Peyronie’s Disease
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Introduction

Peyronie’s disease is a connective tissue disorder characterized by the formation of fibrous plaques and scar tissue in the erectile tissue of the penis. Patients typically experience symptoms during erections as the scar tissue forces the penis to curve, making sexual intercourse painful and often impossible. Peyronie’s disease occurs most frequently in males aged 40-60 years old, but can also be found in men as young as 18.¹

Penile Anatomy and Physiology

The penis is a sexual organ that also acts as a conduit for urine. It is composed of three cylinders or chambers: two corpora cavernosa, and one corpus spongiosum. During sexual arousal, the corpora cavernosa fill with blood, creating an erection. The cavernosa run the length of the penis and are attached proximally to the pubic arch. Distally, the cavernosa fuse to the glans—which is the distal aspect of the corpus spongiosum. Situated superiorly to the cavernosa are paired dorsal arteries, paired dorsal nerves, and the superficial and deep vein of the penis. The superficial vein lies superior to the deep fascial layer of the penis (Buck’s fascia); the deep vein, paired arteries, and nerves lie inferior to this layer. The superficial vein drains to the branches of the internal pudendal vein, and the deep vein drains into the prostatic plexus.

The corpus spongiosum lies ventral to the two cavernosa and contains the urethra. The spongiosum is anchored at its base to the perineal membrane and then extends to form the ventral body and glans of the penis.

Both cavernosa and spongiosum are enclosed by a connective tissue sheath called the tunica albuginea. The tunica is composed of 2 collagenous layers, the outer longitudinal and inner circular layer. It contains elastin, which permits tissue expansion during erection. Peyronie’s disease affects this layer of tissue, causing fibrosis and calcifications. It is important to note that the tunica surrounding the spongiosum is much thinner (0.5 mm diameter) than that of the cavernosa (2 mm diameter)². This ensures the urethra is not entirely constricted during erection.
An erection is a unique vascular event which requires appropriate innervation, blood supply and muscle function. Erections are generated by the parasympathetic nervous system, specifically nerve fibers running in the pelvic splanchnic nerves arising from spinal cord nerve roots at the S2-S4 level. These nerves are responsible for innervating the paired deep arteries of the penis that stem from the internal pudendal artery. Once stimulated, these arteries relax and fill with blood, leading to an erection. Two important muscle groups are also present to help force blood into the distal regions of the penis during an erection. Around each proximal corpora cavernosa is the ischiocavernosus muscle, and surrounding the corpora spongiosum proximally is the bulbospongious muscle. As the erectile tissue engorges with blood, the tunica albuginea expands. Ultimately Buck’s fascia will also expand but less so, resulting in venous compression and sustained engorgement.

**Presentation and Diagnosis**

A proper diagnosis of Peyronie’s disease requires a pertinent history and physical exam. Patients will typically present with complaints of curved erections and dyspareunia (pain during intercourse). The characteristic fibrous plaques are easily identified on the penis. Peyronie’s Disease will progress through two unique stages. The first or acute stage lasts for approximately 8-18 months and is characterized by penile pain, worsening curvature, penile shortening and plaque formation. The second or chronic phase is a relatively static state in which the curvature during erections remains the same. In younger men, the curvature may resolve without treatment.
Although difficult to pinpoint the exact cause of Peyronie’s disease, it is believed that minor penile trauma is capable of triggering plaque formation. Athletic injury may contribute to forming plaques. However, the majority of cases arise from vigorous sexual intercourse. It is believed that injury to the tunica albuginea can initiate a number of cellular events, which ultimately lead to fibrosis and scar tissue formation. It is also important to note that not all patients with Peyronie’s disease experience initial trauma. Some authors suggest that there is a genetic component to the disease such that relatives of patients have a higher chance of developing plaques. The Urology Care Foundation also reported that men with certain connective tissue disorders, such as Dupuytren’s contracture and tympanosclerosis, have a higher likelihood of developing Peyronie’s Disease.

**Treatment**

**Medical:**

A small number of cases may resolve without treatment. The majority, however, require medical or surgical intervention. Nonsurgical treatment methods are typically recommended during the acute phase of the disease. Although there is no standard treatment regimen, multiple oral treatment methods exist that aim to alleviate symptoms. For example, Vitamin E was examined as a potential treatment option, but results have been lackluster as Vitamin E shows no known benefit in reducing plaque size or improving penile curvature (Table 1).

Additional research examined Colchicine and its effects on reducing symptoms. Colchicine inhibits fibrosis and plaque formation by disrupting neutrophil microtubules. Like Vitamin E, Colchicine offers no significant help in alleviating the symptoms of Peyronie’s disease; however, Prieto et al, showed that when Colchicine (1 mg every 12 hours) and Vitamin E (600 mg/day) are used in combination for 6 months, plaque size and penile curvature are significantly reduced.

Pentoxifylline, a nonspecific phosphodiesterase inhibitor (PDE), has also been examined as a potential treatment option. The results of studies testing Pentoxifylline have shown patients to have
reduced penile curvature and plaque width following administration of 400 mg twice a day for at least six months\textsuperscript{6}. This agent blocks the transforming growth factor (TGF)-β1-mediated pathway of inflammation and so inhibits the fibrosis and collagen deposition\textsuperscript{6}.

Additional research by Lue et al supports the efficacy of Pentoxifylline as a potential treatment for Peyronie’s disease\textsuperscript{8}. In this study, the patient was prescribed Pentoxifylline at 400 mg three times a day for 6 months. At six months follow-up, the patient’s penis had straightened to 10° from a 30° dorsolateral curvature, but still demonstrated an hourglass deformity. The patient did, however, report less pain during sexual intercourse. At 2 year follow-up, the patient presented with a decrease in penile plaque size and improved erections without the need for sildenafil\textsuperscript{8}.

Sildenafil citrate can also serve as an agent in Peyronie’s disease\textsuperscript{8}. Levine and colleagues showed that of the patients receiving sildenafil, 70.8% reported satisfaction with this treatment option\textsuperscript{9}. Additionally no patients experienced an injury to their penis during intercourse or a worsening in penile curvature. These results led Levine and colleagues to recommend sildenafil as a primary treatment for patients presenting with erectile dysfunction associated with Peyronie’s disease.

**Table 1: Summary of oral therapies for treatment of Peyronie’s disease\textsuperscript{19}.

<table>
<thead>
<tr>
<th>Treatment (dose)</th>
<th>Mechanism of action</th>
<th>Efficacy</th>
<th>Side effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vitamin E 400 IU qDay to BID</td>
<td>Antioxidant</td>
<td>No benefit</td>
<td>Possible stroke, nausea, vomiting, diarrhea, headache, dizziness</td>
</tr>
<tr>
<td>Colchicine 2.5 mg qDay</td>
<td>Inhibits microtubules, decreasing fibrosis and collagen deposition</td>
<td>No benefit</td>
<td>Myelosuppression, diarrhea, nausea, vomiting</td>
</tr>
<tr>
<td>Potassium aminobenzoate 3 g q6 h</td>
<td>Inhibits fibroblast glycosaminoglycan secretion; anti-fibrotic</td>
<td>Decrease plaque size by 74.3%; no change in curvature</td>
<td>Anorexia, nausea, fever, skin rash, hypoglycemia</td>
</tr>
<tr>
<td>Pentoxifylline 400 mg BID\textsuperscript{17}</td>
<td>Nonspecific phosphodiesterase inhibitor; decreases collagen deposition and elastin production</td>
<td>Decrease curvature by 23° in 37% of patients</td>
<td>Myelosuppression, indigestion, nausea, vomiting, dizziness, headache, angina</td>
</tr>
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</table>

Intralesional injection therapy can be offered if oral therapy fails. Levine et al. popularized the administration of verapamil (a calcium channel blocker) directly into the scar\textsuperscript{10}. Verapamil generally
reduces cell proliferation and myofibroblast activity. Specifically, calcium channel blockers reduce inflammation and the formation of fibrous tissue by altering the release of cytokines IL-6 and IL-8. This helps dissolve the plaque, improving sexual function and reducing deformity. According to the Male Health Center in Lewisville, Texas, verapamil is typically administered every two weeks at the base of the penis at 20-30 different locations. An alternative intralesional agent is clostridial collagenase. Jordan et al showed that 3 injections of clostridial collagenase (10,000 units in a small volume (0.25 cm³ per injection)) over a 1 week period helped to reduce plaque length, width and penile curvature.

A new intralesional therapy involves injection of enzyme AA4500. The investigators showed that 89% of patients who received injections three times a day, separated by one day for a one week time frame achieved clinical success; clinical success was defined as a change from baseline in deviation angle of at least 25%.

Surgical:

Advanced Peyronie’s Disease is characterized with severe deformities which prohibit satisfying sexual intercourse. The Urology Care Foundation recommends surgery only for those patients with stable plaques. We wait 18 months to verify stability and allow enough time for non-surgical regimens to demonstrate lack of efficacy. Although adverse effects are limited, surgical treatment can result in penile shortening and erectile dysfunction. Two common surgical approaches include plication procedures and plaque excision/incision with grafting.

The Nesbit procedure, involves excising tunica tissue opposite the side of the lesion (or the convex side of the curvature). The remaining tunica edges are then sutured together. This results in straightening of the penis during erection, though the penis is shortened. Dorsal curvature requires a distal circumferential incision to deglove the penis, exposing Buck’s fascia. Buck’s fascia is then entered laterally, avoiding the urethra and the dorsal neurovascular bundle. Plicating sutures with thick absorbable monofilament long-lasting suture like polydiaxanone are then placed ventrally to straighten the penis. Artificial erections are then performed to verify successful correction. Ventral curvatures require more dissection since the dorsal neurovascular bundle needs to be freed off the corpora cavernosa to allow safe placement of dorsal plication sutures. A less invasive plication surgery is the 16-dot technique which involves straightening the penis without excising any tunical tissue.

Fig. 3
Nesbit procedure. In step 3 of this image, tunica tissue is removed opposite the side of the curvature. The plaque in this image is located on the dorsal surface.
Penile plaque excision with subsequent replacement by a biologic graft is also an option. The plaque can be partially or completely excised. The defect is then repaired with full thickness skin grafts, venous tissue, allografts from cadaveric skin, acellular porcine pericardial (Tutoplast™) or bladder tissue (ACell™), and small intestinal mucosal grafts. Levine and Estrada examined the efficacy of replacing the plaque with pericardial tissue and found that following surgery, 39 of 40 patients had successful penile straightening with 28 patients (70%) able to obtain unprovoked erections\textsuperscript{15}. Some patients get plaque excision and grafting with simultaneous inflatable penile prosthesis placement, especially if their curved erections are already soft.

Results and Outcomes

Intralesional enzyme AA4500 injection led to 89% clinical success\textsuperscript{13}. It improved penile curvature, decreased penile pain with erection, and improved sexual satisfaction. The primary adverse effect of this treatment was injection site reaction that ranged from mild to moderate pain/irritation that resolved with time without medical intervention.

There have been mixed results regarding Peyronie’s plaque excision and graft repair. Levine and Taylor reported on 111 patients that received porcine pericardial grafts\textsuperscript{17}. The majority of patients were satisfied, with 92% reporting straighter erections at 58 months follow-up. It should note though that 35% of patients reported diminished post-operative rigidity, requiring PDE-5 inhibitor supplemental therapy. Nevertheless, 89% of the patients reported the ability to achieve orgasm following surgery. Favorable results were also reported by Kovac and colleagues who reviewed 36 patients that received dermal, pericardial, and small intestinal submucosal grafts. The overall patient follow-up time was 673 +/- 98 days. At follow-up, patients reported resolution of penile curvature in 60% of dermal, 100% of Tutoplast, and 76.9% of Stratasis (small intestinal mucosa) graft placements\textsuperscript{18}. Additionally, Kovac and colleagues reported that 54 % of patients receiving small intestinal grafts maintained pre-surgery penile length and 77% of these patients maintained their erection rigidity. These results were superior to the self-reported numbers of patients receiving the dermal and Tutoplast grafts. Of the patients receiving dermal grafts, 30% maintained their length and 60% maintained their rigidity versus 23% of Tutoplast patients maintaining their length and 39% their rigidity. Surgical treatment of Peyronie’s via graft repair
results in correction of penile curvature and high rates of patient satisfaction with close to two years followup, with Stratasis grafts being the best at preserving penile length and rigidity.\textsuperscript{18}

Although the results of Kovac’s study appear promising, Chung and colleagues attained different results with a similar experimental approach. In this study, 86 total patients underwent graft repair where 20 patients received dermal grafts, 33 patients had Tutoplast grafts and 33 patients received a Stratasis graft.\textsuperscript{16} Chung extended the follow up period from Kovac’s study to five years. The results show that at the initial 6 month follow-up, patients reported a significant decrease in penile curvature. However, at 5 year follow-up, patients did not report as great of a decrease in penile curvature. Patients receiving dermal grafts were least satisfied. Additionally, penile length shortening was reported 5 years postoperatively with 65% of patients being dissatisfied with their outcomes.\textsuperscript{16} Thus, when speaking with patients about Peyronie’s surgery, it is necessary to discuss all pertinent information regarding expectations and outcomes in order to make a coherent treatment plan in their best-interest.

The less invasive 16-dot plication technique can be extremely successful in properly chosen patients. Gholami and Lue described their experience with 116 Peyronie’s patients treated with the 16-dot technique and reported close to 90% improvement in erections.\textsuperscript{20} Recurrence of curvature recurred in 15% of patients after 2.6 years followup and only 4 patients reported worse erectile function. The slightly more invasive Nesbit operation had an overall success rate of 90% over 8 years with minimal complications like penile shortening.\textsuperscript{21}

**Additional Concerns Regarding Peyronie’s Disease:**

**Does Peyronie’s disease develop into Cancer?**
The Urology Care Foundation reported that although fibrous plaques may have some similarities to cancerous cells such as reduced susceptibility to apoptosis, plaques typically do not become cancerous.

**Susceptibility to Other Conditions?**
Patients with connective tissue disorders like Dupuytren's contracture are at a higher risk for developing Peyronie’s disease. Although typically seen together it is not known why the plaques in the palmar fascia influence the formation of plaques in the tunica albuginea.\textsuperscript{4}
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8 Lue T, Dean R, and Brant W. Treatment of Peyronie's disease with oral pentoxifylline. NCPU. 2006; 3, 111-115.


