexing double crossover stitches of 2/0 Prolene, grasping deep into the tunica in four positions. Twenty-four patients with penile curvature underwent this procedure, with successful results in all of them, even if 2 patients experienced recurring penile curvature [57].

Penile Lengthening

Grafting techniques are more complex, but provide satisfactory results in most cases, although with a higher risk of ED and long-term penile retraction in several cases [58]. The excision or incision of the plaque with appo-

sition of grafts after plaque removal can be performed in young patients with severe PD, large extension of fibrotic pathology, severe bending without retraction, and good erectile function. The choice of patch and its remodeling is of utmost importance in order to obtain a substitute of the tunica albuginea with adequate biophysical, anatomical, and clinical features as close as possible to the healthy tissue [59]. An array of grafting materials has been studied as substitutes of the tunica albuginea which can be classified in autologous and heterologous.

Autologous Graft. A vein is one of the most frequently used materials because of the similarity of the endothelial structure to the corpus cavernosum (vascular structure) and its elasticity. Penile deep dorsal vein [60], inferior tibial vein, and, particularly, saphenous vein (good for larger areas but needing reconfiguration) are the preferred veins cited in the literature [61]. Veins demonstrated the best biocompatibility and elasticity at medium-term and long-term follow-up. On the other hand, their use requires a second operation to isolate the vein itself and so significantly prolonging the operating time. Furthermore, the size of the patch after saphenous resection is not adequate to restore large tissue defects. For the same reason, penile deep dorsal vein patches are only used in case of plaque incision rather than excision. In addition, the vein is no longer available for coronary surgery, so a specific informed consent should be signed by the patients.

Heterologous Graft: Gore-Tex®. Gore-Tex was the first and most commonly used heterologous material before the introduction of new materials with improved elasticity and biocompatibility. Gore-Tex as well as Teflon [62] have been rarely used, as they are very hard and difficult to manage in case of reoperation due to a high grade of fibrotic reactions. Finally, the rate of aneurysmal and septic complications is too high in our experience. Thus we do not suggest these grafts, especially if associated with prosthetic implants.

Heterologous Graft: AlloDerm®. Cadaveric dermis, treated under aseptic conditions using the LifeCell method. The allograft is not immunologically active, and it favors fibroblast migration and neovascularization. The basal membrane is preserved to aid epithelial migration and adhesion. It has been employed to replace the penile tunica albuginea for 5 years, showing good elasticity and long-term clinical results.

Heterologous Graft: Tutopatch®. It consists of human pericardium which undergoes a process of preservation and sterilization by viral and immunological deactivation. All tissues come from cadaveric donors that fit all

Fig. 3. Multiple plaque incisions after prosthetic implant.

legal and ethical standards [63]. Tutopatch seems to be a reliable graft due to its preserved elasticity at long-term follow-up. Hellstrom, after a medium follow-up period of 30 months, showed good results in terms of penile curvature resolution and absence of ED, especially when the plaque is small to medium in size ($<2 \times 5$ cm) and dorsally located.

Heterologous Graft: SIS® (Porcine Jejunal Submucosal Graft). A biomaterial consisting of an acellular matrix protein (several types of collagen, fibronectin, fibroblast growth factor, transforming growth factor beta) that maintains biomechanical and anatomical features very similar to the tunica albuginea. Several studies have demonstrated the biocompatibility features of SIS. It has been used in urological reconstructive surgery to substitute urothelial tissue with excellent results [64]. Biopsies performed after implantation showed that it is integrated into the urothelium without any inflammatory or immunogenic reaction. The literature shows that this biomaterial offers properties of tissue repairing and remodeling, as it is completely reabsorbed without any general or specific fibrotic reaction ('smart remodeling'). Knoll [65] showed about 90% penile straightness and erectile function, and similar results have been reported by our institution [66].

Few papers in reported in the literature compared clinical outcomes of multiple graft procedures. In recent years the use of new biomaterials (AlloDerm, SIS, Tutopatch) has reduced the rate of penile retraction associated with an increasing rate of satisfactory sexual results [66,

67]. This is due to graft reabsorption, leading to decreased fibrosis and tissue remodeling. The old criticisms such as hemodynamic damage and ED [68] after patch grafting should be reconsidered, both for the low rate of potency loss reported in the literature and thanks to the new oral drugs for ED (phosphodiesterase type 5 inhibitors) that increase the erectile response postoperatively. Plaque incision procedures – if compared with plaque excision – have reduced the risk of postoperative erectile failure because of the sparing of smooth muscle tissue and of the smaller area of tunica albuginea substitution, so that the veno-occlusive mechanism is not impaired, and less complications such as graft and penile retractions have been reported.

Pharmacological support with phosphodiesterase type 5 inhibitors is recommended during the first 3 months after surgery in order to achieve a better penile vascular response and to reduce fibrotic shortening via better corpora cavernosa oxygenation and penile stretching, preventing ischemic damage. Corpora cavernosa oxygenation is very important, because it allows an increase of the pO_2 which is essential in the process from flaccidity to erection and in the protection of cavernous tissue from hypercapnia (Haldane effect) [69].

Some authors suggest that the aim of surgical treatment should be not only to stop disease progression and to straighten the penis, but also to reconstruct the penis to the original size. Plaque surgery without prosthesis implant not always avoids the penile shortening due to progression of disease [70, 71]. Montorsi et al. [72] showed the long-term results of plaque incision and vein grafting performed in 50 patients affected by penile curvature of 45 degrees or higher. The penile length was equal to that preoperatively in 30 patients only (60%), whereas 40% noticed penile shortening.

Penile Prostheses

If patients present ED due to PD or a particularly severe form of retraction of the penis, penile prosthesis implantation could be required [73].

In the treatment of PD, malleable or inflatable prostheses, associated or not with plaque surgery, can be used. If excision or incision of plaque is performed, the use of graft depends on the area size to cover and on the plaque position (fig. 3). Ghanem et al. [74] showed the outcome of malleable penile prosthesis implantation without plaque surgery, performed in 20 PD patients. Straightening of the penis was achieved in all cases, but deviation of the glans persisted in 35% of them, and 12.5% of the patients were dissatisfied.

In 2005, in a series of 145 patients, Austoni et al. [75] showed the results of an original technique using an intracavernous cylinder, soft but axially rigid in consistency, in association with tunical relaxing incisions and saphenous vein grafting – in exact this sequence. All patients presented severe forms of PD with sufficient preoperative erectile function. The average penile lengthening was 1.5 cm, and no cases of bending recurrence or penile shortening were reported at 6 months of follow-up. The large majority of the patients expressed complete satisfaction.

Lateral corporotomies are performed, away from the area affected by disease, and measurements of diameter and length of the corpora cavernosa are obtained by a one-time dilator insertion. The small diameter of the cylinders allows a minimally invasive measurement, with sparing of the erectile tissue which displaced peripherally the prosthesis. The length of prosthesis cylinder is determined adding 1 cm for 30 degrees of curvature, without adding more than 3 cm to avoid traction of the neurovascular bundle and the following risk of ischemia and necrosis of the gland. An axial rigid prosthesis implant determines a longitudinal tension developing in the tunica albuginea and increases the degree of the curvature. Full-thickness incisions are carried out into the plaque along the point of maximal tension, until a complete relaxing and elongation of the penis is achieved. Complete plaque excision may be necessary, if the plaque is calcified or cannot be incised. Austoni et al. [75] suggest the use of a saphenous vein, adequately modeled, to cover the tunical defect.

Wilson et al. [76] reported a series of 104 patients with PD undergoing inflatable penile prosthesis implantation and modeling procedure. After cylinders placement, the prosthesis is inflated to absolute maximum distension. Successively the penis is bent in a direction opposite the curvature, and the bending pressure is maintained for 90 s. Two successive modeling sessions are performed. Successful straightening (<20–30 degrees of curvature) was achieved in all patients of this series, and patient dissatisfaction was 1%. Tunical incisions have to be closed or covered with grafts to prevent cylinder herniation. Occasionally, during modeling, cylinder damage of the outer layer may occur, but in this series the modeling procedure did not increase the risk of reoperation for mechanical failures (around 12.5% as compared with implantation without modeling). The modeling procedure seemed to increase the risk of acute urethral damage (4% of the cases) which always occurred at the distal urethra due to cylinder tip erosion.

Montorsi et al. [77] performed multiple relaxing plaque incisions associated with a prosthetic three-piece inflatable implant. These authors proposed this technique to patients with severe penile curvature, shortening, and impaired penile rigidity due to penile fibrosis, in order to offer a safe and effective surgical option.

We actually associate malleable prosthetic implant with plaque incisions with or without graft apposition, proposing this technique to patients older than 60 years with ED and severe and retractive forms of PD.

Prosthetic implants allow promising results in straightening and lengthening of the penis and simultaneously ameliorate ED. According to Austoni et al. [75], we prefer to use malleable prostheses, because they reduce the possibility of retraction after disease reactivation – and because of their lower cost.

Conclusions

The etiopathogenesis of PD represents still an enigma, although it may be thought to be an immune inflammation, having its first step in penile microtrauma. No medical therapy is fully effective, and surgery remains the gold standard in cases of severe deformity and/or ED.

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